Aus der Klinik für Psychiatrie und Psychotherapie
der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Veränderung und Vorhersagekraft distinkter depressiver Symptome während der Behandlung mit Elektrokonvulsionstherapie

Change of depressive symptoms during the course of electroconvulsive therapy (ECT) and predictive value of these symptoms for ECT outcome

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von

Luisa Pauline Charlotte Carstens (geb. Bönke)

aus Hamburg

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I Abkürzungsverzeichnis

ACC	Anterior cingulate cortex
ADs	Antidepressants
ANOVA	Analysis of variance
BDI-II	Beck Depression Inventory-II
CBASP	Cognitive Behavioral Analysis System of Psychotherapy
CBT	Cognitive-behavioral therapy
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
F	Female
HRSD	Hamilton Depression Rating Scale
M	Male
MADRS	Montgomery-Åsberg Depression Rating Scale
MAOIs	Monoamine oxidase inhibitors
MDD	Major depressive disorder
N	No
NDRIs	Norepinephrine-dopamine reuptake inhibitors
No.	Number
ROC	Receiver operating characteristic
SARIs	Serotonin antagonist and reuptake inhibitors
SPSS	Statistical Package for the Social Sciences
SSNRIs	Selective serotonin–norepinephrine reuptake inhibitors
SSRIs	Selective serotonin-reuptake-inhibitors
TCAs	Tricyclic antidepressants
TeCAs	Tetracyclic antidepressants
T0	Baseline
T1	Mid-treatment
T2	End of treatment
Y	Yes

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IV Deutsche Zusammenfassung

Ziel: Bislang liegen wenig belastbare Ergebnisse zur Veränderung distinkter depressiver Symptome durch die Behandlung mit EKT sowie zu zuverlässigen Prädiktoren einer erfolgreichen antidepressiven Behandlung mit EKT vor. Vorangegangene Studien haben zudem teils widersprüchliche Ergebnisse hervorgebracht. Diese Dissertation untersucht daher die Veränderung depressiver Symptome während der Behandlung mit EKT sowie die Vorhersagekraft initial bestehender depressiver Symptome und ihrer Veränderungen für eine erfolgreiche EKT-Behandlung. Einzelne depressive Symptome wurden dabei mittels Einzel-Items der Montgomery-Åsberg Depression Rating Scale (MADRS) erfasst.

Methodik: In dieser naturalistischen retrospektiven Studie wurden MADRS Daten von 96 depressiven Patienten ausgewertet, die sich in stationärer psychiatrischer Behandlung befanden. Dabei wurden Daten von drei Messzeitpunkten im Verlauf der EKT-Behandlung analysiert. ANOVAs für Messwiederholungen wurden verwendet, um die Veränderung der depressiven Symptome im Verlauf der EKT-Behandlung zu untersuchen. Logistische und lineare Regressionsmodelle wurden angewandt, um die Vorhersagekraft distinkter depressiver Symptome und ihrer Veränderungen für eine erfolgreiche EKT-Behandlung zu explorieren.

Ergebnisse: Die stärkste Symptomreduktion im Verlauf der EKT-Behandlung wurde für affektive Symptome gefunden; für die Items *Sichtbare Traurigkeit*, *Berichtete Traurigkeit* und *Gefühllosigkeit*. Die geringste Symptomreduktion wurde in Bezug auf Konzentrationsschwierigkeiten sowie Suizidgedanken gefunden. MADRS Einzel-Items waren wirksame Prädiktoren für das Ergebnis der EKT-Behandlung, insbesondere die o.g. affektiven Symptome. Die stärksten Effekte wurden dabei für Regressionsmodelle mit dem Item *Berichtete Traurigkeit* gefunden, mit bis zu 80% korrekter Vorhersage des Behandlungsergebnisses. Mittels ROC-Analysen konnten Schwellenwerte für die Vorhersage einer erfolgreichen EKT-Behandlung definiert werden.

Schlussfolgerungen: Im Verlauf der antidepressiven Behandlung mit EKT reduzierte sich die affektive depressive Symptomatik am meisten. Eine stärker ausgeprägte affektive Symptomatik zu Behandlungsbeginn sowie eine stärkere Abnahme dieser affektiven Symptome im Behandlungsverlauf scheinen mit einem günstigeren Behandlungsergebnis einherzugehen. Dementsprechend könnten depressive Symptome erfasst anhand von MADRS Einzel-Items einfache, zuverlässige sowie zeit- und kostensparende Prädiktoren für erfolgreiche EKT-Behandlungen darstellen und somit einen wertvollen Beitrag zur klinischen Entscheidungsfindung leisten. Diese Befunde verdeutlichen zudem den zusätzlichen Nutzen

symptombasierter Depressionsforschung und –behandlung als Ergänzung zur weiterhin vorherrschenden Fokussierung auf Summenscores und übergeordnete Diagnosekriterien.

V English Abstract

Aim: Research examining change in symptoms of depression during treatment with electroconvulsive therapy (ECT) and proposing reliable predictors of ECT outcome is limited and previous studies have led to inconclusive results. This dissertation aims to explore the change of depressive symptomatology assessed with Montgomery-Åsberg Depression Rating Scale (MADRS) single items throughout the course of ECT and analyse the predictive value of these MADRS single items and their change throughout the course of ECT treatment regarding ECT outcome.

Methods: This retrospective naturalistic study analysed MADRS data from 96 depressed psychiatric inpatients. MADRS data were routinely collected at three time points during the course of ECT treatment. ANOVAs for repeated measures were used to explore change of depressive symptomatology throughout the course of ECT. In order to analyse the predictive value of depressive symptomatology and its change regarding ECT treatment outcome logistic and linear regression models were applied.

Results: Strongest reductions throughout the course of ECT treatment were found for MADRS items *apparent sadness*, *reported sadness* and *inability to feel*, assessing affective symptoms of depression. Lowest reductions were found for items assessing concentration difficulties and suicidal thoughts. MADRS single items were found to be potent predictors of ECT outcome, particularly the following items addressing affective symptomatology: *apparent sadness, reported sadness,* and *inability to feel*. Regression models that contained *reported sadness* indicated the most potent effects with as much as 80% correct prediction of ECT outcome. In order to determine a favorable MADRS cutoff value for ECT response, we conducted ROC analyses.

Conclusions: Affective symptoms of depression decreased the most throughout the course of antidepressant ECT treatment. A favorable ECT outcome appears to be associated with more pronounced affective depressive symptomatology at baseline before treatment start and a stronger decline of affective symptomatology throughout the course of ECT. Additionally, precise cut-off values for clinical use after future validation were suggested. In search of reliable and easy-to-assess predictors of ECT outcome, depressive symptoms measured with MADRS single items could be regarded as a cost- and time-effective, valuable addition to clinical decision-making. In general, these findings illustrate the potential of a symptom-based approach, which might pose a useful expansion to the prevailing focus on depression sum-scores and generalized diagnostic categories in depression research and treatment.

VI Manteltext

1. Introduction

1.1. Depressive disorders

Depressive disorders are the most common mental disorders worldwide with a prevalence of 4%.[1] Worldwide more than 300 million people suffer from depressive disorders; depressive disorders are one of the major contributors to the burden of disease, ranking third place worldwide and first place in middle- and high-income countries.[1,2] According to the DSM-5, depressive disorders can be characterized by the following symptoms: depressed mood, loss of interest or pleasure, significant unintentional weight loss or weight gain, decrease or increase of appetite, sleep disturbances, psychomotor changes, tiredness, fatigue, or low energy, a sense of worthlessness or excessive inappropriate guilt, impaired ability to think, concentrate, or make decisions and recurrent thoughts of death, suicidal ideation, or suicide attempts. For the diagnosis of a depressive episode, at least five symptoms have to persist over a period of at least two weeks, one symptom has to be depressed mood or loss of interest. Moreover, these symptoms have to cause clinically significant distress or impairment in social, occupational, or other important areas of psychosocial functioning. Depending on the number of present symptoms and their severity, depressive disorders can be categorized as mild, moderate, or severe.

The German Health Interview and Examination Survey[3] assessed depressive symptoms in a large representative sample of 7988 adults in Germany. Prevalence of current depressive symptoms was 10.2% for women and 6.1% for men. The 12-months prevalence of a diagnosed depressive disorder was 8.1% for women and 3.8% for men.[3] This implies a total of 6.2 million people suffering from clinically relevant depression in Germany during a 12-month period, needing treatment.[4] Patients report to suffer the most from suicidal ideation, mental pain, anxiety and sadness.[5] Accordingly, depressive symptoms contribute significantly to a reduced quality of life.[6] Apart from the direct impact of depressive symptoms on patients' wellbeing, various indirect consequences are associated with untreated depressive disorders. For example, depressive disorders are associated with lower relationship quality, lower income, increased physical symptoms, and lower work performance.[7] This lower productivity at work is associated with high economic costs (up to 33 Billion US Dollar) due to depression-related absence from work or impairment whilst at work.[8] Considering the international lifetime-prevalence of 16-20% and the high direct and indirect impact of depressive disorders on patients' quality of life as well as the impact on general productivity and public health expanses, it is clear that effective, fast-acting treatment options are needed. This seems especially

important as depressive disorders bear the risk of recurrent episodes or chronicity and imply a high risk of suicide. Empirically well-founded antidepressant treatment options are psychotherapeutic offers like cognitive behavioral therapy, pharmacotherapy, and other somatic therapies such as light therapy.[4] Even though routinely administered treatments are often effective, most pharmacological therapies have a delayed onset of action and about 30% of patients suffering from MDD do not respond sufficiently to established psychotherapeutic, pharmacological, or somatic treatments.[9] After a lack of response to two adequate treatments, patients are described as suffering from treatment-resistant depression. So-called treatment-resistant depression is not only associated with illness chronicity but also a further reduced quality of life, and an even higher risk for suicide.[10] For these patients with severe or treatment-resistant depression, electroconvulsive therapy (ECT) is one of the most recommended acute treatment strategies.[11]

1.2. Electroconvulsive therapy as a treatment for depressive disorders

In general, electroconvulsive therapy (ECT) can be regarded as a very potent, rapid acting treatment option for severe as well as treatment-resistant depressive disorders.[11] Its origin goes back to the 1930s when Laszlo Meduna successfully treated a patient suffering from schizophrenia with a pharmacologically induced grand mal seizure. A few years later, Ugo Cerletti and Lucio Bini successfully implemented the idea of inducing grand mal seizures with an electric current as a treatment option for depressed patients. Since then, the technique has undergone constant revision and development. Nowadays, an electric current is administered to the brain through the scalp under anesthesia and induces a therapeutic seizure. Patients are hospitalized and usually receive a series of 9 to 12 ECT sessions over the period of one month. In the United States, ECT has been used successfully since the 1940s. Modern research has supported the efficacy of ECT, improved its safety, and helped to reduce adverse side effects. In general, ECT appears to be a well-tolerated treatment option, promoting patients psychosocial functioning and quality of life. However, after repeated treatment sessions, transient cognitive adverse effects can occur.[12,13] Especially verbal episodic memory seems to be affected by ECT treatment, while working memory remains intact. These cognitive impairments are mostly restricted to the three days directly after ECT treatment and tend to diminish within the two weeks after treatment end. No long-term memory impairments are reported. On the contrary, in association with clinical improvement, memory seems to improve as well after around a month.[12] Standard pharmacotherapeutic interventions are often accompanied by adverse effects such as sexual dysfunctions, weight gain and discontinuation

symptoms. Thus, due to the short duration of adverse effects and the relatively fast speed of recovery ECT could be regarded as a favorable treatment option for some patients.[12] Psychiatric guidelines around the world recommend the use of ECT as first-line treatment option for patients suffering from severe and treatment-resistant depression, where a fast relief of depressive symptoms is required. This could, for example, be the case for example if severe psychotic symptoms, suicidality, or food refusal prevail.[4,9,11,14] In western countries, the majority of patients treated with ECT are older women diagnosed with major depressive disorders. Worldwide the average number of administered ECT sessions per patient is 8.[15] However, despite its widespread use for nearly a century, the underlying antidepressant mechanisms of action remain only partly understood, potentially contributing to the still existent stigmatization. Several mechanisms of actions have been discussed in the literature, such as volumetric and functional brain changes, change in neurotransmission, or effects on inflammatory processes. Yet, due to inconsistent findings, future longitudinal studies combining modalities such as peripheral physiological measures, magnetic resonance imaging, and spectroscopy are required for deeper insights.[12] Moreover, even though general response rates for ECT in depressed patients are relatively high (60-80%),[16] there is still a notable proportion of patients who do not respond or only respond partially. Hence, there has been an ongoing search for demographic, neurobiological, and clinical factors that might predict ECT outcome.[8,9]

1.3. Prediction of electroconvulsive therapy outcome in depressed patients

In a recent meta-analysis, some aspects such as older age, presence of psychotic symptoms, and higher depression severity are suggested as promising predictors of effective ECT treatment in depressed patients.[18] Other factors that have been discussed in the literature are neurobiological factors such as pre-treatment hyperconnectivity between key brain circuits of depression, and reduced pre-treatment glutamine/glutamate levels particularly in the anterior cingulate cortex (ACC). Potentially relevant clinical factors include speed of response, polarity (unipolar or bipolar), current presence of manic symptoms, chronicity of episode, suicidal ideation, and presence of melancholic features. However, especially findings concerning potentially predictive depressive symptoms or depression subtypes seem to be unclear.[17,18] Following the idea of depression subtypes as potential predictors of ECT response, Okazaki et al.,[19] Tominaga et al.,[20] and Spashett et al.[21] pursued a factor-analytic approach and explored the predictive value of different factors based on the Montgomery-Åsberg Depression Rating Scale (MADRS).[22] The MADRS is one of the most commonly used clinical interviews for depression

severity. Depression severity is assessed with 10 items addressing the following symptoms: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. It seems very promising to determine reliable response predictors based on a widely used clinical interview for depression severity. Unfortunately, results varied substantially for all three studies, impeding reliable conclusions. Okazaki et al.[19] and Tominaga et al.[20] both employed a three-factor model of the MADRS proposed by Suzuki et al.[23]. Okazaki et al.[19] found higher pre-treatment scores for a factor labeled "dysphoria" to be positively associated with ECT response in patients with treatment-resistant MDD. The factor "dysphoria" included the following three items: reported sadness, pessimistic thoughts, and suicidal thoughts. Tominaga et al.[20] examined a sample of older patients diagnosed with MDD and found lower pre-treatment scores for a factor labeled "retardation" to be positively associated with ECT response. The factor "retardation" included the following four items: lassitude, inability to feel, apparent sadness, and concentration difficulties. Spashett et al.[21] restrained from the factor model proposed by Suzuki et al.[23] and performed a separate principal component analysis in a large sample of depressed patients treated with ECT. Patients with and without psychotic symptoms were examined separately and two distinct three-factor models of the MADRS were proposed. In the subgroup including patients with psychotic symptoms, no association between MADRS factors and ECT response could be found. For patients without psychotic symptoms, higher pre-treatment scores on a factor labeled "despondency" were positively associated with ECT response. This factor "despondency" included the following five items: apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel. Thus, while two studies referred to the same three-factor MADRS model, they found different factors and therefore symptom subtypes to be associated with ECT treatment outcome. Spashett et al.[21] proposed their own factor model, yet did not find it to be useful for patients with psychotic symptoms. For patients without psychotic symptoms a predictive factor including a combination of five MADRS items was proposed. In summary, all three studies proposed a certain combination of MADRS items to be helpful as predictors of ECT response, yet these three studies proposed three different predictive factors including different combinations of seven of the ten MADRS items. Thus, these factor-analytic findings are rather inconsistent, inconclusive, and currently cannot be regarded as a reliable, easy addition to decision-making prior to ECT treatment.

1.4. Research question

As described above, effective therapeutic measures for depressive disorders are needed. ECT can be regarded as one of the most effective acute treatment choice, recommended by psychiatric guidelines around the world particularly for treating patients suffering from severe and treatment-resistant depression.[4,11,16] However, a relevant percentage of patients does not benefit sufficiently and mechanisms of action remain only partly understood, which might potentially further impede treatment prediction. In general, ECT treatment implies for the patients to be hospitalized for a few weeks and receiving recurrent anaesthesia for every ECT treatment. Thus, ECT can be regarded as a relatively complex, cost- and time-intensive treatment, for the individual patient as well as for the health system. Additionally, the psychological distress for patients receiving ECT treatment without achieving the desired antidepressant results as well as potential distress from transient cognitive adverse effects should be taken into account. However, empiric findings suggest that ECT might be a highly effective alternative treatment option for patients who are severely depressed and often have long been treated with limited success. Thus, in order to adequately address and inform patients who might genuinely benefit from this treatment and promote treatment confidence and compliance, it seems of the utmost importance to determine reliable, easy-to-assess predictors of successful antidepressant ECT treatments.[13,17]

As mentioned above, investigating response predictors based on the MADRS, a short, well-established clinical interview for severity of depression, seems a valuable addition to clinical decision-making. Nonetheless, the previously mentioned inconclusive results regarding MADRS factors as potentially new predictors of ECT outcome need to be considered. Thus, instead of further pursuing one of these previously described factor-analytic approaches, the objective of this dissertation is to explore the potential use of MADRS single items as predictors of ECT outcome. Especially as previously examined factors lack theoretic foundation,[19–21] single items could be regarded as potentially simple, clear predictors easy to interpret. To the author's best knowledge this is the first study that examines MADRS single items before, during (mid-treatment), and immediately after the course of ECT. These three time points allow for detailed insight beyond pre-post comparison, as they facilitate considering potential time-specific effects such as early response or general speed of response. Thus, the aim of this dissertation is not only to assess the predictive value of MADRS single items and hence distinct symptoms of depression, it additionally also aims to illustrate the change of these distinct symptoms of depression throughout the course of ECT treatment. Thereby, this dissertation hopes to contribute to a more elaborate understanding of the antidepressant mechanisms during

ECT. On a broader note, these findings might help to potentially pave the way for a more personalized approach in ECT treatment, where patients and clinicians are enabled to make more precise, well-informed decisions about treatment options.

2. Methods[1]

2.1. Design

In this retrospective study design, we analysed data from 96 psychiatric patients diagnosed with a current depressive episode (according to DSM-5) who received antidepressant treatment with electroconvulsive therapy at Charité – Universitätsmedizin Berlin. The study was carried out in accordance with the Declaration of Helsinki and authorized by the institutional review board of the Charité. Due to the naturalistic study design, no clinical trials registration is available. The present study analyses depression severity routinely assessed with the MADRS[22] at three different time points throughout treatment with ECT. The MADRS was administered before ECT treatment at baseline (T0), at mid-treatment after 6 ECT sessions (T1) and at treatment end 1 to 3 days after the last ECT session (T2). A graphic depiction of the study procedure can be found in figure 1.

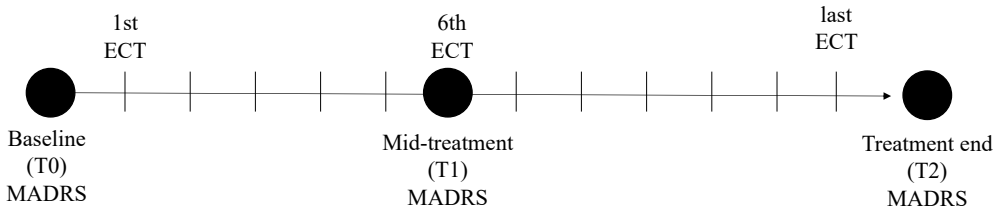

Figure 1. Study procedure. ECT = Electroconvulsive therapy. MADRS = Montgomery-Åsberg Depression Rating Scale.

[1] Selected sections of the here described methods and results have been previously reported in the following original article of which I am the sole first author: "A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items" Carstens, L., Hartling, C., Stippl, A., Domke, A.- K., Herrera-Mendelez, A. - L., Aust, S., Gärtner, M., Bajbouj, M., & Grimm, S. (2021). *European Archives of Psychiatry and Clinical Neuroscience*, 1-10. https://doi.org/10.1007/s00406-021-01301-8**.** Open Access (CC BY 4.0).[24]

2.2. Treatment with electroconvulsive therapy

ECT treatment was conducted according to the standard protocol at the Psychiatric Hospital, Charité – Universitätsmedizin Berlin. This protocol comprises three ECT treatments per week, usually for four weeks, resulting in a total of 12 ECT sessions. Patients received anesthesia with etomidate (approximately 0.75 mg/kg) or propofol (approximately 1.5 mg/kg). Ultra-brief pulse stimuli (0.3 ms) for right unilateral ECT were applied using the Thymatron IV System (Somatics, LLC, Venice, Florida, United States). The average number of conducted ECT sessions per patient in our sample was 13.60 (*SD* = 2.66). A detailed description of the applied ECT procedure can be found in Basso et al.,[25] Brakemeier et al.,[26] or Carstens et al.[24]

2.3. Depression severity

The MADRS (Montgomery-Åsberg Depression Rating Scale)[22] was employed to assess depression severity. In our hospital, the MADRS is routinely carried out by trained professionals for all inpatients. The MADRS is a standardized clinical interview. It comprises 10 items that assess the following symptoms of depression, each on a 7-point scale: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. In accordance with a well-established definition by Maust et al.[27] the following classifications were made: A reduction of MADRS total score of 50% or more at the end of treatment (T2) was defined as response, a MADRS total score ≤ 10 at the end of treatment (T2) was defined as remission and a 50% reduction or more at mid-treatment (T1) was defined as early response. A definition of response as 50% symptom reduction is widely used, however, these artificial dichotomizations of not only response but also remission can be perceived as a rough simplification. This leads to a loss of potentially useful information. In our opinion, a meaningful outcome measure for successful antidepressant ECT treatment should not only include dichotomous response or remission status, but also a more general measure of decrease in symptomatology. Hence, we decided to define an additional outcome measure for overall symptom reduction based on the MADRS. In this study, overall symptom reduction is specified as change of MADRS total score in percentage from baseline to treatment end (called MADRS total change score T0:T2).

2.4. Statistical Analyses

SPSS statistical software, version 26 (IBM Corp., USA) was used for all statistical analyses. Responders and non-responders were compared with regards to clinical and demographic variables. Since distribution of sex and presence of psychotic symptoms significantly differed for these patient groups, we included these variables into the statistic models.

Change of depressive symptomatology throughout the course of electroconvulsive therapy: ANOVAs for repeated measures (T0, T1, T2) were used, individually for all single items and MADRS total score. Sex and presence of psychotic symptoms were included as covariates. Interaction effects were regarded, however, interaction effects within the covariates are not reported here, as this would have exceeded the scope of this synopsis. ANOVAs were computed for the overall sample and individually for responders and non-responders. We additionally included the classification responders vs. non-responders as a covariate for ANOVAs examining the overall sample.

Prediction of electroconvulsive therapy outcome: In order to predict ECT outcome with MADRS single items, we implemented regression models. As outcome variables, we used response, remission and early response after ECT treatment. Two-step logistic regression models were employed to predict these variables. As mentioned above, we added another, non-dichotomous outcome variable to our research: overall symptom reduction, defined as MADRS total score change from baseline (T0) to treatment end (T2). In order to predict overall symptom reduction, we employed a two-step linear regression model. For all these regression models, we included sex, presence of psychotic symptoms, and number of received ECT sessions in step one to control for these variables. In step two, we added MADRS total score and MADRS single items to distinct models separately.

Receiver operating characteristic analyses: We used receiver operating characteristic (ROC) analyses to determine the optimal cut point for MADRS items and total score at baseline as well as change scores T0:T1 for response at the end of treatment. Cut points were estimated with the help of Youden-index and respective consideration of sensitivity and specificity.

All *p*-values are Bonferroni-corrected where applicable, except for baseline (T0) as predictor of ECT response.

3. Results[1]

3.1. Descriptive data

We analysed the data of n = 96 psychiatric patients diagnosed with a depressive episode. An overview of psychiatric and demographic information for the overall sample, as well as responders, and non-responders can be found in table 1. Additionally, table 1 also includes a comparison of these variables between responders and non-responders. As mentioned above, distribution of sex and presence of psychotic symptoms differed for responders and non-responders, hence these variables were included into the statistic models.

Table 1
Psychiatric and demographic data

Variable	Overall Sample			Responders			Non-Responders			*t*	*df*	*p*	*d*
	M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*				
Age	52.60	14.79	96	54.67	15.15	51	50.27	14.18	45	-1.46	94	.147	-0.30
Years of education	14.05	2.85	88	13.84	2.83	44	14.29	2.93	42	0.72	84	.476	0.16
No. of psychiatric hospitalizations[a]	3.98	3.33	94	4.18	4.15	50	3.75	2.02	44	-0.65	73	.518	-0.15
No. of depressive episodes	7.24	9.59	46	9.04	11.36	28	4.44	4.97	18	-1.61	44	.114	-0.49
Duration of present episode in months[a]	9.61	9.44	46	8.53	9.44	27	11.13	9.66	19	0.92	44	.364	0.28
No. of ECT sessions	13.60	2.66	96	13.27	2.65	51	13.98	2.66	45	1.30	94	.198	0.27
										χ^2		*p*	φ
Sex (F:M)	58:38		96	37:14		51	21:24		45	5.66	1	.017	.26
Presence of psychotic symptoms[b] (Y:N)	11:85		96	10:41		51	1:44		45	5.51	1	.019	.27
Lifetime suicide attempt[b] (Y:N)	30:41		71	17:23		50	13:18		31	0.00	1	.962	.01

Note. No. = number. [a] Assumption of equality of error variances violated (Levene's test: $p < .05$).[b] Yates corrected. d = Cohen's d, φ = Phi coefficient. Adapted with permission from my previously published original article of which I am the sole first author: "A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items" Carstens, L., Hartling, C., Stippl, A., Domke, A.- K., Herrera-Mendelez, A. - L., Aust, S., Gärtner, M., Bajbouj, M., & Grimm, S. (2021). *European Archives of Psychiatry and Clinical Neuroscience*, 1-10. https://doi.org/10.1007/s00406-021-01301-8**.** Open Access (CC BY 4.0).[24]

Mean MADRS total scores for the overall sample, responders and non-responders as well as their comparison between responders and non-responders can be found in table 2. In accordance with the definitions described above,[27] 53% of the patients were defined as responders, 34% were defined as remitters. All patients who were defined as remitters met criteria for response definiton as well. Additionally, 24% of our patients could be classified as early responders.

Table 2
Mean MADRS total scores

Variable	Overall Sample			Responders			Non-Responders			*t*	*df*	*p*	*d*
	M	*SD*	*n*	*M*	*SD*	*n*	*M*	*SD*	*n*				
T0 (Baseline) MADRS total score	30.20	5.42	96	31.47	5.34	51	28.76	5.21	45	-2.52	94	.014	-0.52
T1 (Mid-treatment) MADRS total score	20.30	7.26	96	16.94	7.02	51	24.11	5.47	45	5.53	94	< .001	1.14
T2 (Treatment end) MADRS total score	14.30	7.91	96	8.24	4.10	51	21.26	5.01	45	13.88	94	< .001	2.86
Change in MADRS total score from T0:T2	50.91	28.29	96	73.26	13.27	51	25.58	17.12	45	15.34	94	< .001	3.16

Note. Change in MADRS total score from T0:T2 is defined as the change in percentage from baseline to treatment end. *d* = Cohen's *d.*

In the overall sample, 87% of the patients were diagnosed with unipolar depression, the most frequent diagnosis type (53%) was recurrent depressive disorder, current episode severe without psychotic symptoms. Moreover, 47% of the patients were diagnosed with psychiatric comorbidities, the most frequent comorbid diagnoses were anxiety, stress-related, or somatoform disorders. A detailed description of all clinical diagnoses can be found in table 3.

Table 3
Frequencies of Psychiatric Diagnoses

Variables	Frequencies
Type of affective disorder	86.5% unipolar (83) 13.5% bipolar (13)
Primary ICD-10 Diagnosis	3.1% F31.3: Bipolar affective disorder, current episode mild or moderate depression (3) 8.3% F31.4: Bipolar affective disorder, current episode severe depression without psychotic symptoms (8) 1.0% F31.5: Bipolar affective disorder, current episode severe depression with psychotic symptoms (1) 1.0% F31.6: Bipolar affective disorder, current episode mixed (1) 2.1% F32.1: Moderate depressive episode (2) 9.4% F32.2 Severe depressive episode without psychotic symptoms (9) 1.0% F32.3: Severe depressive episode with psychotic symptoms (1) 8.3% F33.1: Recurrent depressive disorder, current episode moderate (8) 53.1% F33.2: Recurrent depressive disorder, current episode severe without psychotic symptoms (51) 9.4% F33.3: Recurrent depressive disorder, current episode severe with psychotic symptoms (9) 3.1% F34.1: Dysthymia (3)
Additional psychiatric diagnoses	46.9% yes (45) 53.1% no (51) 5.2% F00-F09: mental disorders due to known physiological disease (5) 16.7% F10-F19: present psychoactive substance use or dependence syndrome (16) 6.3% F10-F19: past psychoactive substance use or dependence syndrome (6) 3.1% F30-F39: affective disorder (3) 18.8% F40-F48: anxiety, stress-related, or somatoform disorders (18) 2.1% F50.-: eating disorders (2) 11.5% F60-F69: personality disorders (11) 1.0% F80-F89: pervasive developmental disorder (1) 1.0% F90-F98: behavioral and emotional disorders with onset occurring in childhood and adolescence (1)

Note. Census data in parentheses. Subgroups of additional psychiatric diagnoses refer to ICD-10 classifications. Percentage scores might not add up to exactly 100% due to patients having more than one diagnosis.

As our data was assessed in clinical routine, no restrictions concerning medication intake were made and 68% of the patients received concomitant antidepressant medication. The most frequently used antidepressants were SSNRIs (selective serotonin–norepinephrine reuptake inhibitors) for 24% of the patients. A detailed description of all psychiatric medication can be found in table 4.

Table 4
Frequencies of Psychiatric Medication

Variable	Frequencies
Antidepressant medication (ADs) at baseline	32.3% none (31) 67.7% ADs (65): 9.4% SSRIs (9) 24.0% SSNRIs (23) 10.4% NDRIs (10) 16.7% SARIs (16) 9.4% TCAs (9) 12.5% TeCAs (12) 2.1% MAOIs (2)
Additional psychotropic medication	28.1% none (27) 71.9% others (69): 56.3% antipsychotics (54) 25.0% mood stabilizer (24) 22.9% benzodiazepines (22)
Overall medication change	19.8% no (19) 77.1% yes (74) 3.1% N/A (3)
Change in antidepressant medication	49.0% no change (47) 31.3% change in type (30): 5.2% switch to different type (5) 9.4% cessation (9) 16.7% start of new AD (16) 16.7% change in dosage (16): 12.5% increase (12) 7.3% reduction (7) 3.1% N/A (3)
Change in other psychotropic medication	36.5% no change (35) 32.3% change in type (31): 2.1% switch to different type (2) 19.8% cessation (19) 10.4% start of new medication (10) 28.1% change in dosage (27): 10.4% increase (10) 24.0% reduction (23) 3.1% N/A (3)

Note. Census data in parentheses. ADs = Antidepressants. SSRIs = selective Serotonin-Reuptake-Inhibitors. SSNRIs = selective Serotonin–norepinephrine reuptake inhibitors. Selective norepinephrine reuptake inhibitor. NDRIs = Norepinephrine-dopamine reuptake inhibitors. SARIs = Serotonin antagonist and reuptake inhibitors. TCAs = Tricyclic antidepressants. TeCAs = Tetracyclic antidepressants. MAOIs = Monoamine oxidase inhibitors. Percentage scores might not add up to exactly 100% due to patients taking more than one psychiatric medication.

3.2. Change of depressive symptoms during the course of ECT

Depressive symptoms at baseline, mid-treatment and treatment end were compared using ANOVAs for repeated measures. ANOVAs were conducted for the overall sample and separately within the responder and non-responder group. Change for the single items is depicted in figures 2 to 4. Figure 5 shows change of MADRS total score for all time points.

Overall sample. ANOVAs for repeated measures found significant main effects for time for all items and MADRS total score, post-hoc tests revealed significant decreases over all time points for items 1, 2, 3, 4, 8, 9, and MADRS total score ($p < .05$). Items 5, 6, 7, and 10 significantly decreased from baseline (T0) to treatment end (T2) and baseline (T0) to mid-treatment (T1) ($p \leq .01$), however no significant decrease from T1 to T2 was found ($p > .05$). For item 8 a significant main effect for responders vs. non-responders was found $F(1, 89) = 5.47$, $p = .022$, $\eta^2 = .06$, responders showed lower scores ($M_{responders} = 1.89$, $SD = 0.13$, $M_{non\text{-}responders} = 2.53$, $SD = 0.24$). For item 10 a significant main effect for psychotic symptoms was found $F(1, 89) = 4.52$, $p = .036$, $\eta^2 = .05$), patients with psychotic symptoms showed lower scores than patients without psychotic symptoms ($M_{psychotic} = 0.30$, $SD = 0.34$, $M_{non\text{-}psychotic} = 1.04$, $SD = 0.11$). For MADRS total score a significant main effect for responders vs. non-responders was found $F(1, 89) = 6.70$, $p = .011$, $\eta^2 = .07$), responders showing lower scores ($M_{responders} = 18.77$, $SD = 0.74$, $M_{non\text{-}responders} = 22.77$, $SD = 1.36$). For items 1, 2, 3, 7, 8, and MADRS total score a significant time*responders interaction was found ($p < .05$, $\eta^2 > .03$), responders showed higher scores at baseline (T0) than non-responders, while at treatment end (T2) responders showed lower scores than non-responders.

Responders. ANOVAs for repeated measures detected a significant main effect for time for all items and MADRS total score ($p < .01$, $\eta^2 > .28$), post-hoc tests revealed significant reductions across all time points for items 1, 2, 3, 7, 8, 9, 10, and MADRS total score ($p < .05$). Items 4, 5, and 6 significantly decreased from baseline (T0) to treatment end (T2) and baseline (T0) to mid-treatment (T1) ($p < .001$), however no significant decrease from mid-treatment (T1) to treatment end (T2) was found ($p > .05$). For items 1, 2, 8, and 9 a significant main effect for sex was found, men showing higher scores than women ($p \leq .05$, $\eta^2 > .07$).

Non-responders. ANOVAs for repeated measures detected a significant main effect for time for item1 and MADRS total score ($p = .001$, $\eta^2 > .14$), no significant main effects for time were found for items 2 – 10 ($p > .05$, $\eta^2 < .06$). Post-hoc tests showed significant reductions from baseline (T0) to treatment end (T2) for item 1, 2, and MADRS total score ($p < .05$), from baseline (T0) to mid-treatment (T1) for MADRS total score ($p < .05$), and from mid-treatment (T1) to treatment end (T2) for item 1 ($p < .001$).

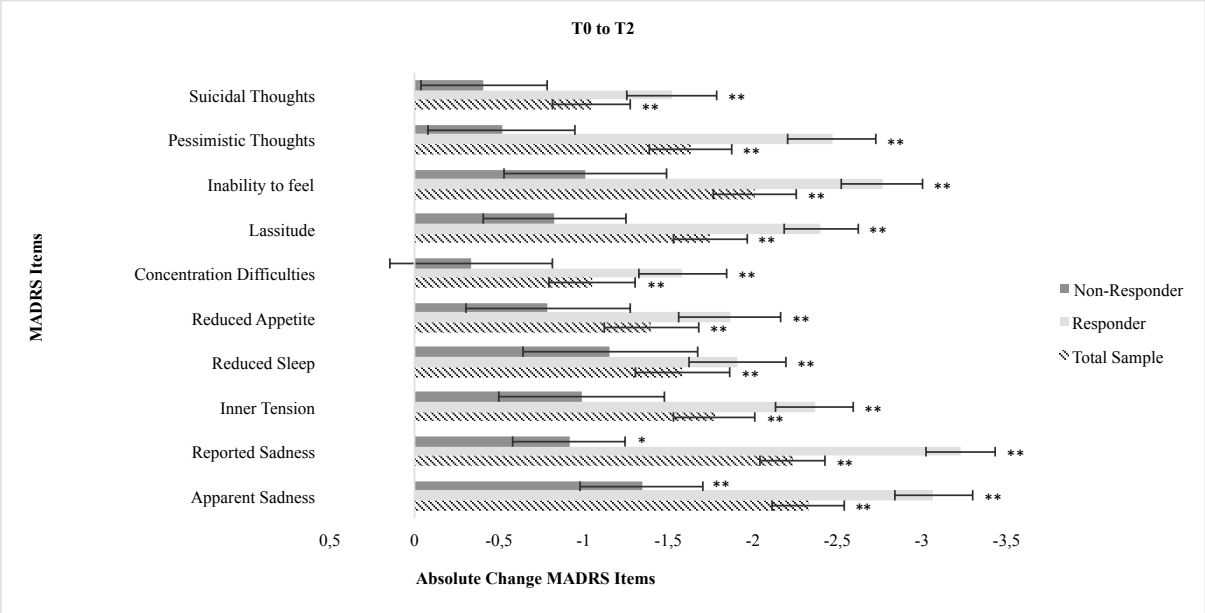

Figure 2. Absolute change of MADRS items from baseline (T0) to treatment end (T2). * = Bonferroni-corrected $p < .05$, ** = Bonferroni-corrected $p < .01$. Error bars represent standard errors. From "A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items" by Carstens, L., Hartling, C., Stippl, A., Domke, A.-K., Herrera-Mendelez, A. - L., Aust, S., Gärtner, M., Bajbouj, M., & Grimm, S. (2021). *European Archives of Psychiatry and Clinical Neuroscience*, 1-10. https://doi.org/10.1007/s00406-021-01301-8**.** Open Access (CC BY 4.0). With permission.[24]

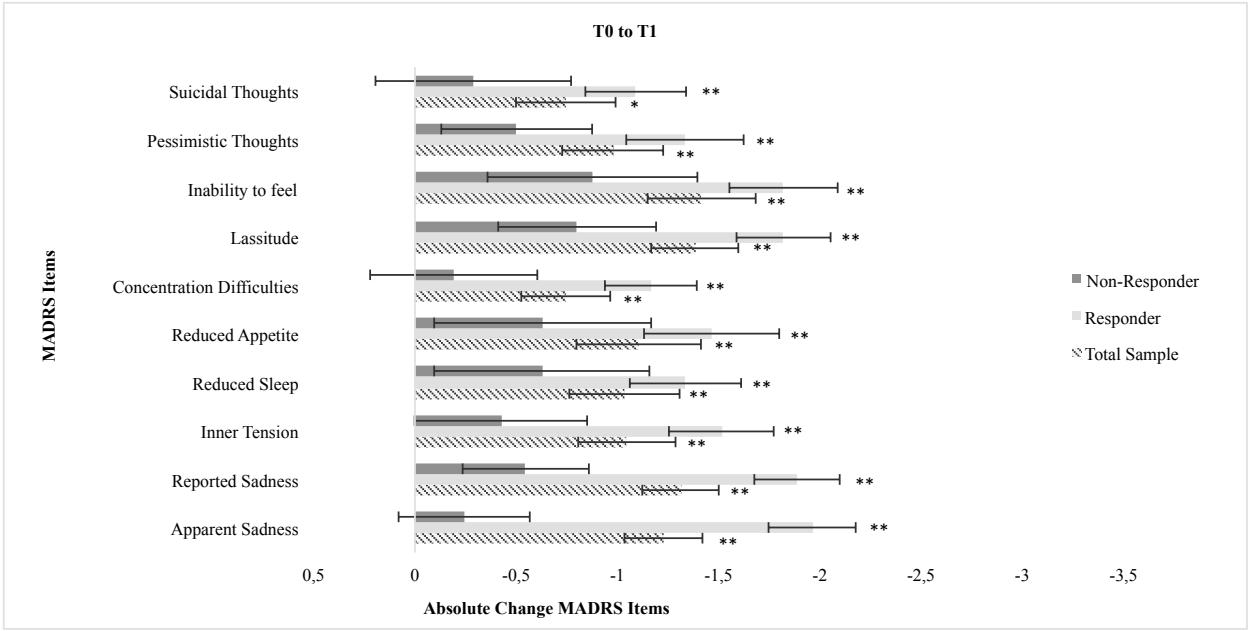

Figure 3. Absolute change of MADRS items from baseline (T0) to mid-treatment (T1). * = Bonferroni-corrected $p < .05$, ** = Bonferroni-corrected $p < .01$. Error bars represent standard errors. From "A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items" by Carstens, L., Hartling, C., Stippl, A., Domke, A.- K., Herrera-Mendelez, A. - L., Aust, S., Gärtner, M., Bajbouj, M., & Grimm, S. (2021). *European Archives of Psychiatry and Clinical Neuroscience*, 1-10. https://doi.org/10.1007/s00406-021-01301-8**.** Open Access (CC BY 4.0). With permission.[24]

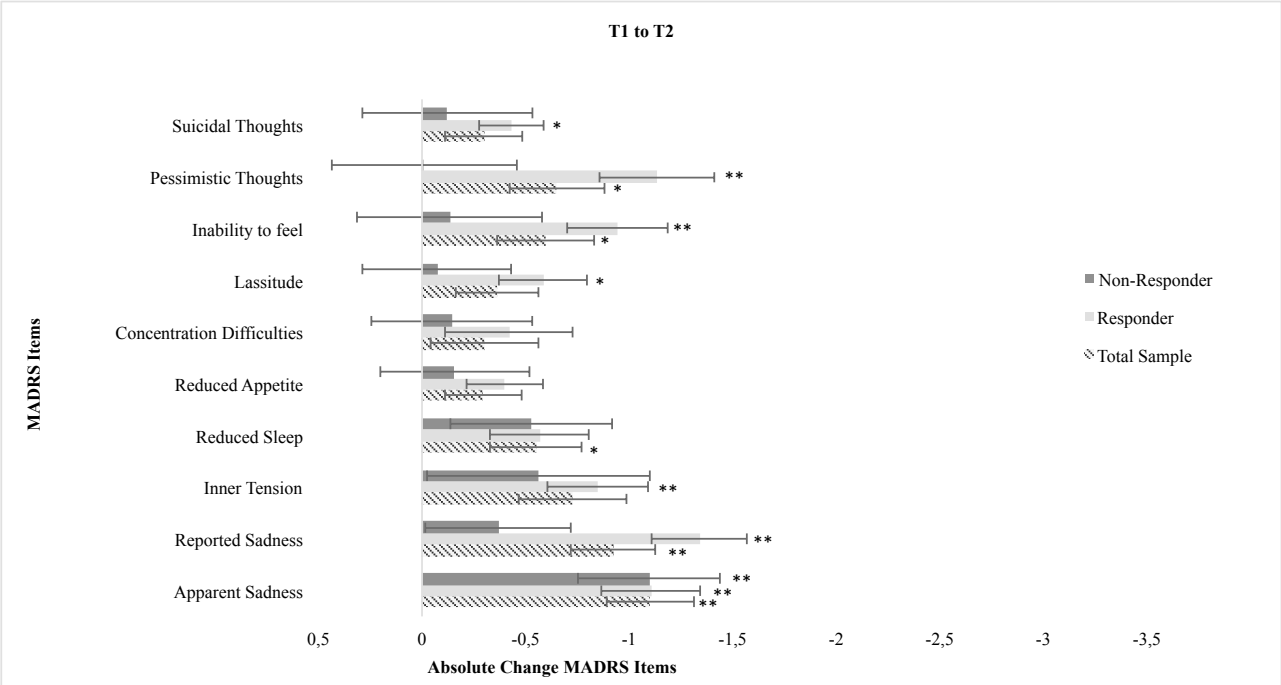

Figure 4. Absolute change of MADRS items from mid-treatment (T1) to treatment end (T2). * = Bonferroni-corrected $p < .05$, ** = Bonferroni-corrected $p < .01$. Error bars represent standard errors. From "A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items" by Carstens, L., Hartling, C., Stippl, A., Domke, A.- K., Herrera-Mendelez, A. - L., Aust, S., Gärtner, M., Bajbouj, M., & Grimm, S. (2021). *European Archives of Psychiatry and Clinical Neuroscience*, 1-10. https://doi.org/10.1007/s00406-021-01301-8**.** Open Access (CC BY 4.0). With permission.[24]

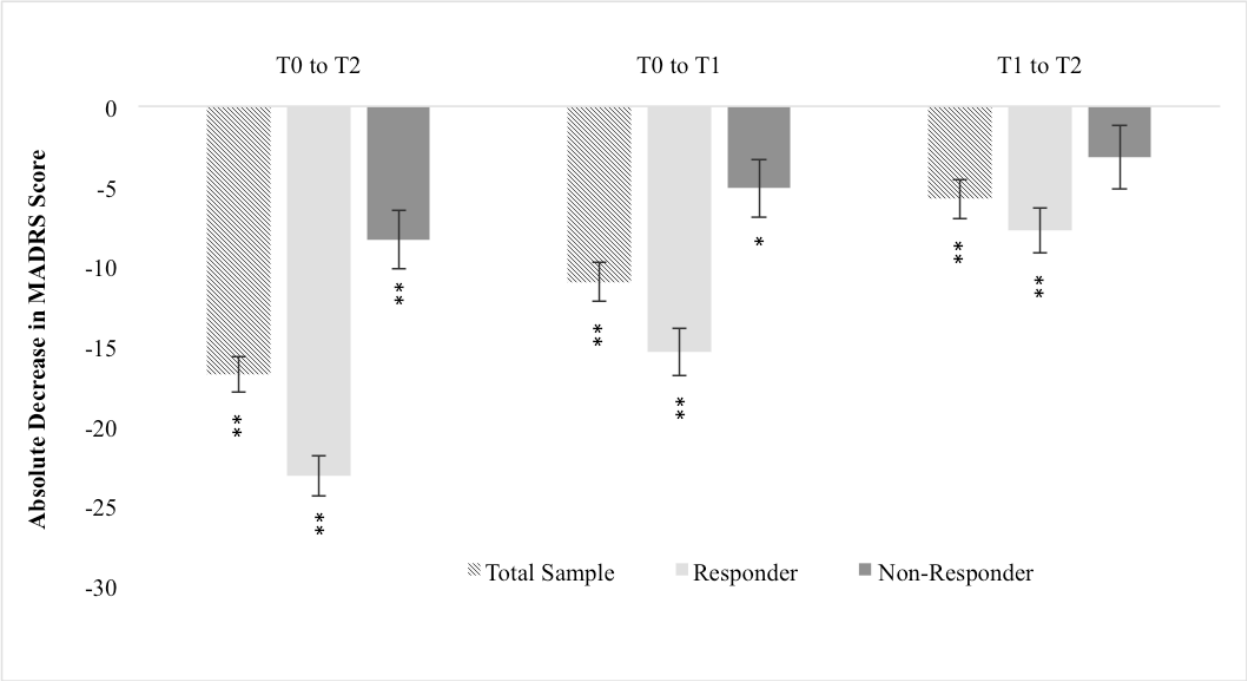

Figure 5. Absolute change of MADRS total score.
* = Bonferroni-corrected p < .05, ** = Bonferroni-corrected *p* < .01. Error bars represent standard errors.

3.3. Prediction of ECT outcome

3.3.1. Prediction of Response

In step one, we added sex, presence of psychotic symptoms, and number of received ECT sessions to the stepwise logistic regression model to control for these three variables. Sex ($p < .01$) and presence of psychotic symptoms ($p \leq .01$) were strongly associated with ECT response, while number of ECT sessions did not significantly contribute to the model ($p > .05$). In step one, 68% correct response prediction was achieved, $p < .001$. A comprehensive presentation of all statistic values can be found in table 5.

In step two, we added MADRS single items and MADRS total score to individual models separately. Hence, each regression model contained sex, presence of psychotic symptoms, number of received ECT sessions in step one and one MADRS item (or MADRS total score) in step two. In step two, we respectively added interaction terms of the relevant MADRS item or total score with sex, presence of psychotic symptoms, and number of received ECT sessions. When these interaction terms were not significant, they were eliminated from the regression models. We not only explored the predictive value of MADRS items and total score at baseline (T0) and mid-treatment (T1), but also analysed the predictive value of the respective change scores of the single items. We determined change scores T0:T1 as the change in percentage from T0 to T1, change scores T0:T2 as the change in percentage from T0:T2.

T0 (Baseline): MADRS total score ($p < .05$), item 1 ($p < .05$), item 2 ($p \leq .01$) and item 8 ($p < .05$) were significantly associated with ECT response, the model with item 2 and sex*item 2 interaction had the best fit: 70% correct response prediction, $p < .001$.

T1 (Mid-treatment): MADRS total score ($p < .001$), item 1 ($p < .01$) and item 2 ($p < .01$) were Bonferroni-corrected significant predictors, the model with item 2 indicated the best fit: 78% correct response prediction, $p < .001$.

Change Scores T0:T1: Change scores for items 1, 2, 8, 10, and MADRS total score were Bonferroni-corrected significant predictors. The two models with item 2 ($p < .001$) and MADRS total score ($p < .001$) had the best fit: Both models showed 80% correct response prediction, $p > .001$.

Change Scores T0:T2: Change scores for items 1, 2, 5, 6, 8, 9, and 10 were Bonferroni-corrected significant predictors, the model with item 2 ($p < .001$) indicated the best fit: 92% correct response prediction, $p < .001$.

A comprehensive presentation of all statistic values can be found in table 5.

Significant predictors and models including significant MADRS predictors are indicated in bold.

Table 5

Stepwise logistic regression analysis for response prediction

	Model 2										
Variables	ß	*Wald*	*df*	*p*	*OR*	R^2	*f*	χ^2	*df*	*p*	%
Step 1:											
Sex	**1.46**	**9.03**	**1**	**.003**	**4.32**						
Presence of Psychotic Symptoms	**2.86**	**6.55**	**1**	**.010**	**17.40**						
ECTs	-0.13	2.37	1	.124	0.88						
			1			.25	0.58	20.11	3	< .001	67.7
Step 2:											
Sex	**1.45**	**8.05**	**1**	**.005**	**4.26**						
Presence of Psychotic Symptoms	**2.59**	**5.37**	**1**	**.020**	**13.28**						
ECTs	1.07	2.98	1	.084	2.92						
ECTs*MADRS T0 Total Score	-0.04	3.65	1	.056	0.96						
MADRS T0 Total Score	**0.62**	**4.71**	**1**	**.030**	**1.88**						
						.34	**0.72**	**28.07**	**5**	**< .001**	**67.7**
Sex	**1.45**	**8.26**	**1**	**.004**	**4.27**						
Presence of Psychotic Symptoms	**2.56**	**5.18**	**1**	**.023**	**12.99**						
ECTs	-0.10	1.16	1	.282	0.91						
MADRS T0 Item 1	**0.65**	**4.78**	**1**	**.029**	**1.91**						
						.31	**0.67**	**25.54**	**4**	**< .001**	**68.8**
Sex	**10.59**	**6.60**	**1**	**.010**	**39753.94**						
Presence of Psychotic Symptoms	2.21	3.28	1	.070	9.15						
ECTs	-.141	2.46	1	.117	0.87						
Sex*MADRS T0 Item 2	**-2.16**	**5.30**	**1**	**.021**	**0.12**						
MADRS T0 Item 2	**4.41**	**6.28**	**1**	**.012**	**82.10**						
						.37	**0.77**	**31.60**	**5**	**< .001**	**69.8**
Sex	**1.47**	**9.03**	**1**	**.003**	**4.33**						
Presence of Psychotic Symptoms	**2.87**	**6.61**	**1**	**.010**	**17.71**						
ECTs	-0.13	2.41	1	.121	0.88						
MADRS T0 Item 3	-0.07	0.09	1	.767	0.93						
						.25	0.58	20.19	4	< .001	68.8
Sex	**1.46**	**9.03**	**1**	**.003**	**4.32**						
Presence of Psychotic Symptoms	**2.87**	**6.43**	**1**	**.011**	**17.55**						
ECTs	-0.13	2.33	1	.127	0.88						
MADRS T0 Item 4	-0.01	.003	1	.960	0.99						
						.25	0.58	20.11	4	< .001	67.7
Sex	**1.44**	**8.678**	**1**	**.003**	**4.22**						
Presence of Psychotic Symptoms	**2.93**	**6.690**	**1**	**.010**	**18.61**						
ECTs	-0.13	2.36	1	.125	0.88						
MADRS T0 Item 5	0.11	.404	1	.525	1.11						
						.26	0.59	20.51	4	< .001	67.7

(Table 5 continued)

Sex	**1.43**	**8.31**	**1**	**.004**	**4.19**						
Presence of Psychotic Symptoms	**2.80**	**6.19**	**1**	**.013**	**16.51**						
ECTs	-0.13	2.29	1	.131	0.88						
MADRS T0 Item 6	0.07	0.08	1	.773	1.08						
						.25	0.58	20.19	4	< .001	67.7
Sex	**1.55**	**9.61**	**1**	**.002**	**4.71**						
Presence of Psychotic Symptoms	**2.97**	**6.47**	**1**	**.011**	**19.44**						
ECTs	-0.13	2.58	1	.108	0.87						
MADRS T0 Item 7	0.31	1.54	1	.215	1.36						
						.27	0.61	21.66	4	< .001	68.8
Sex	**1.49**	**8.55**	**1**	**.003**	**4.42**						
Presence of Psychotic Symptoms	**2.81**	**6.34**	**1**	**.012**	**16.53**						
ECTs	0.45	2.29	1	.131	1.57						
ECTs* MADRS T0 Item 8	**-.17**	**3.99**	**1**	**.046**	**0.84**						
MADRS T0 Item 8	**2.59**	**4.67**	**1**	**.031**	**13.27**						
						.32	**0.69**	**26.33**	**5**	**< .001**	**71.9**
Sex	**1.45**	**8.57**	**1**	**.003**	**4.27**						
Presence of Psychotic Symptoms	**2.86**	**5.44**	**1**	**.020**	**17.46**						
ECTs	0.22	1.05	1	.306	1.25						
ECTs* MADRS T0 Item 9	-0.14	2.89	1	.089	0.87						
MADRS T0 Item 9	2.04	3.40	1	.065	7.68						
						.30	0.65	24.27	5	< .001	71.9
Sex	**1.55**	**9.60**	**1**	**.002**	**4.71**						
Presence of Psychotic Symptoms	**3.10**	**7.38**	**1**	**.007**	**22.29**						
ECTs	-0.11	1.63	1	.202	0.90						
MADRS T0 Item 10	0.23	1.87	1	.171	1.26						
						.27	0.61	22.02	4	< .001	69.8
Sex	**1.29**	**5.37**	**1**	**.020**	**3.64**						
Presence of Psychotic Symptoms	**3.16**	**6.17**	**1**	**.013**	**23.64**						
ECTs	-0.10	1.15	1	.283	0.90						
MADRS T1 Total Score*	**-0.17**	**14.48**	**1**	**< .001**	**0.84**						
						.45	**0.90**	**39.79**	**4**	**< .001**	**76.0**
Sex	**1.53**	**8.60**	**1**	**.003**	**4.62**						
Presence of Psychotic Symptoms	**2.96**	**6.46**	**1**	**.011**	**19.38**						
ECTs	-0.11	1.38	1	.240	0.90						
MADRS T1 Item 1*	**-0.68**	**8.240**	**1**	**.004**	**0.51**						
						.36	**0.75**	**29.64**	**4**	**< .001**	**70.8**

(Table 5 continued)

Sex	**1.47**	**7.68**	**1**	**.006**	**4.33**						
Presence of Psychotic Symptoms	**3.07**	**6.61**	**1**	**.010**	**21.48**						
ECTs	-0.11	1.55	1	.213	0.89						
MADRS T1 Item 2*	**-0.67**	**8.83**	**1**	**.003**	**0.51**						
						.37	**0.77**	**30.64**	**4**	**< .001**	**78.1**
Sex	**1.43**	**7.64**	**1**	**.006**	**4.18**						
Presence of Psychotic Symptoms	**3.22**	**7.25**	**1**	**.007**	**24.93**						
ECTs	-0.15	2.74	1	.098	0.86						
MADRS T1 Item 3	**-0.64**	**7.93**	**1**	**.005**	**0.53**						
						.35	**0.73**	**29.12**	**4**	**< .001**	**68.8**
Sex	**1.38**	**7.61**	**1**	**.006**	**3.98**						
Presence of Psychotic Symptoms	**3.00**	**6.80**	**1**	**.009**	**20.08**						
ECTs	-0.09	1.06	1	.304	0.91						
MADRS T1 Item 4	**-0.50**	**4.70**	**1**	**.030**	**0.61**						
						.31	**0.67**	**25.25**	**4**	**< .001**	**70.8**
Sex	**1.48**	**8.67**	**1**	**.003**	**4.37**						
Presence of Psychotic Symptoms	**2.53**	**5.04**	**1**	**.025**	**12.57**						
ECTs	-0.14	2.38	1	.123	0.87						
MADRS T1 Item 5	**-0.45**	**4.75**	**1**	**.029**	**0.64**						
						.31	**0.67**	**25.34**	**4**	**< .001**	**72.9**
Sex	**1.54**	**9.09**	**1**	**.003**	**4.67**						
Presence of Psychotic Symptoms	**3.01**	**6.68**	**1**	**.010**	**20.30**						
ECTs	-0.15	2.74	1	.098	0.87						
MADRS T1 Item 6	**-0.52**	**5.41**	**1**	**.020**	**0.60**						
						.32	**0.69**	**25.99**	**4**	**< .001**	**76.0**
Sex	**1.41**	**7.77**	**1**	**.005**	**4.09**						
Presence of Psychotic Symptoms	**2.78**	**5.86**	**1**	**.016**	**16.11**						
ECTs	-0.11	1.45	1	.229	0.90						
MADRS T1 Item 7	**-0.58**	**5.53**	**1**	**.019**	**0.56**						
						.32	**0.69**	**26.29**	**4**	**< .001**	**71.9**
Sex	**1.33**	**6.87**	**1**	**.009**	**3.79**						
Presence of Psychotic Symptoms	**2.94**	**6.33**	**1**	**.012**	**18.87**						
ECTs	-0.13	2.04	1	.153	0.88						
MADRS T1 Item 8	**-0.57**	**6.81**	**1**	**.009**	**0.57**						
						.34	**0.72**	**27.77**	**4**	**< .001**	**75.0**
Sex	**1.21**	**5.57**	**1**	**.018**	**3.35**						
Presence of Psychotic Symptoms	**3.13**	**6.81**	**1**	**.009**	**22.91**						
ECTs	-0.10	1.33	1	.248	0.90						
MADRS T1 Item 9	**-0.55**	**6.44**	**1**	**.011**	**0.58**						
						.33	**0.70**	**27.18**	**4**	**< .001**	**71.9**

(Table 5 continued)

Sex	**1.41**	**7.80**	**1**	**.005**	**4.08**						
Presence of Psychotic Symptoms	**2.62**	**5.42**	**1**	**.020**	**13.72**						
ECTs	-0.14	2.62	1	.106	0.87						
MADRS T1 Item 10	**-0.51**	**4.39**	**1**	**.036**	**0.60**						
						.31	**0.67**	**25.01**	**4**	**< .001**	**69.8**
Sex	**1.17**	**3.92**	**1**	**.048**	**3.21**						
Presence of Psychotic Symptoms	**2.63**	**4.62**	**1**	**.032**	**13.86**						
ECTs	-0.10	0.87	1	.352	0.91						
Change Score T0:T1 MADRS Total score*	**-0.07**	**19.03**	**1**	**< .001**	**0.94**						
						.55	**1.11**	**50.56**	**4**	**< .001**	**80.2**
Sex	**1.49**	**7.03**	**1**	**.008**	**4.43**						
Presence of Psychotic Symptoms	**2.39**	**4.33**	**1**	**.038**	**10.86**						
ECTs	-0.05	0.23	1	.631	0.95						
Change Score T0:T1 Item 1*	**-0.04**	**15.02**	**1**	**< .001**	**0.96**						
						.45	**0.90**	**39.38**	**4**	**< .001**	**77.9**
Sex	1.10	3.70	1	.055	3.00						
Presence of Psychotic Symptoms	2.17	3.45	1	.063	8.79						
ECTs	-0.11	1.13	1	.287	0.90						
Change Score T0:T1 Item 2*	**-0.05**	**16.54**	**1**	**< .001**	**0.95**						
						.49	**0.99**	**44.08**	**4**	**< .001**	**80.2**
Sex	**2.09**	**9.13**	**1**	**.003**	**8.06**						
Presence of Psychotic Symptoms	**3.45**	**6.66**	**1**	**.010**	**31.56**						
ECTs	-0.14	2.64	1	.105	0.87						
Sex*Change Score T0:T1 Item 3	0.02	2.62	1	.106	1.02						
Change Score T0:T1 Item 3	**-0.05**	**4.08**	**1**	**.044**	**0.95**						
						.34	**0.72**	**27.75**	**5**	**< .001**	**72.9**
Sex	**1.59**	**9.24**	**1**	**.002**	**4.89**						
Presence of Psychotic Symptoms	**3.08**	**6.76**	**1**	**.009**	**21.73**						
ECTs	-0.12	1.80	1	.179	0.88						
Change Score T0:T1 Item 4	-0.01	2.11	1	.146	0.99						
						.32	0.69	24.03	4	< .001	71.9
Sex	**1.41**	**8.11**	**1**	**.004**	**4.09**						
Presence of Psychotic Symptoms	**2.60**	**5.26**	**1**	**.022**	**13.51**						
ECTs	-0.14	2.57	1	.109	0.87						
Change Score T0:T1 Item 5	-0.00	1.68	1	.195	1.00						
						.25	0.58	19.04	4	.001	66.7

(Table 5 continued)

Sex	**1.44**	**7.03**	**1**	**.008**	**4.23**						
Presence of Psychotic Symptoms	**2.74**	**5.68**	**1**	**.017**	**15.45**						
ECTs	-0.03	0.09	1	.759	1.00						
ECTs*Change Score T0:T1 Item 6	0.01	3.51	1	.061	1.01						
Change Score T0:T1 Item 6	**-1.00**	**5.30**	**1**	**.021**	**0.91**						
						.41	**0.83**	**34.81**	**4**	**< .001**	**70.5**
Sex	**1.55**	**9.17**	**1**	**.002**	**4.71**						
Presence of Psychotic Symptoms	**2.58**	**5.22**	**1**	**.022**	**13.20**						
ECTs	-0.14	2.52	1	.112	0.87						
Change Score T0:T1 Item 7	**-0.02**	**6.31**	**1**	**.012**	**0.98**						
						.33	**0.70**	**27.37**	**4**	**< .001**	**71.9**
Sex	**1.12**	**4.05**	**1**	**.044**	**3.06**						
Presence of Psychotic Symptoms	**2.83**	**5.88**	**1**	**.015**	**16.93**						
ECTs	0.15	1.04	1	.309	1.16						
ECTs* Change Score T0:T1 Item 8	**0.01**	**7.41**	**1**	**.006**	**1.01**						
Change Score T0:T1 Item 8*	**-0.13**	**9.20**	**1**	**.002**	**0.87**						
						.48	**0.96**	**42.29**	**5**	**< .001**	**77.1**
Sex	**1.25**	**6.02**	**1**	**.014**	**3.47**						
Presence of Psychotic Symptoms	**2.44**	**4.61**	**1**	**.032**	**11.42**						
ECTs	-0.12	1.84	1	.175	0.89						
Change Score T0:T1 Item 9	**-0.01**	**4.55**	**1**	**.033**	0.99						
						.29	**0.64**	**22.41**	**4**	**< .001**	**69.9**
Sex	**1.55**	**7.62**	**1**	**.006**	**4.72**						
Presence of Psychotic Symptoms	**2.99**	**6.39**	**1**	**.011**	**19.79**						
ECTs	0.19	1.85	1	.174	1.20						
ECTs* Change Score T0:T1 Item 10	**0.01**	**6.95**	**1**	**.008**	**1.01**						
Change Score T0:T1 Item 10*	**-1.00**	**9.34**	**1**	**.002**	**0.91**						
						.43	**0.87**	**35.47**	**5**	**< .001**	**78.0**
Sex	**1.45**	**5.38**	**1**	**.020**	**4.26**						
Presence of Psychotic Symptoms	1.89	2.52	1	.113	6.63						
ECTs	0.01	.01	1	.946	1.01						
Change Score T0:T2 Item 1*	**-0.06**	**20.61**	**1**	**< .001**	**0.95**						
						.57	**1.15**	**53.19**	**4**	**< .001**	**83.2**

(Table 5 continued)

Sex	**1.89**	**3.90**	**1**	**.048**	**6.62**						
Presence of Psychotic Symptoms	2.02	2.68	1	.102	7.51						
ECTs	-0.16	1.16	1	.281	0.85						
Change Score T0:T2 Item 2*	**-0.12**	**19.48**	**1**	**< .001**	**0.89**						
						.81	**2.06**	**89.42**	**4**	**< .001**	**91.7**
Sex	-1.61	1.50	1	.221	0.20						
Presence of Psychotic Symptoms	**2.82**	**5.57**	**1**	**.018**	**16.78**						
ECTs	-0.19	3.08	1	.079	0.83						
Sex*Change Score T0:T2 Item 3	**-0.06**	**6.79**	**1**	**.009**	**0.94**						
Change Score T0:T2 Item 3	0.05	2.37	1	.124	1.05						
						.58	1.18	55.26	5	< .001	83.3
Sex	**1.30**	**6.54**	**1**	**.011**	**3.68**						
Presence of Psychotic Symptoms	**2.67**	**5.61**	**1**	**.018**	**14.45**						
ECTs	-0.10	1.10	1	.296	0.91						
Change Score T0:T2 Item 4	**-0.01**	**4.74**	**1**	**.030**	**0.99**						
						.32	**0.69**	**25.83**	**4**	**< .001**	**72.0**
Sex	**1.41**	**6.48**	**1**	**.011**	**4.08**						
Presence of Psychotic Symptoms	**2.62**	**4.96**	**1**	**.026**	**13.71**						
ECTs	**-0.27**	**6.02**	**1**	**.014**	**0.76**						
Change Score T0:T2 Item 5*	**-0.02**	**11.70**	**1**	**.001**	**0.98**						
						.41	**0.83**	**33.45**	**4**	**< .001**	**73.9**
Sex	**1.80**	**9.19**	**1**	**.002**	**6.02**						
Presence of Psychotic Symptoms	**3.32**	**7.34**	**1**	**.007**	**27.66**						
ECTs	-0.13	1.96	1	.162	0.88						
Change Score T0:T2 Item 6*	**-0.03**	**15.11**	**1**	**< .001**	**0.97**						
						.49	**0.99**	**43.21**	**4**	**< .001**	**80.0**
Sex	**1.39**	**6.00**	**1**	**.014**	**4.02**						
Presence of Psychotic Symptoms	**3.61**	**3.74**	**1**	**.053**	**37.10**						
ECTs	**-0.46**	**3.95**	**1**	**.047**	**0.63**						
ECTs*Change Score T0:T2 Item 7	-0.01	3.10	1	.078	0.99						
Change Score T0:T2 Item 7	0.06	1.15	1	.283	1.06						
						.53	1.06	48.50	5	< .001	83.3
Sex	**1.37**	**4.59**	**1**	**.032**	**3.95**						
Presence of Psychotic Symptoms	2.22	3.56	1	.059	9.24						
ECTs	-0.15	1.84	1	.175	0.86						
Change Score T0:T2 Item 8*	**-0.06**	**18.23**	**1**	**< .001**	**0.94**						
						.65	**1.36**	**63.67**	**4**	**< .001**	**84.4**

(Table 5 continued)

Sex	**1.80**	**6.71**	**1**	**.010**	**6.07**						
Presence of Psychotic Symptoms	0.91	0.53	1	.467	2.47						
ECTs	**-0.22**	**3.85**	**1**	**.050**	**0.80**						
Change Score T0:T2 Item 9*	**-0.05**	**17.39**	**1**	**< .001**	**0.95**						
						.62	**1.28**	**58.28**	**4**	**< .001**	**81.7**
Sex	**1.46**	**7.17**	**1**	**.007**	**4.31**						
Presence of Psychotic Symptoms	**3.28**	**7.18**	**1**	**.007**	**26.56**						
ECTs	-0.03	0.07	1	.788	0.97						
Change Score T0:T2 Item 10*	**-0.02**	**13.86**	**1**	**< .001**	**0.98**						
						.45	**0.90**	**38.67**	**4**	**< .001**	**76.3**

Note. R^2 = Nagelkerkes R^2. % = Percentage of correct prediction. ECTs = Number of received ECT sessions. Significant predictors and models including significant MADRS predictors are indicated in bold. *Bonferroni-corrected significance. *f* = Cohen's *f*. T0 = Baseline, T1 = Mid-treatment, T2 = Treatment end. Item 1 = apparent sadness. Item 2= reported sadness. Item 3 = inner tension. Item 4 = reduced sleep. Item 5 = reduced appetite. Item 6 = concentration difficulties. Item 7 = lassitude. Item 8 = inability to feel. Item 9 = pessimistic thoughts. Item 10 = suicidal thoughts.

3.3.2. Prediction of Early Response

A similar logistic regression model as described for response prediction was applied. Per definition, early response was assessed after the 6th ECT treatment. Thus, in contrast to the other models, number of ECTs is not included in these regression models. In the first step, presence of psychotic symptoms ($p \leq .01$) was associated with early response, whereas no significant effect of sex was found ($p > .05$). In the first step, 49% correct early response prediction was achieved, $p \leq .01$. A comprehensive presentation of all statistic values can be found in table 6.

In step two, we added MADRS single items and MADRS total score to individual models separately. Hence, each regression model contained sex and presence of psychotic symptoms in step one and one MADRS item (or MADRS total score) in step two.

In step two, no significant effects of MADRS items predicting early response to ECT were detected (all $p > .05$).

A comprehensive presentation of all statistic values can be found in table 6. Significant predictors are indicated in bold.

Table 6

Stepwise logistic regression analysis for early response prediction

	Model 2										
Variables	ß	*Wald*	*df*	*p*	*OR*	R^2	*f*	χ^2	*df*	*p*	%
Step 1:											
Sex	1.06	3.32	1	.069	2.88						
Presence of Psychotic Symptoms	**1.84**	**6.66**	**1**	**.010**	**6.29**						
						.14	0.40	9.20	2	.010	49.0
Step 2:											
Sex	1.14	3.54	1	.060	3.12						
Presence of Psychotic Symptoms	**1.78**	**6.17**	**1**	**.013**	**5.91**						
MADRS T0 Total Score	0.09	3.14	1	.076	1.09						
						.18	0.47	12.50	3	.006	66.7
Sex	1.06	3.31	1	.069	2.88						
Presence of Psychotic Symptoms	**1.82**	**6.27**	**1**	**.012**	**6.19**						
MADRS T0 Item 1	0.03	0.01	1	.916	1.03						
						.14	0.40	9.21	3	.027	49.0
Sex	1.05	3.26	1	.071	2.87						
Presence of Psychotic Symptoms	**1.80**	**6.30**	**1**	**.012**	**6.02**						
MADRS T0 Item 2	0.12	0.15	1	.696	1.12						
						.14	0.40	9.36	3	.025	49.0
Sex	1.08	3.41	1	.065	2.95						
Presence of Psychotic Symptoms	**1.80**	**6.36**	**1**	**.012**	**6.08**						
MADRS T0 Item 3	0.28	1.01	1	.314	1.33						
						.15	0.42	10.25	3	.017	65.6
Sex	1.06	3.32	1	.069	2.88						
Presence of Psychotic Symptoms	**1.94**	**6.95**	**1**	**.008**	**6.98**						
MADRS T0 Item 4	-0.12	0.36	1	.550	0.88						
						.14	0.40	9.56	3	.023	54.2
Sex	0.97	2.72	1	.099	2.63						
Presence of Psychotic Symptoms	**2.00**	**7.16**	**1**	**.007**	**7.38**						
MADRS T0 Item 5	0.31	2.87	1	.090	1.36						
						.18	0.47	12.17	3	.007	60.9
Sex	1.05	3.20	1	.074	2.87						
Presence of Psychotic Symptoms	**1.77**	**6.17**	**1**	**.013**	**5.84**						
MADRS T0 Item 6	0.23	0.56	1	.456	1.25						
						.15	0.42	9.78	3	.020	59.4
Sex	1.07	3.37	1	.066	2.91						
Presence of Psychotic Symptoms	**1.83**	**6.53**	**1**	**.011**	**6.22**						
MADRS T0 Item 7	0.08	0.10	1	.758	1.09						
						.14	0.40	9.30	3	.026	55.2

(Table 6 continued)

Sex	1.15	3.66	1	.056	3.15						
Presence of Psychotic Symptoms	**1.98**	**7.49**	**1**	**.006**	**7.26**						
MADRS T0 Item 8	0.43	2.72	1	.099	1.54						
						.18	0.47	12.14	3	.007	67.7
Sex	1.13	3.57	1	.059	3.10						
Presence of Psychotic Symptoms	**1.78**	**6.30**	**1**	**.012**	**5.93**						
MADRS T0 Item 9	0.17	0.71	1	.401	1.18						
						.15	0.42	9.91	3	.019	69.8
Sex	**1.16**	**3.84**	**1**	**.050**	**3.20**						
Presence of Psychotic Symptoms	**2.22**	**8.37**	**1**	**.004**	**9.25**						
MADRS T0 Item 10	0.34	3.44	1	.064	1.40						
						.19	0.48	12.66	3	.005	70.8

Note. R^2 = Nagelkerkes R^2. % = Percentage of correct prediction. Significant predictors are indicated in bold. *f* = Cohen's *f*. T0 = Baseline. Item 1 = apparent sadness. Item 2= reported sadness. Item 3 = inner tension. Item 4 = reduced sleep. Item 5 = reduced appetite. Item 6 = concentration difficulties. Item 7 = lassitude. Item 8 = inability to feel. Item 9 = pessimistic thoughts. Item 10 = suicidal thoughts.

3.3.3. Prediction of Remission

A similar logistic regression model as described for response prediction was applied. In step one of the logistic regression, sex ($p < .01$), presence of psychotic symptoms ($p < .05$) and number of ECT sessions ($p < .05$) were strongly associated with remission after ECT treatment. In step one, 69% correct prediction of remission was achieved, $p \leq .001$. A comprehensive presentation of all statistic values can be found in table 7.

In step two, we added MADRS single items and MADRS total score to individual models separately. Hence, each regression model contained sex, presence of psychotic symptoms, number of received ECT sessions in step one and one MADRS item (or MADRS total score) in step two.

T0 (Baseline): Neither MADRS total score nor MADRS single items could predict remission after ECT treatment.

T1 (Mid-treatment): MADRS total score, item 2, and item 3 were Bonferroni-corrected significant predictors, the model with MADRS total score ($p < .01$) showed the best fit: 71% correct prediction of remission, $p < .001$.

Change Scores T0:T1: Item change scores from baseline (T0) to mid-treatment (T1) for MADRS total score and item 2 were Bonferroni-corrected significant predictors. The models with MADRS

total score ($p \leq .001$), 75% correct prediction of remission, $p < .001$, and item 2 ($p < .001$), 69% correct prediction of remission, $p < .001$, showed the best fit.

Change Scores T0:T2: Item change scores from baseline (T0) to treatment end (T2) for items 1, 2, 3, 4, 6, 8, and 9 were Bonferroni-corrected significant predictors, the models with item 2 ($p < .001$), 84% correct prediction of remission, $p < .001$ and item 8 ($p < .01$) and number of ECT sessions*item 8 interaction ($p < .05$), 84% correct prediction of remission, $p < .001$, showed the best fit.

A comprehensive presentation of all statistic values can be found in table 7. Significant predictors are indicated in bold.

Table 7

Stepwise logistic regression analysis for remission prediction

	Model 2										
Variables	ß	*Wald*	*df*	*p*	*OR*	R^2	*f*	χ^2	*df*	*p*	%
Step 1:											
Sex	**1.60**	**8.57**	**1**	**.003**	**4.97**						
Presence of Psychotic Symptoms	**1.44**	**3.96**	**1**	**.047**	**4.24**						
ECTs	**-0.23**	**5.76**	**1**	**.016**	**0.79**						
			1			.23	0.55	17.48	3	.001	68.8
Step 2:			1								
Sex	**1.61**	**8.46**	**1**	**.004**	**4.98**						
Presence of Psychotic Symptoms	1.35	3.52	1	.061	3.87						
ECTs	**-0.22**	**5.03**	**1**	**.025**	**0.80**						
MADRS T0 Total Score	0.04	0.89		.347	1.05						
						.24	**0.56**	**18.38**	**4**	**.001**	**66.7**
Sex	**1.60**	**8.54**	**1**	**.003**	**4.97**						
Presence of Psychotic Symptoms	1.41	3.60	1	.058	4.07						
ECTs	**-0.23**	**5.37**	**1**	**.020**	**0.80**						
MADRS T0 Item 1	0.07	0.06	1	.806	1.07						
						.23	0.55	17.54	4	.002	68.8
Sex	**1.59**	**8.26**	**1**	**.004**	**4.90**						
Presence of Psychotic Symptoms	1.35	3.44	1	.064	3.84						
ECTs	**-0.23**	**5.58**	**1**	**.018**	**0.80**						
MADRS T0 Item 2	0.21	0.56	1	.456	1.24						
						.24	0.56	18.06	4	.001	65.6
Sex	**1.60**	**8.57**	**1**	**.003**	**4.97**						
Presence of Psychotic Symptoms	**1.44**	**3.89**	**1**	**.049**	**4.21**						
ECTs	**-0.23**	**5.60**	**1**	**.018**	**0.79**						
MADRS T0 Item 3	0.03	0.02	1	.900	1.03						
						.23	0.55	17.50	4	.002	68.8

(Table 7 continued)

Sex	**1.60**	**8.52**	**1**	**.004**	**4.93**						
Presence of Psychotic Symptoms	1.35	3.36	1	.067	3.86						
ECTs	**-0.24**	**5.98**	**1**	**.014**	**0.79**						
MADRS T0 Item 4	0.12	0.41	1	.525	1.13						
						.24	0.56	17.89	4	.001	67.7
Sex	**1.57**	**8.15**	**1**	**.004**	**4.79**						
Presence of Psychotic Symptoms	**1.47**	**4.05**	**1**	**.044**	**4.34**						
ECTs	**-0.24**	**5.76**	**1**	**.016**	**0.79**						
MADRS T0 Item 5	0.11	0.43	1	.513	1.12						
						.24	0.56	17.91	4	.001	67.7
Sex	**1.63**	**8.73**	**1**	**.003**	**5.09**						
Presence of Psychotic Symptoms	**1.50**	**4.03**	**1**	**.045**	**4.49**						
ECTs	**-0.24**	**5.86**	**1**	**.016**	0.79						
MADRS T0 Item 6	-0.11	0.16	1	.686	0.90						
						.23	0.55	17.64	4	.001	67.7
Sex	**1.63**	**8.69**	**1**	**.003**	**5.10**						
Presence of Psychotic Symptoms	**1.42**	**3.77**	**1**	**.052**	**4.13**						
ECTs	**-0.24**	**5.83**	**1**	**.016**	**0.79**						
MADRS T0 Item 7	0.11	0.19	1	.666	1.12						
						.23	0.55	17.66	4	.001	66.7

Table A5 (continued)

Sex	**1.62**	**8.60**	**1**	**.003**	**5.06**						
Presence of Psychotic Symptoms	**1.47**	**4.13**	**1**	**.042**	**4.38**						
ECTs	**-0.22**	**5.10**	**1**	**.024**	**0.80**						
MADRS T0 Item 8	0.21	0.86	1	.354	1.24						
						.24	0.56	18.35	4	.001	66.7
Sex	**1.69**	**8.94**	**1**	**.003**	**5.43**						
Presence of Psychotic Symptoms	1.34	3.43	1	.064	3.82						
ECTs	**-0.22**	**4.99**	**1**	**.025**	**0.80**						
MADRS T0 Item 9	0.26	1.72	1	.190	1.30						
						.25	0.58	19.26	4	.001	66.7
Sex	**1.60**	**8.53**	**1**	**.003**	**4.97**						
Presence of Psychotic Symptoms	1.40	3.62	1	.057	4.07						
ECTs	**-0.24**	**5.83**	**1**	**.016**	**0.79**						
MADRS T0 Item 10	-0.06	.12	1	.732	0.94						
						.23	0.55	17.60	4	.001	67.7
Sex	**1.33**	**5.30**	**1**	**.021**	**3.80**						
Presence of Psychotic Symptoms	1.08	1.79	1	.181	2.95						
ECTs	**-0.21**	**4.02**	**1**	**.045**	0.81						
MADRS T1 Total Score*	**-0.12**	**9.23**	**1**	**.002**	0.89						
						.36	**0.75**	**28.55**	**4**	**< .001**	**70.8**

(Table 7 continued)

Sex	**1.57**	**7.67**	**1**	**.006**	**4.80**						
Presence of Psychotic Symptoms	1.30	2.86	1	.091	3.66						
ECTs	**-0.21**	**4.50**	**1**	**.034**	**0.81**						
MADRS T1 Item 1	**-0.58**	**6.03**	**1**	**.014**	**0.56**						
						.31	**0.67**	**24.25**	**4**	**< .001**	**68.8**
Sex	**1.50**	**6.68**	**1**	**.010**	**4.49**						
Presence of Psychotic Symptoms	1.28	2.49	1	.115	3.59						
ECTs	**-0.23**	**4.65**	**1**	**.031**	**0.80**						
MADRS T1 Item 2*	**-0.67**	**9.41**	**1**	**.002**	**0.51**						
						.35	**0.73**	**28.30**	**4**	**< .001**	**68.8**
Sex	**1.58**	**7.29**	**1**	**.007**	**4.84**						
Presence of Psychotic Symptoms	**1.57**	**3.84**	**1**	**.050**	**4.78**						
ECTs	**-0.26**	**6.22**	**1**	**.013**	**0.77**						
MADRS T1 Item 3*	**-0.72**	**9.21**	**1**	**.002**	**0.49**						
						.35	**0.73**	**28.21**	**4**	**< .001**	**70.8**
Sex	**1.53**	**7.64**	**1**	**.006**	**4.61**						
Presence of Psychotic Symptoms	**1.42**	**3.73**	**1**	**.053**	**4.14**						
ECTs	**-0.22**	**4.83**	**1**	**.028**	**0.81**						
MADRS T1 Item 4	-0.19	0.73	1	.394	0.82						
						.24	0.56	18.22	4	.001	67.7
Sex	**1.55**	**7.92**	**1**	**.005**	**4.69**						
Presence of Psychotic Symptoms	1.16	2.42	1	.120	3.19						
ECTs	**-0.23**	**5.54**	**1**	**.019**	**0.79**						
MADRS T1 Item 5	-0.35	2.35	1	.125	0.71						
						.26	0.59	20.04	4	< .001	72.9
Sex	**1.57**	**8.23**	**1**	**.004**	**4.81**						
Presence of Psychotic Symptoms	1.38	3.58	1	.059	3.99						
ECTs	**-0.24**	**5.88**	**1**	**.015**	**0.79**						
MADRS T1 Item 6	-0.21	0.99	1	.319	0.81						
						.24	0.56	18.45	4	.001	67.7
Sex	**1.48**	**7.16**	**1**	**.007**	**4.38**						
Presence of Psychotic Symptoms	1.28	2.97	1	.085	3.61						
ECTs	**-0.22**	**4.92**	**1**	**.027**	**0.80**						
MADRS T1 Item 7	-0.42	2.99	1	.084	0.66						
						.27	0.61	20.65	4	< .001	69.8
Sex	**1.41**	**6.26**	**1**	**.012**	**4.10**						
Presence of Psychotic Symptoms	1.29	2.87	1	.091	3.63						
ECTs	**-0.22**	**5.06**	**1**	**.024**	**0.80**						
MADRS T1 Item 8	**-0.61**	**6.44**	**1**	**.011**	**0.54**						
						.32	**0.69**	**24.97**	**4**	**< .001**	**69.8**

(Table 7 continued)

Sex	**1.39**	**6.07**	**1**	**.014**	**3.99**						
Presence of Psychotic Symptoms	1.38	3.40	1	.065	3.96						
ECTs	**-0.21**	**4.50**	**1**	**.034**	**0.81**						
MADRS T1 Item 9	-0.41	3.56	1	.059	0.66						
						.27	0.61	21.26	4	< .001	68.8
Sex	**1.57**	**7.98**	**1**	**.005**	**4.80**						
Presence of Psychotic Symptoms	1.30	3.07	1	.080	3.66						
ECTs	**-0.24**	**5.92**	**1**	**.015**	**0.79**						
MADRS T1 Item 10	-0.29	1.43	1	.231	0.75						
						.25	0.58	19.01	4	.001	66.7
Sex	**1.26**	**4.46**	**1**	**.035**	**3.52**						
Presence of Psychotic Symptoms	0.86	1.15	1	.284	2.36						
ECTs	-0.19	3.20	1	.074	0.83						
Change Score T0:T1 MADRS Total Score*	**-0.04**	**11.77**	**1**	**.001**	**0.96**						
						.39	**0.64**	**32.10**	**4**	**< .001**	**75.0**
Sex	**1.55**	**7.09**	**1**	**.008**	**4.71**						
Presence of Psychotic Symptoms	1.03	1.82	1	.178	2.81						
ECTs	-0.18	3.17	1	.075	0.83						
Change Score T0:T1 Item 1	**-0.03**	**8.02**	**1**	**.005**	**0.97**						
						.33	**0.80**	**25.97**	**4**	**< .001**	**68.4**
Sex	**1.26**	**4.27**	**1**	**.039**	**3.51**						
Presence of Psychotic Symptoms	0.84	1.15	1	.283	2.31						
ECTs	**-0.21**	**3.84**	**1**	**.050**	**0.81**						
Change Score T0:T1 Item 2*	**-0.04**	**13.26**	**1**	**< .001**	**0.96**						
						.42	**0.70**	**34.64**	**4**	**< .001**	**68.8**
Sex	**1.59**	**7.63**	**1**	**.006**	**4.92**						
Presence of Psychotic Symptoms	1.49	3.57	1	.059	4.42						
ECTs	**-0.23**	**5.29**	**1**	**.021**	**0.80**						
Change Score T0:T1 Item 3	**-0.02**	**6.78**	**1**	**.009**	**0.98**						
						.33	**0.85**	**25.71**	**4**	**< .001**	**70.8**
Sex	**1.49**	**7.02**	**1**	**.008**	**4.45**						
Presence of Psychotic Symptoms	1.38	3.55	1	.059	3.98						
ECTs	**-0.23**	**5.34**	**1**	**.021**	**0.79**						
Change Score T0:T1 Item 4	0.00	0.36	1	.548	1.00						
						.24	0.70	17.10	4	.002	67.4
Sex	**1.61**	**8.27**	**1**	**.004**	**4.98**						
Presence of Psychotic Symptoms	1.11	2.16	1	.142	3.04						
ECTs	**-0.23**	**5.52**	**1**	**.019**	**0.79**						
Change Score T0:T1 Item 5	0.00	0.39	1	.535	1.00						
						.22	0.56	16.28	4	.003	66.7

(Table 7 continued)

Sex	**1.87**	**8.70**	**1**	**.003**	**6.50**						
Presence of Psychotic Symptoms	**1.57**	**3.97**	**1**	**.046**	**4.79**						
ECTs	-0.12	1.17	1	.279	0.89						
ECTs* Change Score T0:T1 Item 6	**0.01**	**4.32**		**.038**	**1.01**						
Change Score T0:T1 Item 6	**-0.08**	**5.05**	**1**	**.025**	**0.92**						
						.33	**0.53**	**25.45**	**5**	**< .001**	**69.5**
Sex	**1.83**	**9.14**	**1**	**.002**	**6.25**						
Presence of Psychotic Symptoms	12.8 6	2.70	1	.100	384782. 83						
ECTs	-0.19	3.54	1	.060	0.83						
Presence of Psychotic Symptoms*ECTs	-0.87	2.11	1	.146	0.42						
Change Score T0:T1 Item 7	-0.01	2.88	1	.090	0.99						
						.30	0.70	23.73	5	< .001	67.7
Sex	**1.41**	**6.00**	**1**	**.014**	**4.11**						
Presence of Psychotic Symptoms	1.30	2.89	1	.089	3.66						
ECTs	**-0.23**	**4.77**	**1**	**.029**	**0.79**						
Change Score T0:T1 Item 8	**-0.02**	**7.94**	**1**	**.005**	**0.98**						
						.37	**0.65**	**29.64**	**4**	**< .001**	**71.9**
Sex	**1.52**	**6.87**	**1**	**.009**	**4.59**						
Presence of Psychotic Symptoms	1.45	3.36	1	.067	4.25						
ECTs	**-0.20**	**3.90**	**1**	**.048**	**0.82**						
Change Score T0:T1 Item 9	-0.01	3.67	1	.055	0.99						
						.28	0.77	21.55	4	< .001	72.0
Sex	**1.59**	**7.51**	**1**	**.006**	**4.89**						
Presence of Psychotic Symptoms	**1.45**	**3.88**	**1**	**.049**	**4.26**						
ECTs	0.01	0.00	1	.966	1.01						
ECTs*Change Score T0:T1 Item 10	**0.01**	**3.95**	**1**	**.047**	**1.01**						
Change Score T0:T1 Item 10	**-0.07**	**4.81**	**1**	**.028**	**0.94**						
						.29	**0.62**	**21.29**	**5**	**.001**	**69.2**
Sex	3.08	2.33	1	.118	21.73						
Presence of Psychotic Symptoms	0.26	0.03	1	.857	1.30						
ECTs	0.03	0.01	1	.909	1.03						
Change Score T0:T2 MADRS Total Score	**-0.42**	**7.81**	**1**	**.005**	**0.66**						
						.92	**0.69**	**106.05**	**4**	**< .001**	**93.8**
Sex	**1.64**	**5.56**	**1**	**.018**	**5.14**						
Presence of Psychotic Symptoms	0.48	0.34	1	.557	1.62						
ECTs	-0.08	0.43	1	.511	0.93						
Change Score T0:T2 Item 1*	**-0.07**	**18.94**	**1**	**< .001**	**0.94**						
						.58	**3.39**	**52.10**	**4**	**< .001**	**81.1**

(Table 7 continued)

Sex	**1.75**	**4.82**	**1**	**.028**	**5.77**					
Presence of Psychotic Symptoms	1.06	1.30	1	.254	2.89					
ECTs	-0.22	2.90	1	.089	0.81					
Change Score T0:T2 Item 2*	**-0.10**	**19.98**	**1**	**< .001**	**0.91**					
						.72	**1.18**	**70.62**	**4**	**< .001**	**84.4**
Sex	**2.30**	**9.18**	**1**	**.002**	**9.98**					
Presence of Psychotic Symptoms	1.51	2.69	1	.101	4.51					
ECTs	**-0.24**	**4.91**	**1**	**.027**	**0.78**					
Change Score T0:T2 Item 3*	**-0.06**	**16.74**	**1**	**< .001**	**0.94**					
						.58	**1.60**	**51.92**	**4**	**< .001**	**78.1**
Sex	**1.28**	**4.76**	**1**	**.029**	**3.58**					
Presence of Psychotic Symptoms	1.19	2.27	1	.132	3.27					
ECTs	-0.15	1.92	1	.166	0.86					
Change Score T0:T2 Item 4*	**-0.03**	**11.29**	**1**	**.001**	**0.97**					
						.41	**1.18**	**32.23**	**4**	**< .001**	**75.3**
Sex	**1.51**	**7.00**	**1**	**.008**	**4.54**					
Presence of Psychotic Symptoms	1.37	3.28	1	.070	3.91					
ECTs	**-0.31**	**7.96**	**1**	**.005**	**0.74**					
Change Score T0:T2 Item 5	**-0.01**	**5.15**	**1**	**.023**	**0.99**					
						.30	**0.83**	**22.84**	**4**	**< .001**	**66.3**
Sex	**2.99**	**11.44**	**1**	**.001**	**19.94**					
Presence of Psychotic Symptoms	**2.34**	**6.28**	**1**	**.012**	**10.37**					
ECTs	**-0.25**	**4.26**	**1**	**.039**	**0.78**					
Change Score T0:T2 Item 6*	**-0.05**	**17.85**	**1**	**< .001**	**0.95**					
						.61	**0.65**	**54.66**	**4**	**< .001**	**76.8**
Sex	**1.60**	**6.18**	**1**	**.013**	**4.96**					
Presence of Psychotic Symptoms	0.76	0.83	1	.363	2.13					
ECTs	**-0.73**	**4.26**	**1**	**.039**	**0.48**					
ECTs*Change Score T0:T2 Item 7	**-0.01**	**2.68**	**1**	**.101**	**0.99**					
Change Score T0:T2 Item 7	0.06	0.92	1	.337	1.07					
						.54	1.25	47.29	5	< .001	82.3
Sex	1.39	2.87	1	.090	4.01					
Presence of Psychotic Symptoms	0.26	0.06	1	.810	1.30					
ECTs	**1.20**	**4.69**	**1**	**.030**	**3.33**					
ECTs*Change Score T0:T2 Item 8	0.02	**6.11**	**1**	**.013**	**1.02**					
Change Score T0:T2 Item 8*	**-0.36**	**8.28**	**1**	**.004**	**0.70**					
						.72	**1.08**	**70.19**	**5**	**< .001**	**84.4**

(Table 7 continued)

Sex	**2.03**	**7.75**	**1**	**.005**	**7.60**						
Presence of Psychotic Symptoms	0.13	0.02	1	.890	1.13						
ECTs	**-0.24**	**4.04**	**1**	**.044**	**0.78**						
Change Score T0:T2 Item 9*	**-0.05**	**16.79**	**1**	**< .001**	**0.95**						
						.56	**1.60**	**51.93**	**4**	**< .001**	**82.8**
Sex	4.88	2.37	1	.124	131.22						
Presence of Psychotic Symptoms	1.44	**3.86**	**1**	**.050**	**4.22**						
ECTs	0.24	0.33	1	.565	1.27						
Change Score T0:T2 Item 10	**-0.01**	**4.18**	**1**	**.041**	**0.99**						
						.32	**1.13**	**24.51**	**5**	**< .001**	**71.0**

Note. R^2 = Nagelkerkes R^2. % = Percentage of correct prediction. ECTs = Number of received ECT sessions. Significant predictors and models including significant MADRS predictors are indicated in bold. *Bonferroni-corrected significance. *f* = Cohen's *f*. T0 = Baseline, T1 = Mid-treatment, T2 = Treatment end. Item 1 = apparent sadness. Item 2= reported sadness. Item 3 = inner tension. Item 4 = reduced sleep. Item 5 = reduced appetite. Item 6 = concentration difficulties. Item 7 = lassitude. Item 8 = inability to feel. Item 9 = pessimistic thoughts. Item 10 = suicidal thoughts.

3.3.4. Prediction of Overall Symptom Reduction

In step one of this linear regression model, sex ($p < .05$) and presence of psychotic symptoms ($p < .01$) were significant predictors of overall symptom reduction, while number of ECT sessions did not significantly predict overall symptom reduction ($p > .05$). In the first step, a significant prediction of overall symptom reduction was achieved, $p < .01$. A comprehensive presentation of all statistic values can be found in table 8.

In step two we added MADRS single items and MADRS total score to individual models separately. Hence, each regression model contained sex, presence of psychotic symptoms, number of received ECT sessions in step one and one MADRS item (or MADRS total score) in step two.

T0 (Baseline): MADRS total score, item 1, 2, 8, and 9 contributed significantly to predicting overall symptom reduction. MADRS total score was a Bonferroni-corrected significant predictor ($p < .01$). The regression model including MADRS total score indicated the best fit: $R^2 = .20$, $p < .001$.

Change Scores T0:T1: Change scores for MADRS total score and items 1, 2, 3, 6, 8, and 10 were Bonferroni-corrected significant predictors. The two models including item 2 ($p < .001$) and MADRS total score ($p < .001$) showed the best fit, $R^2 = .37$, $p < .001$.

Change Scores T0:T2: Change scores from baseline (T0) to treatment end (T2) for items 2, 4, 5, 7, 8, 9, and 10 were Bonferroni-corrected significant predictors. The regression model with item 2 ($p < .001$) and number of ECT sessions*item 2 interaction ($p = .001$) indicated the best fit: $R^2 = .74$, $p < .001$.

A comprehensive presentation of all statistic values can be found in table 8. Significant predictors are indicated in bold.

Table 8

Stepwise linear regression analysis for overall symptom reduction prediction

		Model 2							
	Variables	ß	*t*	*p*	*F*	*df*	*p*	R^2	*f*
Step 1									
	Sex	**-0.25**	**-2.59**	**.011**					
	Presence of Psychotic Symptoms	**-0.27**	**-2.76**	**.007**					
	ECTs	0.16	1.61	.111					
					4.99	3.92	.003	.11	0.35
Step 2									
	Sex	**-0.24**	**-2.57**	**.012**					
	Presence of Psychotic Symptoms	**-0.23**	**-2.51**	**.014**					
	ECTs	0.11	1.22	.227					
	MADRS Total Score T0*	**-0.30**	**-3.25**	**.002**					
					6.77	**4.91**	**< .001**	**.20**	**0.50**
	Sex	**-0.23**	**-2.46**	**.016**					
	Presence of Psychotic Symptoms	**-0.22**	**-2.28**	**.025**					
	ECTs	0.10	1.05	.295					
	MADRS T0 Item 1	**-0.24**	**-2.41**	**.018**					
					5.39	**4.91**	**.001**	**.16**	**0.44**
	Sex	**-0.22**	**-2.33**	**.022**					
	Presence of Psychotic Symptoms	**-0.23**	**-2.39**	**.019**					
	ECTs	0.14	1.53	.130					
	MADRS T0 Item 2	**-.025**	**-2.60**	**.011**					
					5.66	**4.91**	**< .001**	**.16**	**0.44**
	Sex	**-0.25**	**-2.58**	**.012**					
	Presence of Psychotic Symptoms	**-0.27**	**-2.72**	**.008**					
	ECTs	0.15	1.58	.118					
	MADRS T0 Item 3	-0.02	-0.25	.803					
					3.72	4.91	.008	.10	0.33
	Sex	**-0.25**	**-2.58**	**.011**					
	Presence of Psychotic Symptoms	**-0.26**	**-2.59**	**.011**					
	ECTs	0.16	1.66	.100					
	MADRS T0 Item 4	-0.06	-0.55	.584					
					3.79	4.91	.007	.11	0.35

(Table 8 continued)

Sex	**-0.24**	**-2.42**	**.017**					
Presence of Psychotic Symptoms	**-0.28**	**-2.87**	**.005**					
ECTs	0.16	1.62	.108					
MADRS T0 Item 5	-0.14	-1.43	.156					
				4.29	4.91	.003	.12	0.37
Sex	**-0.24**	**-2.42**	**.017**					
Presence of Psychotic Symptoms	**-0.26**	**-2.59**	**.011**					
ECTs	0.15	1.50	.136					
MADRS T0 Item 6	-0.09	-0.860	.392					
				3.91	4.91	.006	.11	0.35
Sex	**-0.26**	**-2.71**	**.008**					
Presence of Psychotic Symptoms	**-0.26**	**-2.70**	**.008**					
ECTs	0.16	1.67	.098					
MADRS T0 Item 7	-0.13	-1.39	.169					
				4.26	4.91	.003	.12	0.37
Sex	**-0.25**	**-2.63**	**.010**					
Presence of Psychotic Symptoms	**-0.28**	**-2.90**	**.005**					
ECTs	0.13	1.33	.186					
MADRS T0 Item 8	**-0.23**	**-2.36**	**.020**					
				5.32	**4.91**	**.001**	**.15**	**0.42**
Sex	**-0.26**	**-2.70**	**.008**					
Presence of Psychotic Symptoms	**-0.24**	**-2.51**	**.014**					
ECTs	0.13	1.37	.175					
MADRS T0 Item 9	**-0.19**	**-1.95**	**.054**					
				4.80	**4.91**	**.001**	**.14**	**0.40**
Sex	**-0.26**	**-2.70**	**.034**					
Presence of Psychotic Symptoms	**-0.30**	**-3.02**	**.003**					
ECTs	0.13	1.36	.176					
MADRS T0 Item 10	-0.15	-1.50	.137					
				4.35	4.91	.003	.12	0.37
Sex	-0.11	-1.29	.202					
Presence of Psychotic Symptoms	-0.14	-1.67	.098					
ECTs	0.07	.88	.383					
Change Score T0:T1 MADRS Total Score*	**0.54**	**6.18**	**< .001**					
				14.80	**4.91**	**< .001**	**.37**	**0.77**
Sex	-0.19	-2.14	.035					
Presence of Psychotic Symptoms	-0.17	-1.88	.064					
ECTs	0.06	.64	.521					
Change Score T0:T1 Item 1*	**0.43**	**4.63**	**< .001**					
				9.65	**4.90**	**< .001**	**.27**	**0.61**
Sex	-0.10	-1.10	.273					
Presence of Psychotic Symptoms	-0.14	-1.62	.108					
ECTs	0.08	.95	.343					
Change Score T0:T1 Item 2*	**0.54**	**6.17**	**< .001**					
				14.77	**4.91**	**< .001**	**.37**	**0.77**

(Table 8 continued)

Sex	**-0.33**	**-3.13**	**.002**					
Presence of Psychotic Symptoms	**-0.26**	**-2.81**	**.006**					
ECTs	0.16	1.75	.083					
Sex*Change Score T0:T1 Item 3	**-0.66**	**-2.20**	**.030**					
Change Score T0:T1 Item 3*	**0.87**	**3.00**	**.003**					
				5.98	**5.90**	**< .001**	**.21**	**0.52**
Sex	**-0.25**	**-2.52**	**.013**					
Presence of Psychotic Symptoms	**-0.27**	**-2.76**	**.007**					
ECTs	0.11	1.10	.275					
Change Score T0:T1 Item 4	**0.22**	**2.20**	**.031**					
				5.26	**4.84**	**< .001**	**.16**	**0.44**
Sex	**-0.25**	**-2.48**	**.015**					
Presence of Psychotic Symptoms	**-0.23**	**-2.32**	**.022**					
ECTs	0.16	1.59	.116					
Change Score T0:T1 Item 5	0.12	1.17	.245					
				3.59	4.88	.009	.10	0.33
Sex	**-0.22**	**-2.26**	**.026**					
Presence of Psychotic Symptoms	**-0.24**	**-2.49**	**.015**					
ECTs	0.15	1.63	.106					
Change Score T0:T1 Item 6*	**0.28**	**2.97**	**.004**					
				6.56	**4.90**	**< .001**	**.19**	**0.48**
Sex	**-0.24**	**-2.54**	**.013**					
Presence of Psychotic Symptoms	**-0.22**	**-2.30**	**.024**					
ECTs	0.16	1.67	.099					
Change Score T0:T1 Item 7	**0.23**	**2.34**	**.021**					
				5.29	**4.91**	**.001**	**.15**	**0.42**
Sex	**-0.19**	**-2.23**	**.029**					
Presence of Psychotic Symptoms	**-0.23**	**-2.70**	**.008**					
ECTs	0.03	0.35	.725					
ECTs*Change Score T0:T1 Item 8*	**-1.11**	**-3.35**	**.001**					
Change Score T0:T1 Item 8*	**1.44**	**4.32**	**< .001**					
				9.63	**5.90**	**< .001**	**.31**	**0.67**
Sex	**-0.19**	**-1.95**	**.054**					
Presence of Psychotic Symptoms	**-0.22**	**-2.22**	**.029**					
ECTs	0.13	1.34	.185					
Change Score T0:T1 Item 9	**0.28**	**2.89**	**.005**					
				5.48	**4.88**	**.001**	**.16**	**0.44**
Sex	**-0.23**	**-2.56**	**.012**					
Presence of Psychotic Symptoms	**-0.26**	**-2.81**	**.006**					
ECTs	-0.17	-1.36	.178					
ECTs*Change Score T0:T1 Item 10*	**-1.61**	**-3.17**	**.002**					
Change Score T0:T1 Item 10*	**1.87**	**3.67**	**< .001**					
				7.22	**5.85**	**< .001**	**.26**	**0.59**
Sex	0.09	0.77	.443					
Presence of Psychotic Symptoms	-0.07	-1.14	.258					
ECTs	-0.06	-0.95	.344					
Sex*Change Score T0:T2 Item 1	**0.49**	**2.02**	**.046**					
Change Score T0:T2 Item 1	0.37	1.75	.084					
				34.30	5.89	< .001	.64	1.42

(Table 8 continued)

Sex	-0.04	-0.68	.497					
Presence of Psychotic Symptoms	**-0.11**	**-2.06**	**.042**					
ECTs	**-0.27**	**-2.65**	**.009**					
ECTs*Change Score T0:T2 Item 2*	**-1.04**	**-3.44**	**.001**					
Change Score T0:T2 Item 2*	**1.84**	**6.08**	**< .001**					
				55.81	**5.90**	**< .001**	**.74**	**1.69**
Sex	-0.02	-0.19	.849					
Presence of Psychotic Symptoms	**-0.19**	**-2.51**	**.014**					
ECTs	0.12	1.53	.129					
Sex*Change Score T0:T2 Item 3	0.49	1.87	.064					
Change Score T0:T2 Item 3	0.17	0.70	.485					
				17.61	5.90	< .001	.47	0.94
Sex	**-0.20**	**-2.16**	**.033**					
Presence of Psychotic Symptoms	**-0.23**	**-2.45**	**.016**					
ECTs	**0.08**	0.82	.412					
Change Score T0:T2 Item 4*	**0.34**	**3.54**	**.001**					
				7.23	**4.88**	**< .001**	**.21**	**0.52**
Sex	-0.18	-1.94	.055					
Presence of Psychotic Symptoms	**-0.22**	**-2.43**	**.017**					
ECTs	**0.24**	**2.67**	**.009**					
Change Score T0:T2 Item 5*	**0.44**	**4.78**	**< .001**					
				9.90	**4.87**	**< .001**	**.28**	**0.62**
Sex	-0.08	-0.86	.391					
Presence of Psychotic Symptoms	**-0.25**	**-3.26**	**.002**					
ECTs	-0.04	-0.42	.675					
Sex*Change Score T0:T2 Item 6	**0.61**	**2.52**	**.013**					
ECTs*Change Score T0:T2 Item 6	**-1.21**	**-2.61**	**.011**					
Change Score T0:T2 Item 6	**1.18**	**2.20**	**.031**					
				15.37	**6.88**	**< .001**	**.48**	**0.96**
Sex	-0.13	-1.65	.103					
Presence of Psychotic Symptoms	-0.15	-1.92	.058					
ECTs	0.07	0.94	.348					
Change Score T0:T2 Item 7*	**0.61**	**7.72**	**< .001**					
				21.02	**4.91**	**< .001**	**.46**	**0.92**
Sex	**-0.16**	**-2.42**	**.018**					
Presence of Psychotic Symptoms	-0.12	-1.81	.073					
ECTs	**0.15**	**2.39**	**.019**					
Change Score T0:T2 Item 8*	**0.72**	**10.91**	**< .001**					
				38.29	**4.91**	**< .001**	**.61**	**1.25**
Sex	**-0.19**	**-2.72**	**.008**					
Presence of Psychotic Symptoms	-0.05	-0.74	.463					
ECTs	**0.21**	**2.95**	**.004**					
Change Score T0:T2 Item 9*	**0.71**	**9.74**	**< .001**					
				30.14	**4.88**	**< .001**	**.56**	**1.13**

(Table 8 continued)

Sex	**-0.24**	**-2.55**	**.013**					
Presence of Psychotic Symptoms	**-0.25**	**-2.77**	**.007**					
ECTs	**0.11**	1.11	.271					
Change Score T0:T2 Item 10*	**0.31**	**3.18**	**.002**					
				7.98	**4.88**	**< .001**	**.23**	**0.55**

Note. R^2 = adjusted R^2. ECTs = Number of received ECT sessions. ß = standardized ß-value. Significant predictors and models including significant MADRS predictors are indicated in bold. *Bonferroni-corrected significance. *f* = Cohen's *f*. T0 = Baseline, T1 = Mid-treatment, T2 = Treatment end. Item 1 = apparent sadness. Item 2= reported sadness. Item 3 = inner tension. Item 4 = reduced sleep. Item 5 = reduced appetite. Item 6 = concentration difficulties. Item 7 = lassitude. Item 8 = inability to feel. Item 9 = pessimistic thoughts. Item 10 = suicidal thoughts.

3.3.5. ROC Analyses

The highest percentage of correct response prediction was achieved with regression models containing MADRS total score and item 2. Thus, ROC analyses were performed to examine the optimal cut points for MADRS baseline and MADRS change score.

Baseline (T0) MADRS Total Score. Area under the curve was .64, p = .017, optimal cut point was MADRS total score = 32 (sensitivity .49, specificity .73).

Baseline (T0) MADRS Item 2. Area under the curve was .65, p = .013, optimal cut point was item 2 = 5 (sensitivity .47, specificity .78).

Change Score T0:T1 MADRS Total Score. Area under the curve was .86, $p < .001$, optimal cut point was change score T0:T1 MADRS total score = -31% (sensitivity .77, specificity .82).

Change Score T0:T1 MADRS Item 2. Area under the curve was .83, $p < .001$, optimal cut point was change score T0:T1 MADRS item 2 = -23% (sensitivity .73, specificity .76).

4. Discussion

4.1. Summary

Data from 96 depressed psychiatric patients was analysed for this naturalistic retrospective study. Patients received antidepressant treatment with electroconvulsive therapy at Charité – Universitätsmedizin Berlin. The first aim of this dissertation was to examine the change of depressive symptomatology throughout the course of ECT. The second aim was to assess, how depressive symptoms and their change during ECT treatment may predict clinical results. Depressive symptoms were measured with the MADRS, a standardized clinical interview for depression severity. MADRS data is regularly assessed in clinical routine and we analysed data from three time points: baseline (T0) before ECT treatment, mid-treatment (T1) after 6 ECT sessions, and at the end of treatment (T2) after finishing ECT treatment. To the author's best knowledge, this is the first study that explored the change of MADRS single items during antidepressant treatment with ECT and their potential relation with ECT outcomes.

4.1.1. Change of depressive symptoms during the course of ECT

Depression severity measured with the MADRS total score decreased significantly from baseline to treatment end for the overall sample. Within the responder group, MADRS total score significantly decreased over all three time points. Within the non-responder group, MADRS total score significantly decreased from baseline to mid-treatment, however, no additional significant decrease from mid-treatment to treatment end could be shown. Regarding distinct depressive symptoms measured with MADRS single items, strongest reductions were detected for items 1 (apparent sadness), 2 (reported sadness), and 8 (inability to feel), lowest reductions for items 6 (concentration difficulties), and 10 (suicidal thoughts). Patients classified as ECT responders showed significant decreases for all single items, decreases were strongest for items 1 (apparent sadness), 2 (reported sadness), 8 (inability to feel), and 9 (pessimistic thoughts). Significant decreases for single items within the non-responder group could only be detected for item 1 (apparent sadness) and 2 (reported sadness). As for the responders and the overall sample, reductions were lowest for item 6 (concentration difficulties) and 10 (suicidal thoughts). However, in contrast to the responders, reduction for item 9 (pessimistic thoughts) was low for non-responders.

4.1.2. Prediction of ECT outcome

Response to antidepressant treatment with electroconvulsive therapy was defined as a reduction in symptom severity measured with the MADRS of 50% or more at treatment end. MADRS total score ≤ 10 at treatment end was defined as remission, 50% reduction or more at mid-treatment was defined as early response.[27] Overall symptom reduction was defined as MADRS score change in

percentage from baseline to treatment end. In our current sample, 53% of the psychiatric inpatients could be classified as responders. These responders showed more severe depression scores at baseline and less severe scores at the end of ECT treatment. MADRS total score, single items, as well as their change throughout the course of ECT appear to be valuable predictors of ECT response, remission, and overall symptom reduction. Regarding the exploration of distinct depressive symptoms measured with MADRS single items, particularly item 1 (apparent sadness), 2 (reported sadness), and 8 (inability to feel) indicated predictive values comparable to or higher than those of MADRS total score. Interestingly, regression models with item 2 (reported sadness) indicated the strongest effects, showing large effect sizes. For example, the regression model containing the change of item 2 from baseline (T0) to treatment end (T2) (thus during the course of ECT treatment) indicated 92% correct prediction of ECT response status at the end of treatment. It is crucial to correctly interpret the direction of these findings: While at baseline, higher depression scores are positively associated with ECT treatment results, at mid-treatment lower depression scores are positively associated with ECT treatment results. Regarding the prediction of early response, no significant effects could be detected, neither for distinct depressive symptoms measured with MADRS single items nor for overall depression severity measured with the MADRS total score. Higher depression severity at baseline seems to be positively associated with treatment outcome. Thus, we computed ROC curves to suggest a precise cut point for MADRS total score and item 2 (reported sadness) before treatment start to predict response at the end of ECT treatment. MADRS total score = 32 and item 2 = 5 were determined as potential cut-off points after future validation.

In our current sample, no association between age and ECT outcome was found. However, female patients were more likely to respond than male, as were patients who were diagnosed with a depressive episode with psychotic features.

4.2. Comparison with previous findings

4.2.1. Change of depressive symptoms during the course of ECT

During the course of ECT, strongest reductions were found for affective symptoms, which can be linked to results from Veltman et al.[28] who reported strongest reductions for a MADRS-derived factor labeled “mood” in older depressed patients treated with ECT. Moreover, Veltman et al.[28] reported low reductions for the factor labeled “suicidality”, which is in line with the low reductions for item 10 (suicidal thoughts) in the current study. We found lowest symptom reduction for concentration difficulties, especially within the non-responder group, where no significant reduction during the course of ECT could be found. Transient concentration difficulties during and

shortly after the course of ECT have been excessively reported in the literature and are acknowledged as a main adverse effect.[13] In accordance with the findings presented here, previous studies reported associations between depression severity and subjective memory impairment after ECT treatment as well as higher subjective memory impairment in non-remitted patients than in remitted patients. However, no associations between depression severity and objective neuropsychological measures were found.[29,30] Thus, as summarized by Mohn and Rund,[31] memory complaints of depressed patients after ECT might be related to the level of depression and not to actual cognitive performance. As subjective memory impairment during ECT treatment might also impede recovery, the exact mechanisms between non-response to ECT and cognitive impairment during treatment remain an interesting question for future research.

4.2.2. Prediction of ECT outcome

In the present study, more severe depressive symptoms at baseline, less severe depressive symptoms mid-treatment as well as a higher decrease in symptom severity until mid-treatment were associated with a more favorable ECT outcome, which is in line with previous findings.[18,32,33] In general, a response rate of 53% in the presented sample can be regarded as relatively low. Apart from our limited sample size, a possible explanation for this could be the relatively low proportion of patients with presence of psychotic features. Moreover, our study focused on patients with a primary diagnoses of depressive disorders, while for example in data sets analysed by Nordenskjöld et al.[34] patients diagnosed with schizoaffective disorders were included as well. Other explanations for this discrepancy in response rate could be differences in electrode placement, dosage, and used anesthetic during ECT treatment.[13] The number of received ECT sessions could not predict ECT outcome and did not differ significantly for responders and non-responders, which, while at the first glance counterintuitive, is in accordance with previous research.[21] A possible explanation for this might be additional ECT sessions given to patients who only partially responded, aiming for a late response.[35]

In our study, response rates after ECT treatment were higher for women. However, the women in our sample did not show more severe depressive symptoms at baseline and were not diagnosed with psychotic features of depression more frequently than men, which might have been a possible explanation for the sex difference in response status. Higher response rates for women have not been reported in previous studies, in contrast, previous research did not find consistent sex specific effects.[17] Age of the included patients' age ranged from 22 to 80 years. No significant association between age and ECT outcome was found, which is in accordance with some previous studies.[36,37] There is some research that describes rather contradicting small effects of age and discusses a potential „turning point" in the mid-fifties, where older patients tend to experience a more

favorable antidepressant ECT effect. Nevertheless, this remains an open question for future research.[18] Some previous findings propose pre-treatment symptom severity as a predictive factor for response but not remission.[18] Correspondingly, this dissertation found predictive effects of baseline depression symptoms for ECT response but not for ECT remission. However, results for depression symptoms mid-treatment and symptom change during the course of ECT were similar for response and remission. This might be due to the strong overlap of patients who responded and patients who remitted in the current sample: The group of 51 responders included all 31 remitters. Considering distinct depressive symptoms measured with MADRS single items, item 2 (reported sadness) showed the strongest predictive effects. Interestingly, this can be connected to the above-mentioned factor-analytic results. Okazaki et al.[19] and Spashett et al.[21] suggested different predictive factors including a distinctive pattern of MADRS single items. Okazaki et al.'s[19] factor is called "dysphoria" and includes the following three items: reported sadness, pessimistic thoughts, and suicidal thoughts. Spashett et al.'s[21] factor is called "despondency" and includes the following five items: apparent sadness, reported sadness, concentration difficulties, lassitude, and inability to feel respectively. However, one MADRS single item is included in both potentially predictive factors: item 2. In the present study, more severe affective symptoms at baseline (item 1 apparent sadness, item 2 reported sadness, item 8 inability to feel) were positively associated with ECT outcome and throughout the course of ECT treatment, these affective depressive symptoms were most strongly reduced. In some ways, findings concerning the potentially predictive factors proposed by Okazaki et al.[19] and Spashett et al.[21] as well as our findings concerning the potential relevance of affective symptoms can be linked to research examining the association between ECT outcome and melancholic features of depression.[17,18] According to the DSM-5[38] melancholic features can be coded additionally when diagnosing depressive episodes. These melancholic features are described as follows: loss of joy or loss of affective reactivity, as well as a special quality of depressed mood, diurnal variation of symptoms (more severe symptoms in the morning), early waking, psychomotor disturbances (agitation or retardation), significant loss of appetite or weight, and excessive feelings of guilt. Nevertheless, findings regarding the predictive value of melancholic features for ECT response in remain inconclusive.[17,18] On a broader note, the general usefulness of the concept of "melancholic features" is controversially discussed. Some authors underline the potentially distinct etiology, associated biological changes and thus the potential for an accordingly aligned treatment.[39] Other authors critically question the clinical value of melancholic features. In a large sample of 3211 depressed patients, Tondo et al.[40] compared patients diagnosed with melancholic features to those without. They found the diagnosis of melancholic features to be highly associated with depression severity. When matched for

depression severity, very few differing clinical characteristics could be detected. Thus, the potential additional value of melancholic features for clinical decisions remains uncertain. This is especially true as definitions and assessment of melancholic features vary and DSM-5 criteria are sometimes regarded as insufficient, as they cover a wide range of different symptoms.[41] Per definition, melancholic features may include affective depressive symptoms, but also somatic depressive symptoms like agitation, loss of appetite, as well as sleeping disturbances.[17,18] This abundance of potential symptom combinations under the label of "melancholic features" could be a possible explanation for the unclear findings concerning the predictive value of melancholic features for ECT outcome. In the present study, somatic depressive symptomatology did not seem to be especially relevant for ECT outcome. Overall, our findings are in line with the previously discussed limited predictive value of melancholic features for ECT outcome[42]. Moreover, our findings are in accordance with a rather symptom-based approach of depression research and treatment as recommended by Fried and Nesse.[43] Fried and Nesse[44] analysed symptom combinations in depressive outpatients and identified a broad variety of symptom profiles. The most common symptom profile was shared by only 1.8% of the examined patients. This illustrates the extensive heterogeneity of depressive orders and the resulting difficulties for effective treatment research. Regarding individual symptoms seems especially important as specific symptoms such as concentration difficulties, suicidal ideation and depressed mood appear to differ from each other regarding associated impairment, risk factors, underlying biological mechanism and hence treatment options.[43]

4.3. Implications for the field

These findings suggest a potent antidepressant effect of ECT. ECT seems to have a particularly strong effect on reducing affective depressive symptoms. Patients who are more severely depressed appear to generally benefit more, particularly those patients with distinctive pre-treatment affective symptoms assessed with the MADRS. In order to facilitate decision-making before starting ECT treatment and to help identify those patients who might especially benefit from ECT treatment, the following potential cut-off points analysed with ROC curves are suggested: MADRS total score = 32 and item 2 = 5 at baseline. After careful future validation in larger samples these values might pose a useful addition to clinical routine. Moreover, our findings indicate that lower symptom severity mid-treatment can be regarded as a valuable predictor of successful ECT treatment. This knowledge could be used for example when communicating with patients about the proceeding of ECT treatment. Patients who benefited after 6 ECT sessions might want to end treatment early, especially when experiencing side effects such as cognitive

impairments at the same time. For these patients it might be very useful to know, that sticking to this treatment method a bit longer could be very rewarding for them. Moreover, distinct depressive symptoms assessed with MADRS single items (especially item 2 reported sadness) and their change throughout the course of ECT could present a valuable, simple, cost- and time-effective, reliable addition in the prediction ECT outcome. This might be especially useful for settings with limited resources. In the current sample, even patients categorized as non-responders still show a significant reduction in affective depressive symptomatology. However, the most notable difference between responders and non-responders can be found with regards to the decrease of pessimistic thoughts. For non-responders, no significant reduction of these cognitive symptoms of depression during the course of ECT treatment could be found. Thus, probably these patients could especially benefit from additional treatment options that more directly address these pessimistic thoughts. One possible option to specifically target these symptoms could be cognitive-behavioral therapy (CBT) after ECT. In short, the basic assumption of CBT is that cognitions (thus thoughts) causally lead to emotions and behaviors. Thus, so-called dysfunctional thoughts are regarded as a major factor for the maintenance of depressive disorders and psychopathology in general. Cognitive-behavioral approaches hence aim to restructure these dysfunctional thoughts, establish new helpful thoughts, and through this cognitive work enable patients to implement new helpful behaviors, which in turn positively influence emotions and thoughts.[45] Until now, there are only very few findings regarding cognitive behavioral interventions after ECT treatment.[26] Moreover, while some pilot studies report encouraging findings, research is mainly dedicated to maintaining response after successful ECT treatment. This excludes those other patients in need, who only partially benefited from ECT treatment.[26,46,47] One recent pilot study by Carstens et al.[48] found favorable results for a manualized group CBT after ECT treatment regardless of response status. The proposed half-open group setting aimed to support patients immediately after ECT treatment, when transitioning from inpatient to outpatient care. Patients were offered to participate in a total of 15 group sessions, comprising a combination of CBT interventions and CBASP (cognitive behavioral analysis system of psychotherapy) elements. Results showed that there was a tendency towards further decreased depression severity for ECT responders and non-responders after group CBT. Moreover, emotion regulation competencies and quality of life showed improvements as well. These improvements could also be maintained six months after group end. After future careful validation, this could be a promising continuation treatment for responders as well as non-responders.

In our current study, depression severity decreased significantly until mid-treatment for non-responders, however no additional symptom reduction from mid-treatment to treatment end was

found for these patients, only clinician-rated apparent sadness continued to significantly diminish. Thus, an earlier termination of ECT treatment could be considered for these patients, as no additional recovery seems to occur after the sixth ECT session. ROC curve analyses proposed overall symptom reduction of at least 31% and reduction of reported sadness of at least 23% until mid-treatment as potential cut-off points for a successful ECT treatment. This is in accordance with findings from Martínez-Amorós et al.[33] who proposed a symptom reduction of 30% after two weeks of ECT treatment as a predictor of ECT outcome and thus a potential criterion for a reevaluation of treatment strategy. Hence, after future validation and under consideration of other important factors like presence of psychotic symptoms and the physicians' general evaluation these proposed cut-off values might provide a valuable addition to clinical decision-making.

4.4. Limitations and suggestions for future research

Due to the naturalistic, retrospective setting, no additional follow-up data after discharge from our hospital was available. Hence, no presumptions about predictive values of MADRS single items concerning future relapse or sustained response can be made. Moreover, confounding effects of depressive symptomatology with psychiatric comorbidities or medication intake cannot be precluded. In order to examine distinctive effects of ECT treatment for depressive symptoms, future studies with a stable concomitant psychiatric medication could also be helpful. On the other hand, our data was collected in clinical routine and with all implied limitations, this setting could also be regarded as an advantage. Overall, depression research aims to support patients who are suffering and those who are treating them in daily life. Our study design can be regarded as relatively representative of clinical routine in our hospital and thus after future validation these findings could be transferred and adapted into real life more easily.

In order to work towards more reliable assumptions and recommendations, it seems necessary to analyse predictive values of depressive symptomatology measured with a range of different depression scales. For example, the Hamilton Depression Rating Scale (HRSD)[49] or self-report measures like the BDI-II (Beck Depression Inventory)[50] could be used. Due to the massive heterogeneity of depression scales, findings might differ.[51] Moreover, considering the interaction of depressive symptoms among each other, as well as their interaction with demographic and clinical variables, future research employing structural equation models for the prediction of ECT outcomes might prove enlightening.[51] Unfortunately, sample size would not allow for meaningful implementation of a structural equation model in this dissertation.

4.5. Conclusion

For this retrospective naturalistic study we analysed data from 96 depressed inpatients who received antidepressant treatment with electroconvulsive therapy. This dissertation examined change of depressive symptomatology throughout the course of ECT and explored, whether these depressive symptoms were valuable predictors of ECT outcome. For the assessment of depressive symptomatology, the MADRS was employed. Affective depressive symptoms showed the strongest decrease throughout the course of ECT treatment. Moreover, these affective symptoms also showed the most promising predictive effects, particularly reported sadness. More severe affective symptoms at baseline before treatment start, less severe affective symptoms mid-treatment, as well as stronger reduction of affective symptoms throughout the course of ECT appear to be valuable predictors of successful ECT treatment in depressed patients. For non-responders, reduction of pessimistic thoughts during the course of ECT was especially limited. In order to better support these patients, additional continuation treatment options addressing these mainly cognitive depressive symptoms such as CBT could be promising. An earlier termination of ECT treatment for those patients who do not benefit sufficiently after the sixth ECT session could also be considered after further research. On a more general note, these findings support a more individualized and symptom-based concept for research and treatment of depressive disorders. In order to further validate the predictive value of distinct depressive symptoms, future longitudinal research utilizing a broad variety of self-report measures and clinical interviews for depressive symptomatology seems advisable.

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VII Eidesstattliche Versicherung & Anteilserklärung

Eidesstattliche Versicherung

„Ich, Luisa Carstens (geb. Bönke), versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Veränderung und Vorhersagekraft distinkter depressiver Symptome während der Behandlung mit Elektrokonvulsionstherapie“ bzw. „Change of depressive symptoms during the course of electroconvulsive therapy (ECT) and predictive value of these symptoms for ECT outcome“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an der erfolgten Publikation

Luisa Carstens hatte folgenden Anteil an der folgenden Publikation:

Publikation 1: Carstens, L., Hartling, C., Stippl, A., Domke, A. K., Herrera-Mendelez, A. L., Aust, S., ... & Grimm, S. (2021). A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items. European Archives of Psychiatry and Clinical Neuroscience, 1-10.

Im Rahmen meiner Promotion habe ich grundlegend zur Implementierung der Studienabläufe und der organisatorischen Infrastruktur am Standort Charité, Campus Benjamin Franklin beigetragen. Des Weiteren war ich für die konstante Kommunikation und Studienkorrespondenz mit den Stationen 16b, sowie 08a/b der Klinik für Psychiatrie und Psychotherapie, Charité Campus Benjamin Franklin verantwortlich. Ich übernahm einen Großteil der Patientendatenakquise auf den Stationen. Darüber hinaus bestand meine Aufgabe in der analogen und digitalen Archivierung von Patientendaten (Fragebögendaten sowie Stationsakten), sowie deren quantitativer Aufbereitung in SPSS und Excel. Die Fragestellung meiner Promotion habe ich in Rücksprache mit meinen Betreuern selbstständig entwickelt. Ebenso habe ich die statistische Auswertung mittels SPSS und Excel selbstständig durchgeführt. Zur Sicherstellung der methodischen Qualität der logistischen Regressionsanalysen habe ich eine Beratung der Charité-Statistikerin in Anspruch genommen. Aus meinen eigenen statistischen Analysen entstanden die Tabelle 1, Abbildungen 1-3 und das komplette supplementary material der Publikation sowie die Tabellen 1 - 8 und Abbildung 1 - 5 in diesem Manteltext.

Ich trug wesentlich dazu bei nach der passenden Literatur zu recherchieren und die Studie in den aktuellen Forschungsstand einzuordnen. Drüber hinaus bin ich alleinige Verfasserin des veröffentlichten Manuskripts und habe die Korrespondenz des mehrstufigen Peer-Reviewprozesses sowie die Überarbeitung in Einklang mit den Anmerkungen der Reviewer gehandhabt.

_____	_____
Unterschrift, Datum und Stempel des erstbetreuenden Hochschullehrers	Unterschrift und Datum der Doktorandin

VIII Auszug Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2020** Selected Editions: SCIE, Selected Categories: **"PSYCHIATRY"** Selected Category Scheme: WoS

Gesamtanzahl: 156 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	World Psychiatry	9,619	49.548	0.020030
2	Lancet Psychiatry	14,839	27.083	0.036240
3	JAMA Psychiatry	19,105	21.596	0.052990
4	AMERICAN JOURNAL OF PSYCHIATRY	48,206	18.112	0.031970
5	PSYCHOTHERAPY AND PSYCHOSOMATICS	6,123	17.659	0.006750
6	MOLECULAR PSYCHIATRY	28,622	15.992	0.046220
7	BIOLOGICAL PSYCHIATRY	50,155	13.382	0.045540
8	JOURNAL OF NEUROLOGY NEUROSURGERY AND PSYCHIATRY	37,094	10.154	0.026380
9	BRITISH JOURNAL OF PSYCHIATRY	30,003	9.319	0.019160
10	SCHIZOPHRENIA BULLETIN	21,642	9.306	0.023290
11	JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY	25,273	8.982	0.021190
12	JOURNAL OF THE AMERICAN ACADEMY OF CHILD AND ADOLESCENT PSYCHIATRY	25,046	8.829	0.017190
13	Evidence-Based Mental Health	1,201	8.141	0.003220
14	NEUROPSYCHOPHARMACOLOGY	30,856	7.853	0.034600
15	PSYCHOLOGICAL MEDICINE	34,876	7.723	0.038850
16	BRAIN BEHAVIOR AND IMMUNITY	24,161	7.217	0.026930
17	Clinical Psychological Science	3,811	7.169	0.010420
18	Epidemiology and Psychiatric Sciences	2,571	6.892	0.005580
19	Journal of Behavioral Addictions	4,024	6.756	0.008100
20	BIPOLAR DISORDERS	6,185	6.744	0.007510

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
21	ADDICTION	23,843	6.526	0.025580
22	DEPRESSION AND ANXIETY	12,440	6.505	0.013220
23	ACTA PSYCHIATRICA SCANDINAVICA	16,412	6.392	0.011290
24	Translational Psychiatry	13,269	6.222	0.030670
25	JOURNAL OF PSYCHIATRY & NEUROSCIENCE	4,100	6.186	0.004200
26	PHARMACOPSYCHIATRY	2,099	5.788	0.001500
27	CNS DRUGS	5,948	5.749	0.007070
28	AUSTRALIAN AND NEW ZEALAND JOURNAL OF PSYCHIATRY	8,920	5.744	0.008520
29	EUROPEAN PSYCHIATRY	7,865	5.361	0.010160
30	Current Psychiatry Reports	7,165	5.285	0.012870
31	EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE	5,451	5.270	0.005150
32	npj Schizophrenia	830	5.200	0.002760
33	PSYCHIATRY AND CLINICAL NEUROSCIENCES	5,454	5.188	0.004700
34	INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY	7,865	5.176	0.008440
35	PROGRESS IN NEURO-PSYCHOPHARMACOLOGY & BIOLOGICAL PSYCHIATRY	13,777	5.067	0.013440
36	Therapeutic Advances in Psychopharmacology	961	5.000	0.001570
37	SCHIZOPHRENIA RESEARCH	26,508	4.939	0.027790
38	PSYCHONEUROENDOCRINOLOGY	22,335	4.905	0.025020
39	INTERNATIONAL JOURNAL OF EATING DISORDERS	12,593	4.861	0.011620
40	JOURNAL OF AFFECTIVE DISORDERS	46,992	4.839	0.062720
41	JOURNAL OF PSYCHIATRIC RESEARCH	20,371	4.791	0.020030
42	EUROPEAN CHILD & ADOLESCENT PSYCHIATRY	7,765	4.785	0.010300

Selected JCR Year: 2020; Selected Categories: "PSYCHIATRY"

IX Publikation

A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items.

European Archives of Psychiatry and Clinical Neuroscience (2021) 1-10.

https://doi.org/10.1007/s00406-021-01301-8

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European Archives of Psychiatry and Clinical Neuroscience
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ORIGINAL PAPER

A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items

Luisa Carstens[1] · Corinna Hartling[1] · Anna Stippl[1] · Ann-Kathrin Domke[1] · Ana Lucia Herrera-Mendelez[1] · Sabine Aust[1] · Matti Gärtner[1,3] · Malek Bajbouj[1] · Simone Grimm[1,2,3]

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Abstract
Establishing symptom-based predictors of electroconvulsive therapy (ECT) outcome seems promising, however, findings concerning the predictive value of distinct depressive symptoms or subtypes are limited; previous factor-analytic approaches based on the Montgomery–Åsberg Depression Rating Scale (MADRS) remained inconclusive, as proposed factors varied across samples. In this naturalistic study, we refrained from these previous factor-analytic approaches and examined the predictive value of MADRS single items and their change during the course of ECT concerning ECT outcome. We used logistic and linear regression models to analyze MADRS data routinely assessed at three time points in 96 depressed psychiatric inpatients over the course of ECT. Mean age was 53 years (SD 14.79), gender ratio was 58:38 (F:M), baseline MADRS score was $M = 30.20$ (SD 5.42). MADRS single items were strong predictors of ECT response, remission and overall symptom reduction, especially items 1 (apparent sadness), 2 (reported sadness) and 8 (inability to feel), assessing affective symptoms. Strongest effects were found for regression models including item 2 (reported sadness) with up to 80% correct prediction of ECT outcome. ROC analyses were performed to estimate the optimal cut-point for treatment response. MADRS single items during the course of ECT might pose simple, reliable, time- and cost-effective predictors of ECT outcome. More severe affective symptoms of depression at baseline and a stronger reduction of these affective symptoms during the course of ECT seem to be positively associated with ECT outcome. Precise cut-off values for clinical use were proposed. Generally, these findings underline the benefits of a symptom-based approach in depression research and treatment in addition to depression sum-scores and generalized diagnoses.

Keywords Electroconvulsive therapy (ECT) · Montgomery–Åsberg Depression Rating Scale (MADRS) · Depression · Response prediction

Introduction

Electroconvulsive therapy (ECT) is one of the most effective treatment options for depressive disorders, recommended especially for the treatment of severe and treatment-resistant depression [1, 2]. Even though response rates are generally high (60–80%) [3], a relevant percentage of patients shows no or only partial response [4]. Moreover, response time and course of action during ECT vary substantially [4]. Different mechanisms of actions are discussed in the literature (e.g. neurobiological factors such as enhancement of serotonergic neurotransmission and activation of the mesocorticolimbic dopamine system) [3]. However, the precise antidepressant mechanisms of ECT remain unclear, potentially further impeding treatment prediction [5]. Generally, electroconvulsive therapy can be regarded as a relatively costly, intensive

✉ Luisa Carstens
luisa.boenke@charite.de

[1] Department of Psychiatry, Centre for Affective Neuroscience (CAN), Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Charité-Universitätsmedizin Berlin, Campus Benjamin, Franklin, Hindenburgdamm 30, 12203 Berlin, Germany

[2] Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, Lenggstrasse 31, 8032 Zurich, Switzerland

[3] Department of Psychology, MSB Medical School Berlin, Rüdesheimer Str. 50, 14197 Berlin, Germany

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treatment, implying patients being hospitalized for several weeks undergoing recurrent anaesthesia. Moreover, transient cognitive side effects and the psychological distress for patients undergoing this treatment without the desired effects need to be considered [6, 7]. At the same time, there is well-established evidence that ECT is a very effective treatment option for severely depressed patients with a long history of treatment efforts [1]. These factors underline the importance of establishing reliable response predictors of antidepressant treatment with ECT. Factors such as age, psychotic symptoms and depression severity appear to be well-founded predictors of successful ECT treatment; however, findings concerning depression symptoms or subtypes are less clear [8]. In their factor-analytic approaches, Okazaki et al. [9] Tominaga et al. [10] and Spashett et al. [11] examined factors derived from the Montgomery–Åsberg Depression Rating Scale (MADRS) [12] as predictors of ECT response. Postulating response predictors employing one of the most established clinical interviews for depression severity seems of great value for clinical decision making, however, proposed factor models varied across samples and implications remained inconclusive. Hence, the current study refrains from this factor-analytic approach and rather aims to examine the value of MADRS single items as predictors of ECT response. As this is the first study examining MADRS single items during the course of ECT, we not only aspire to examine the predictive value of MADRS single items and, therefore, depressive symptoms but also seek to depict the change of these depressive symptoms during the course of ECT to deepen the understanding of the antidepressant mechanisms of ECT.

Method

Participants

Participants were psychiatric inpatients diagnosed with a current depressive episode in accordance with DSM-5 who were treated with ECT at Charité—Universitätsmedizin Berlin. The present study analyses routinely assessed depression severity employing the MADRS [12], so no restrictions concerning comorbidities or medication intake were made and no clinical trials registration is available. However, the retrospective study design was approved by the institutional review board of the Charité, performed in accordance with the Declaration of Helsinki and patients' informed consent was obtained. Routine MADRS ratings were available for 120 moderately to severely depressed inpatients, additional clinical and demographic data was collected from medical records. To facilitate interpretation and enhance comparability with other studies, patients who received ketamine treatment right before ECT, changed to ketamine treatment during the course of ECT or received ketamine as an anaesthetic during ECT were excluded ($n = 10$), as well as patients older than 80 years ($n = 4$), patients who had to pause ECT due to urgent other medical reasons ($n = 2$), were rehospitalized shortly after release and received a second course of ECT ($n = 1$), received only one ECT session per week in the beginning ($n = 1$) or received very few (6 or 7) ECT sessions ($n = 2$). Patients with baseline MADRS total score 2 SD > Mean were identified as outliers and excluded ($n = 4$), resulting in our total sample size of $n = 96$.

ECT treatment

ECT was administered in accordance with standard protocol at the Department of Psychiatry, Charité—Universitätsmedizin Berlin, which includes three ECT sessions per week (for details see Basso et al. [13] and Brakemeier et al. [14]). In short, patients were anesthetized either with etomidate (approximately 0.75 mg/kg) or propofol (approximately 1.5 mg/kg). A Thymatron IV System (Somatics, LLC, Venice, Florida, United States) was used to deliver ultra-brief pulse stimuli (0.3 ms) for right unilateral ECT. Succinylcholine (approximately 0.75 mg/kg) was used for muscular relaxation. Motor and electroencephalogram (EEG) seizure duration, ictal-EEG wave amplitude and post-ictal suppression index were monitored for seizure quality. During the first ECT session, seizure threshold was titrated and voltage was subsequently modified if patients showed insufficient seizures. The mean number of administered ECT sessions was 13.60 (SD 2.66).

Study design and assessment

A routinely assessed German version of the Montgomery–Åsberg Depression Rating Scale (MADRS) [12] conducted by trained professionals at baseline before ECT treatment (T0), mid-treatment after six ECT sessions (T1) and at the end of treatment 1–3 days after the last ECT session (T2) was analysed. The MADRS consists of ten items assessing the following depressive symptoms on a seven-point scale: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts and suicidal thoughts. Reduction of MADRS total score of 50% or more at T2 was defined as response, MADRS total score ≤ 10 at T2 as remission, 50% reduction or more at T1 was defined as early response [15]. In our sample, 53% of the patients responded, 34% remitted, all patients who remitted responded as well, 24% were classified as early responders.

Statistical analyses

All analyses were conducted using SPSS® 26.0 (IBM Corporation, Armonk NY, USA) for Windows®/Apple Mac®. *T* tests for independent samples were used to examine differences between responders and non-responders concerning clinical or demographic variables, chi-squared tests were used to assess differences between categorical variables. As distribution of gender differs between responders and non-responders, gender was added to the regression models.

Change of depressive symptoms during the course of ECT

ANOVAs for repeated measures (T0, T1, T2) were applied, separately for all single items and MADRS total score, gender and psychotic symptoms were added as covariates. These ANOVAs were performed for the overall sample and separately for responders and non-responders. For the overall sample, classification as responders vs. non-responders was additionally added as a covariate.

Prediction of response

A two-step logistic regression model was used to predict response. In order to control for gender, psychotic symptoms and number of received ECT sessions these three variables were added in the first step, in the second step, MADRS single items and MADRS total score were each added to a distinct model individually, thus each regression model consisted of gender, psychotic symptoms, number of ECT sessions in the first step and one MADRS item (or MADRS total score) in the second step. In the second step interaction terms of the respective MADRS item or total score with gender, psychotic symptoms and number of ECT sessions were added as well, these were removed when not significant. In addition to the predictive value of MADRS items and total score at baseline (T0) and mid-treatment (T1), we also examined the predictive value of the change scores. Change scores T0:T1 are defined as the change in percentage from T0 to T1, change scores T0:T2 as the change in percentage from T0:T2.

Prediction of early response

The same two-step logistic regression model as described above was applied.

Prediction of remission

Considering the relatively small amount of remitted patients (34%) in our sample, the fact that in the group of 51 responders all 31 remitters are included, and that from a clinical perspective we consider response prediction to be a more urgent matter, we decided to only briefly report remission prediction here, the same two-step logistic regression model as described above was applied.

Prediction of overall symptom reduction

Even though the response definition of 50% symptom reduction is well established, this dichotomisation can be regarded as a rough simplification which undoubtedly implies loss of information. Thus, we decided that an important criterion for successful ECT treatment is not only response, but also overall symptom reduction, which we defined as change of MADRS total score in percentage from T0 to T2 (change score MADRS total score T0:T2). To predict overall symptom reduction, we used a two-step linear regression model, similar to the logistic regression model mentioned above. To control for gender, psychotic symptoms and number of ECT sessions these three variables were added in the first step, in the second step, MADRS single items and MADRS total score were each added to a distinct model individually.

ROC curves

Additionally, receiver operating characteristic (ROC) analyses were performed to estimate the optimal cut point for MADRS items and total score at baseline for response at the end of treatment.

All p values are Bonferroni-corrected where applicable, except for T0 as predictor of ECT response. All assumptions of the respective tests were satisfied or it was reasonable to conclude that the tests were robust against the respective violations, thus only parametric tests were used. Normality of distribution was tested with the Shapiro–Wilk test, equality of error variances was tested with Levene's test, Greenhouse–Geisser correction was applied were necessary. Cohen's f, Cohen's d, Phi coefficient (φ), or partial η^2 are reported as effect sizes.

Results

Clinical and demographic data

Our sample consisted of $n = 96$ psychiatric inpatients diagnosed with a depressive episode. Demographic and clinical characteristics for the overall sample, responders and non-responders are shown in Table 1. In our overall sample, 47% of the inpatients were diagnosed with psychiatric comorbidities, 67% received concomitant antidepressant medication. For detailed description of diagnosis type, psychiatric comorbidities and antidepressant medication, please see Tables 2 and 3, supplementary material.

Table 1 Demographic and clinical characteristics

Variable	Overall sample			Responders			Non-responders			*t*	*df*	*p*	*d*
	M	SD	*n*	*M*	SD	*n*	*M*	SD	*n*				
Age	52.60	14.79	96	54.67	15.15	51	50.27	14.18	45	−1.46	94	0.147	−0.30
Education (years)	14.05	2.85	88	13.84	2.83	44	14.29	2.93	42	0.72	84	0.476	0.16
Number of psychiatric hospitalizations[a]	3.98	3.33	94	4.18	4.15	50	3.75	2.02	44	−0.65	73	0.518	−0.15
Number of depressive episodes	7.24	9.59	46	9.04	11.36	28	4.44	4.97	18	−1.61	44	0.114	−0.49
Duration of current episode (months)[a]	9.61	9.44	46	8.53	9.44	27	11.13	9.66	19	0.92	44	0.364	0.28
Baseline (T0) MADRS total score	30.20	5.42	96	31.47	5.34	51	28.76	5.21	45	−2.52	94	0.014	−0.52
Mid-treatment (T1) MADRS total score	20.30	7.26	96	16.94	7.02	51	24.11	5.47	45	5.53	94	< 0.001	1.14
Treatment end (T2) MADRS total score	14.30	7.91	96	8.24	4.10	51	21.26	5.01	45	13.88	94	< 0.001	2.86
Change MADRS total score T0:T2	50.91	28.29	96	73.26	13.27	51	25.58	17.12	45	15.34	94	< 0.001	3.16
Number of ECT sessions	13.60	2.66	96	13.27	2.65	51	13.98	2.66	45	1.30	94	0.198	0.27
										χ^2		*p*	*φ*
Gender (F:M)	58:38		96	37:14		51	21:24		45	5.66	1	0.017	0.26
Psychotic Symptoms[b] (Y:N)	11:85		96	10:41		51	1:44		45	5.51	1	0.019	0.27
Suicide Attempt Lifetime[b] (Y:N)	30:41		71	17:23		50	13:18		31	0.00	1	0.962	0.01

[a]Assumption of equality of error variances violated (Levene's test: $p < 0.05$)

[b]Yates corrected. Change MADRS total score T0:T2 is defined as the change in percentage from T0 to T2. *d* = Cohen's *d*, *φ* = Phi coefficient

Change of depressive symptoms during the course of ECT

ANOVAs for repeated measures (baseline, mid-treatment and treatment end) were performed for the overall sample and within the responder and non-responder group. For the overall sample, all MADRS single items significantly decreased from baseline (T0) to treatment end (T2), Bonferroni-corrected $p < 0.01$. However, decreases within the responder and non-responder group differ, detailed results are shown in Figs. 1, 2 and 3.

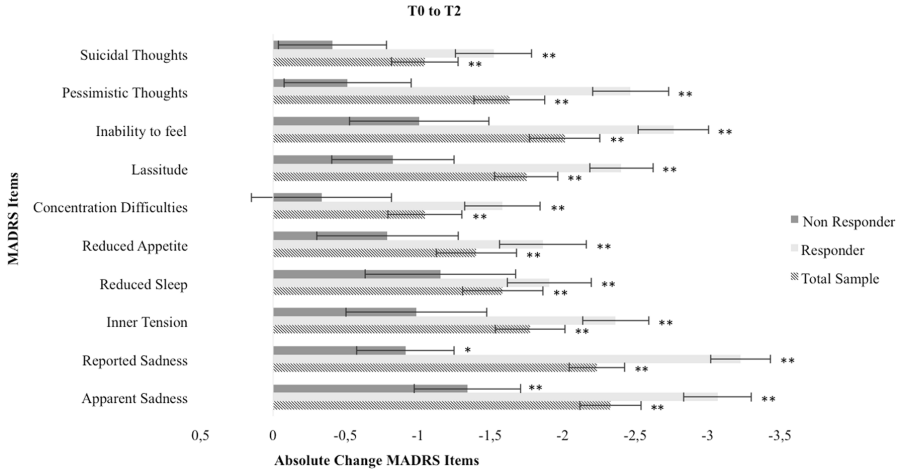

Fig. 1 Absolute change of MADRS items from baseline (T0) to treatment end (T2). * = Bonferroni-corrected $p < 0.05$, ** = Bonferroni-corrected $p < 0.01$

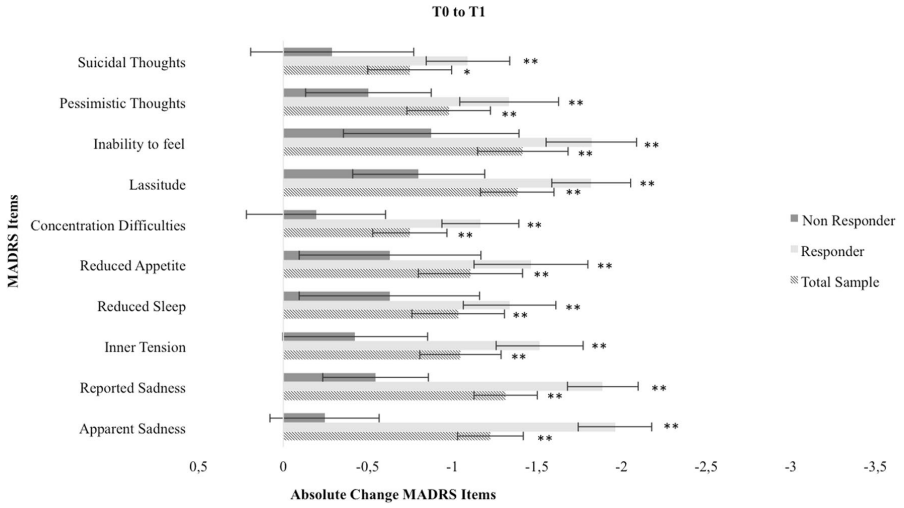

Fig. 2 Absolute change of MADRS items from baseline (T0) to mid-treatment (T1). *=Bonferroni-corrected $p<0.05$, **=Bonferroni-corrected $p<0.01$

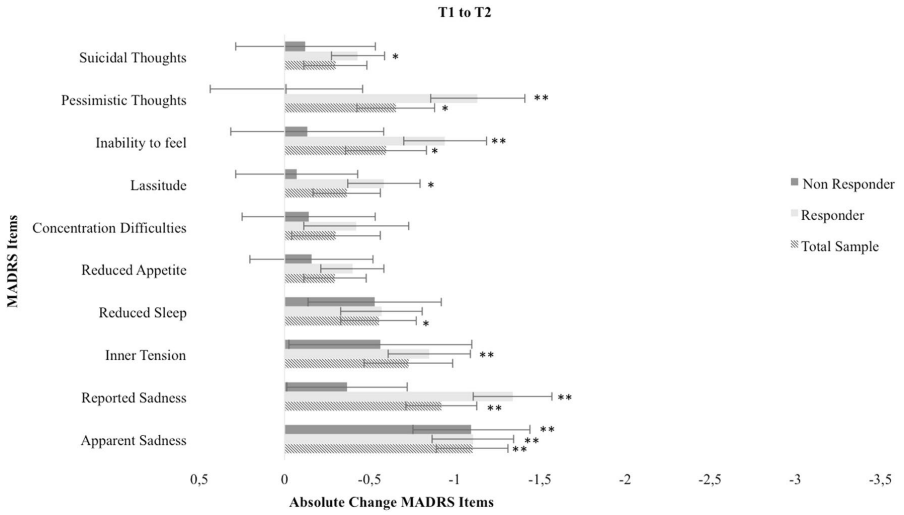

Fig. 3 Absolute change of MADRS items from mid-treatment (T1) to treatment end (T2). *=Bonferroni-corrected $p<0.05$, **=Bonferroni-corrected $p<0.01$

Prediction of response

Stepwise logistic regression showed that in the first step gender ($\beta=1.46$, Wald(1)=9.03, $p=0.003$, OR 4.32) and psychotic symptoms ($\beta=2.86$, Wald(1)=6.55, $p=0.010$, OR 17.40) were strongly associated with response, while number of ECT sessions did not contribute significantly to the model ($\beta=-0.13$, Wald(1)=2.37, $p=0.124$, OR 0.88), $\chi^2(3)=20.11$, $p<0.001$, $R^2=0.25$, $f=0.58$, 68% correct prediction.

In the second step, MADRS single items and MADRS total score were each added to a distinct model individually, thus each model consisted of gender, psychotic symptoms, number of ECT sessions, and one MADRS item (or MADRS total score).

Baseline (T0)

MADRS total score ($\beta = 0.62$, Wald(1) = 4.71, $p = 0.030$, OR 1.88), item 1 ($\beta = 0.65$, Wald(1) = 4.78, $p = 0.029$, OR 1.91), item 2 ($\beta = 4.41$, Wald(1) = 6.28, $p = 0.012$, OR 82.10) and item 8 ($\beta = 2.59$, Wald(1) = 4.67, $p = 0.031$, OR 13.27) were significantly associated with ECT response, the model including item 2 and gender*item 2 interaction showed the best fit: $\chi^2(5) = 31.60$, $p < 0.001$, $R^2 = 0.37$, $f = 0.77$, 70% correct prediction.

Mid-treatment (T1)

MADRS total score ($\beta = -0.17$, Wald(1) = 14.48, $p < 0.001$, OR 0.84), item 1 ($\beta = -0.68$, Wald(1) = 8.24, $p = 0.004$, OR 0.51) and item 2 ($\beta = -0.67$, Wald(1) = 8.83, $p = 0.003$, OR 0.51) were Bonferroni-corrected significant predictors, the model including item 2 showed the best fit: $\chi^2(4) = 30.64$, $p < 0.001$, $R^2 = 0.37$, $f = 0.77$, 78% correct prediction.

Change Scores T0:T1

Change scores for items 1, 2, 8, 10, and MADRS total score were Bonferroni-corrected significant predictors. The two models including item 2 ($\beta = -0.05$, Wald(1) = 16.54, $p < 0.001$, OR 0.95), $\chi^2(4) = 44.08$, $p < 0.001$, $R^2 = 0.49$, $f = 0.98$, 80% correct prediction and MADRS total score ($\beta = -0.07$, Wald(1) = 19.03, $p < 0.001$, OR 0.94), $\chi^2(4) = 50.56$, $p < 0.001$, $R^2 = 0.55$, $f = 1.11$, 80% correct prediction, showed the best fit.

Change Scores T0:T2

Change scores for items 1, 2, 5, 6, 8, 9, and 10 were Bonferroni-corrected significant predictors, the model including item 2 ($\beta = -0.12$, Wald(1) = 19.48, $p < 0.001$, OR 0.89) showed the best fit: $\chi^2(4) = 89.42$, $p < 0.001$, $R^2 = 0.81$, $f = 2.06$, 92% correct prediction.

Complete information for all regression analyses predicting response can be found in Table 4, supplementary material.

Prediction of early response

Stepwise logistic regression showed that in the first step psychotic symptoms ($\beta = 1.84$, Wald(1) = 6.66, $p = 0.010$, OR 6.29) were associated with early response, whereas no effect of gender was found ($\beta = 1.06$, Wald(1) = 3.32, $p = 0.069$, OR 2.88), $\chi^2(2) = 9.20$, $p = 0.010$, $R^2 = 0.14$, $f = 0.40$, 49% correct prediction.

In the second step, no effects of MADRS items predicting early response were found (all $p > 0.05$).

Complete information for all regression analyses predicting early response can be found in Table 5, supplementary material.

Prediction of remission

Stepwise logistic regression showed that in the first step gender ($\beta = 1.60$, Wald(1) = 8.57, $p = 0.003$, OR 4.97), psychotic symptoms ($\beta = 1.44$, Wald(1) = 3.96, $p = 0.047$, OR 4.24) and number of ECT sessions ($\beta = -0.23$, Wald(1) = 5.76, $p = 0.016$, OR 0.79) were strongly associated with remission, $\chi^2(3) = 17.48$, $p = 0.001$, $R^2 = 0.23$, $f = 0.55$, 69% correct prediction.

In the second step, MADRS single items and MADRS total score were each added to a distinct model individually, thus each model consisted of gender, psychotic symptoms, number of ECT sessions and one MADRS item (or MADRS total score).

Baseline (T0) MADRS total score and MADRS single items could not predict ECT remission. For mid-treatment (T1), Change Scores T0:T1 and Changes Scores T0:T2 as predictors, results were similar to prediction of response, the two models either including MADRS total score or item 2, respectively, showed the best fit. Complete information for all regression analyses predicting remission can be found in Table 6, supplementary material.

Prediction of overall symptom reduction

Stepwise linear regression showed that in the first step gender ($\beta = -0.25$, $t = -2.59$, $p = 0.011$) and psychotic symptoms ($\beta = -0.27$, $t = -2.76$, $p = 0.007$) significantly contributed to predicting overall symptom reduction, while number of ECT sessions did not significantly contribute to the prediction ($\beta = 0.16$, $t = 1.61$, $p = 0.111$), $F(3, 92) = 4.99$, $p = 0.003$, $R^2 = 0.11$, $f = 0.35$.

In the second step, MADRS single items and MADRS total score were each added to a distinct model individually, thus each model consisted of gender, psychotic symptoms, number of ECT sessions and one MADRS item (or MADRS total score).

Baseline (T0)

MADRS total score, item 1, 2, 8, and 9 significantly contributed to predicting overall symptom reduction, MADRS total score was a Bonferroni-corrected significant predictor

($\beta = -0.30$, $t = -3.25$, $p = 0.002$), $F(4, 91) = 6.77$, $p < .001$, $R^2 = 0.20$, $f = 0.50$.

Change Scores T0:T1

Change scores for MADRS total score and items 1, 2, 3, 6, 8, and 10 were Bonferroni-corrected significant predictors. The two models including item 2 ($\beta = 0.54$, $t = 6.17$, $p < 0.001$), $F(4, 91) = 14.77$, $p < .001$, $R^2 = 0.37$, $f = 0.77$ and MADRS total score ($\beta = 0.54$, $t = 6.18$, $p < 0.001$), $F(4, 91) = 14.80$, $p < .001$, $R^2 = 0.37$, $f = 0.77$ showed the best fit.

Change Scores T0:T2

Change scores from T0 to T2 for items 2, 4, 5, 7, 8, 9, and 10 were Bonferroni-corrected significant predictors. The model including item 2 ($\beta = 1.84$, $t = 6.08$, $p < 0.001$) and number of ECT sessions*item 2 interaction ($\beta = -1.04$, $t = -3.44$, $p = 0.001$) showed the best fit: $F(5, 90) = 55.81$, $p < 0.001$, $R^2 = 0.74$, $f = 1.69$.

Complete information for all regression analyses predicting overall symptom reduction can be found in Table 7, supplementary material.

ROC curves

As regression models including MADRS total score and item 2 showed the best fit, ROC curves were computed for these variables.

MADRS total Score baseline (T0)

Area under the curve was 0.64, $p = 0.017$, optimal cut point by Youden-index was MADRS total score = 32 (sensitivity 0.49, specificity 0.73).

MADRS item 2 baseline (T0)

Area under the curve was 0.65, $p = 0.013$, optimal cut point by Youden-index was item 2 = 5 (sensitivity 0.47, specificity 0.78).

Discussion

Main findings

In this retrospective naturalistic study, we examined 96 psychiatric inpatients diagnosed with a depressive episode who were treated with ECT at Charité—Universitätsmedizin Berlin. We studied change of depressive symptoms during the course of ECT and explored whether depressive symptoms and their change during the course of ECT could predict treatment outcomes. We analysed the routinely assessed MADRS from three time points: baseline (T0), mid-treatment (T1) and end of treatment (T2). For the first time, MADRS single items and their association with ECT outcomes were examined.

For all patients, MADRS total score significantly decreased from baseline to treatment end. Considering the single items, highest reductions were found for items 1 (apparent sadness), 2 (reported sadness) and 8 (inability to feel). Responders showed significant reductions for all single items. Significant reductions for single items within the non-responder group were only found for item 1 (apparent sadness) and 2 (reported sadness).

In our sample, 53% of the patients responded, women were more likely to respond to ECT than men, as were patients who experienced psychotic symptoms during their current episode, age was not associated with response. Responders showed higher depression scores at baseline and lower scores at the end of treatment.

MADRS total score, single items and their change during the course of ECT were useful predictors of ECT response, remission and overall symptom reduction. Single items, especially item 1 (apparent sadness), 2 (reported sadness) and 8 (inability to feel) showed predictive values comparable with or higher than that of MADRS total score. Strongest effects were found for item 2 with large effect sizes, e.g. the regression model including the change of item 2 (reported sadness) from baseline to treatment end showed 92% correct prediction of ECT response or non-response. It is important to note the direction of these effects: at baseline, higher depression scores are positively associated with ECT outcome, at mid-treatment lower depression scores are positively associated with ECT outcome. No effects for prediction of early response were found. ROC curves were computed to estimate the optimal cut point for MADRS total score and item 2 (reported sadness) at baseline for response at the end of treatment: MADRS total score = 32, item 2 = 5.

Comparison with findings from other studies

In accordance with previous findings, depression severity at baseline and a larger symptom reduction until mid-treatment was positively associated with ECT outcome [8, 16, 17]. Response rate in our sample was relatively low, this might be due to the relatively low percentage of patients with psychotic features and the exclusion of patients diagnosed with schizoaffective disorders in contrast to other studies such as Nordenskjöld et al. [18], as well as differences in electrode placement, dosage and utilized anaesthetic [6]. Even though women were not more severely depressed at baseline and did not report psychotic features more frequently, we found higher response rates for women in our sample, which has not been reported by previous studies [7]. Patients' age

ranged from 22 to 80 years, however, in accordance with some other studies, no association between age and ECT response was found [19, 20]. Contradicting previously reported effects of age were rather small and a possible "turning-point" in the mid-fifties is discussed, however, this remains an open question for further research [8].

Strongest predictive effects were found for item 2 (reported sadness), this can be linked to previous factor-analytic findings. Even though Okazaki et al. [9] and Spashett et al. [11] proposed two distinct predicting factors, consisting of different MADRS single item combinations (called "dysphoria" and "despondency", respectively), item 2 occurs to be the one item these two distinct factors have in common. ECT outcome was positively associated with a higher affective symptomatology at baseline (item 1 apparent sadness, item 2 reported sadness, item 8 inability to feel) and during the course of ECT these symptoms showed the strongest decrease. Partly, this can be associated with previous findings linking melancholic features of depression to ECT outcome [21]. However, findings remain inconsistent, especially as definitions and assessment of melancholic features vary. Melancholic features often imply a broad variety of differing symptoms, not only affective but also somatic symptoms such as agitation, loss of appetite and sleeping disturbances [7, 8]. We found no evidence for strong predictive values of somatic symptoms for ECT outcome. Our findings underline the proposed limited usefulness of melancholic features as predictor of ECT outcome [22] and support a more symptom-based approach of depression research as proposed by Fried and Nesse [23] corresponding to the heterogeneity of depressive disorders [24].

Implications

Our findings imply a strong antidepressant effect of ECT, especially in decreasing affective symptomatology. More severely depressed patients seem to benefit more, especially patients reporting pronounced affective symptoms measured with MADRS at baseline. We propose MADRS total score = 32 and item 2 = 5 at baseline as potential cut-off points determined with ROC curves. After future validation and in combination with other aspects such as age, psychotic symptoms, psychomotor symptoms and the physicians' general assessment, these cut-off points might pose a useful addition to clinical decision-making. MADRS single items and their change during the course of ECT (especially item 2 reported sadness) can provide a simple, reliable, cost- and time-effective contribution to predicting ECT outcome. While patients classified as non-responders also show significant decrease in affective symptoms, responders and non-responders differ particularly concerning the reduction of pessimistic thoughts. Thus, patients who did not sufficiently benefit from ECT might particularly benefit from additional interventions such as cognitive behavioural therapy after ECT. Unfortunately, the limited research examining cognitive behavioural interventions after ECT, while promising, until now mainly focused on maintaining ECT response, disregarding those other patients in need [14, 25, 26].

Limitations

No follow-up data were available, thus no assumptions about long-term predictive values of MADRS single items regarding maintained response or potential relapse can be made. Due to the naturalistic setting, potential confounding of depressive symptoms with psychiatric medication or comorbidities cannot be ruled out. Future studies with a constant concomitant psychotropic medication might also be enlightening to determine specific effects of ECT. Considering the heterogeneity of depression scales [27], analysing predictive values of depressive symptoms assessed with a different depression scale such as the Hamilton Depression Rating Scale (HRSD) [28] or self-report measures such as the BDI-II (Beck Depression Inventory) [29] seems advisable for robust conclusions. Taking into account the importance of other demographic and clinical predictors such as age and psychomotor symptoms [30], future studies with larger samples might examine more comprehensive regression models including all these factors. This might help to gain a better understanding of their respective, potentially interacting, effects [31].

Conclusions

In this naturalistic retrospective study, we examined 96 patients diagnosed with a depressive episode in accordance with DSM-5 who were treated with ECT at Charité—Universitätsmedizin Berlin. We studied change of depressive symptoms assessed with the MADRS during the course of ECT and tested, whether these could predict ECT outcome. Strongest reduction during the course of ECT and strongest predictive effects were found for affective symptoms, especially item 2 (reported sadness). Future longitudinal studies employing a variety of clinical interviews and self-report measures for depression severity are needed to validate our findings.

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Author contributions LB made substantial contributions to the conception and design of the work, the acquisition, analysis and interpretation of data and wrote the manuscript. CH made substantial contributions to the analysis and interpretation of data. AS and AD made substantial contributions to the acquisition and interpretation of data. AH made substantial contributions to the acquisition of data. SA made substantial

contributions to the conception and design of the study and acquisition of data. MG made substantial contributions to the analysis and interpretation of data. MB made substantial contributions to conception and design of the study and has been involved in drafting the manuscript. SG made substantial contributions to conception and design of the study as well as analysis and interpretation of data and co-wrote the paper. All authors revised the work critically for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials The data that support the findings of this study are available from the corresponding author, LB, upon reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest The author declares that they have no competing interest.

Ethics approval The retrospective study design was approved by the institutional review board of the Charité, performed in accordance with the Declaration of Helsinki.

Consent to participate Patients' informed consent was obtained.

Consent for publication Not applicable.

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X Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

XI Vollständige Publikationsliste

Carstens, L., Hartling, C., Aust, S., Domke, A. K., Stippl, A., Spies, J., ... & Grimm, S. EffECTively treating depression: A pilot study examining manualized group CBT as follow-up treatment after ECT. *Frontiers in Psychology*, 3662.

Carstens, L., Hartling, C., Stippl, A., Domke, A. K., Herrera-Mendelez, A. L., Aust, S., ... & Grimm, S. (2021). A symptom-based approach in predicting ECT outcome in depressed patients employing MADRS single items. European Archives of Psychiatry and Clinical Neuroscience, 1-10.

Basso, L.*, Bönke, L.*, Aust, S., Gärtner, M., Heuser-Collier, I., Otte, C., ... & Grimm, S. (2020). Antidepressant and neurocognitive effects of serial ketamine administration versus ECT in depressed patients. *Journal of Psychiatric Research, 123*, 1-8.
***** Both authors contributed equally to the manuscript.

Bönke L., Hartling C., Stippl A., Domke, A., Aust, S., Gärtner M., Grimm, S., & Bajbouj M. (2020, July 4–7). *EffECTively treating depression: Feasibility and effectiveness of a manualized group CBT as continuation treatment after acute ECT – a naturalistic study [*Conference poster*].* 28th European Congress of Psychiatry, Madrid, Spain.

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