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Research paper

Negative cognitive schema modification as mediator of symptom improvement after electroconvulsive therapy in major depressive disorder

Dominique S. Scheepens [a,*], Jeroen A. van Waarde [b], Freek ten Doesschate [a,b], Mirjam Westra [c], Marijn C.W. Kroes [e], Aart H. Schene [d,e,†], Robert A. Schoevers [c], Damiaan Denys [a,f], Henricus G. Ruhé [d,e], Guido A. van Wingen [a,f]

[a] Amsterdam UMC, University of Amsterdam, Department of Psychiatry, Amsterdam Neuroscience, Amsterdam, the Netherlands
[b] Rijnstate Hospital, Department of Psychiatry, Arnhem, the Netherlands
[c] University of Groningen, University Medical Center Groningen, Department of Psychiatry, Groningen, the Netherlands
[d] Radboud University Nijmegen Medical Center, Department of Psychiatry, Nijmegen, the Netherlands
[e] Department of Cognitive Neuroscience, Donders Institute for Brain Cognition and Behaviour, Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands
[f] Amsterdam Brain & Cognition, University of Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is a potent option for treatment-resistant major depressive disorder (MDD). Cognitive models of depression posit that negative cognitions and underlying all-or-nothing negative schemas contribute to and perpetuate depressed mood. This study investigates whether ECT can modify negative schemas, potentially via memory reactivation, and whether such changes are related to MDD symptom improvement.

Method: Seventy-two patients were randomized to either an emotional memory reactivation electroconvulsive therapy (EMR-ECT) or control memory reactivation electroconvulsive therapy (CMR-ECT) intervention prior to ECT-sessions in a randomized controlled trail. Emotional memories associated with patients' depression were reactivated before ECT-sessions. At baseline and after the ECT-course, negative schemas and depression severity were assessed using the Dysfunctional Attitude Scale (DAS) and Hamilton Depression Rating Scale HDRS. Mediation analyses were used to examine whether the effects of ECT on HDRS-scores were mediated by changes in DAS-scores or vice versa.

Results: Post-ECT DAS-scores were significantly lower compared to baseline. Post-ECT, the mean HDRS-score of the whole sample (15.10 ± 8.65 [SD]; n = 59) was lower compared to baseline (24.83 ± 5.91 [SD]). Multiple regression analysis showed no significant influence of memory reactivation on schema improvement. Path analysis showed that depression improvement was mediated by improvement of negative cognitive schemas.

Conclusion: ECT is associated with improvement of negative schemas, which appears to mediate the improvement of depressive symptoms. An emotional memory intervention aimed to modify negative schemas showed no additional effect.

1. Introduction

Major depressive disorder (MDD) is characterized by low mood, a reduced ability to experience pleasure, several physiological symptoms, suicidality and frequently very negative cognitions about the self and the future (Beck and Clark, 1988). MDD comprises a large proportion of health burden worldwide due to lifelong trajectories of recurring episodes, increasing severity and progressive treatment resistance (Marcus et al., 2012). In daily practice, psychotherapy and pharmacotherapy are effective treatments for most patients, but these also regularly fail as first-line treatments for MDD. At least one third of depressed patients do not recover even after four successive steps of pharmacological and/or psychotherapeutic treatments, and one out of five MDD-patients meet the criteria for 'chronic depression' (i.e., MDD duration

* Corresponding author.
E-mail addresses: d.s.scheepens@amsterdamumc.nl (D.S. Scheepens), g.a.vanwingen@amsterdamumc.nl (G.A. van Wingen).
† In memoriam.

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longer than two years) (Rush et al., 2006). Chronic depression and treatment resistant depression (TRD) are not interchangeable since depression longer than 2 years does not necessarily have to be therapy resistant. However, both conditions are indications for ECT. Electroconvulsive therapy (ECT) is highly effective for these treatment-resistant patients, but approximately 50% of patients still do not respond sufficiently (Heijnen et al., 2010), and relapse rates after successful ECT are typically about 40–50% at 6 months despite vigorous continuation therapy (Sackeim et al., 2001).

Cognitive-behavioral models of MDD suggest that the presence of negative life events and one's perception of, or reaction to, those events may impact the development, maintenance and recurrence of depressive symptoms (Beck and Clark, 1988). These cognitive models posit that negative cognitions and underlying 'all-or-nothing' negative schemas contribute to and perpetuate depressed mood (Blazer, 2003). Such negative schemas are unobserved constructs which are measured as negative cognitions, often using the Dysfunctional Attitude Scale (DAS). A maladaptive negative schema represents a pervasive self-defeating or dysfunctional theme or pattern of memories, emotions and physical sensations, which develops during childhood or adolescence and elaborates throughout one's lifetime, that often has the form of a belief about the self or the world. Exemplary negative schemas are: "I will always fail", "I am not worth it" and "It is always my fault" (Beck and Clark, 1988). These negative schemas are presumed risk factors and latent in the nondepressed or remitted phase, but can be become in an active state triggered by life events, stress or sad mood. Negative schemas thus represent both an underlying trait with additional state-related changes. According to the classical cognitive theory, change in this negative content of dysfunctional beliefs precedes symptom reduction (Beck, 1979). Psychotherapeutic and pharmacological treatments can reduce these negative schemas (Cristea et al., 2015; Dozois et al., 2009; Simons et al., 1984). Several studies imply that negative cognitive schema modification is fundamental for depressive symptom improvement, regardless of how it is achieved (Dobson and Dozois, 2010). Though others suggest that negative cognitive schema modification is not essential for symptom improvement but a mere consequence of successful antidepressive treatment (Simons et al., 1984). It is thus debated whether schemas and depressive symptoms change alongside or whether schema modification precedes depressive symptom improvement (Beck and Dozois, 2011; Lorenzo-Luaces et al., 2015).

We recently reported the results from a randomized controlled trial (RCT) which aimed to improve the outcome of ECT by reactivating patients' underlying negative cognitive schemas just prior to ECT-sessions (Scheepens et al., 2020). This hypothesis was based on a previous study, which showed that reactivation of a recently learned emotionally aversive story just prior to ECT can disrupt memory (Kroes et al., 2014). Unfortunately, our RCT failed to show increased efficacy of emotional memory reactivation before ECT (EMR-ECT) compared to a control condition (control memory reactivation before ECT; CMR-ECT) on remission and relapse rates within six months, as assessed with the primary outcome measure the Hamilton Depression Rating Scale (HDRS) (Scheepens et al., 2020). Although additional improvement of ECT was not shown, the EMR-ECT interventions or the ECT-course itself may have altered the patients' underlying negative schemas. Moreover, lack of change in underlying negative schemas by ECT may explain why not all patients benefit this treatment, as well as the substantial relapse rates after successful ECT. Because, to our knowledge, the influence of ECT on negative schemas is not known, further study of change in negative schemas after the ECT-course may provide more insight.

Therefore, in this study we investigated secondary outcome measures from the RCT: 1) whether dysfunctional attitudes, as measured with the DAS (i.e., the patient's negative schemas), alter by the ECT-course, 2) whether post-ECT DAS-scores differ between patients treated with EMR-ECT and CMR-ECT, and 3) whether changes in negative schemas relate to changes in HDRS-scores after the ECT-course.

2. Methods

2.1. Study sites and participants

This multicenter study (see further details in Scheepens et al., 2020) was conducted at the Departments of Psychiatry of three hospitals in the Netherlands from 2014 to 2018. Participants, referred to one of these hospitals were in- and outpatient patients, aged 18–70 years. They could be included if they were primarily diagnosed with MDD, classified according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision DSM-IV-TR), and had a clinical indication for ECT (i.e., a history of insufficient response to several previous antidepressive treatments; the primary indication for ECT in the Netherlands (van Waarde et al., 2013)). Patients were willing and able to understand, to participate and to comply with the study requirements. Exclusion criteria were the presence of: 1) psychotic features (preventing the possibility that psychotic features might worsen because of the cognitive intervention itself); 2) bipolar disorder; 3) schizophrenia or other primarily psychotic disorders; 4) substance abuse; and 5) cognitive disorders. We excluded patients with psychotic features to prevent the possibility that psychotic features might worsen because of the cognitive intervention itself. We also excluded bipolar patients, because this patient group may show pre-ECT differences in cognitive functioning compared to MDD patients (Hill et al., 2009) (Hill et al., 2009). Psychiatric diagnoses were classified according to DSM-IV-TR-criteria by using the Mini Neuropsychiatric Interview (Sheehan et al., 1998) and no subtypes were described. The study protocol was approved by the Medical Ethical Committee of the Academic Medical Center (Amsterdam, The Netherlands) and registered in the Dutch Trial Register (NL4289). All patients provided written informed-consent and all procedures were carried out in accordance to the Declaration of Helsinki. The study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for RCTs. The trial protocol is available in Supplement 1.

2.2. Intervention and control conditions

Patients were randomized 1:1 to EMR-ECT or CMR-ECT. In patients receiving EMR-ECT, an experienced clinical psychologist identified autobiographical memories associated with maladaptive schemas, within two weeks before the ECT-course started. Recurring maladaptive schema thoughts were identified using the Automatic Thoughts Questionnaire-Revised (ATQ-R) (Raes and Hermans, 2015). Subsequently, patients selected six maladaptive thoughts most central to their current depressive episode. These thoughts were related to autobiographical episodes and these were written down in short narratives, as vivid as possible (i.e., events as detailed as possible, feelings, thoughts, sensory modalities, other people involvement, et cetera) and reactivated according to a standardize protocol (Scheepens et al., 2020). In the EMR-ECT-group, approximately 10 min prior to the ECT-stimulus, a research assistant reactivated an autobiographical episode. This intervention lasted approximately 3 min with reading one of the narratives, slowly and carefully paced, which provided the patient time to recall the maladaptive thoughts in detail. Only one autobiographical memory was reactivated per ECT-session, alternating between the three selected narratives. In the CMR-group, an identical procedure was followed using neutral information (e.g., about the importance of sleep, physical exercise and substance use in mental health).

2.3. Psychometric instruments

At baseline and within 3 till 14 days after finishing the ECT-course several psychometric instruments were scored.

Hamilton Depression Rating Scale. The HDRS is an observer-rated instrument, consisting of 17 items leading to a maximum score of 52

(Hamilton, 1960). After the last ECT-session, remission and response were defined as HDRS-score ≤ 7 and ≥ 50% reduction in HDRS-score compared to baseline, respectively.

Dysfunctional Attitude Scale. Negative cognitive schemas were measured using the DAS (Weissman, 1979). The DAS consists of 40 items and identifies dysfunctional attitudes on a 7-point Likert-scale, ranging from 'completely disagree' (score of 1) to 'completely agree' (score of 7), and has good psychometric properties (α = 0.86). Having more dysfunctional attitudes resulted in higher DAS-scores.

Dutch Measure of quantification of Treatment Resistant Depression (DM-TRD). The DM-TRD consists of 11 items leading to a maximum score of 27. The DM-TRD has good psychometric properties and predictive validity (van Dijk et al., 2019) (Peeters et al., 2016). At baseline, the DM-TRD was scored to quantify treatment resistance.

Dutch Adult Reading Test (DART). The DART was scored at baseline as proxy for verbal intelligence (intelligence quotient; IQ). The DART is the Dutch version of the National Adult Reading Test. Both tests consist of a series of words with an irregular pronunciation. The score on the test is a predictor of premorbid intelligence of brain damaged patients.

2.4. Electroconvulsive therapy

ECT-sessions were performed according to Dutch guidelines (Van den Broek et al., 2010): anesthesia with etomidate; muscle paralysis with succinylcholine; applying appropriate 100% oxygenation; using constant-current (0.9 A), brief-pulse (0.5 milliseconds) stimuli (Thymatron IV ECT-device; Somatics Incorporation, Lake Bluff, Illinois, USA). For the specified study protocol see Supplement 1. Lithium carbonate and benzodiazepines were tapered off before starting the ECT-course (due to its possible negative effect during an ECT course) and other concomitant medications were kept constant. The ECT-sessions were administered twice a week. Most patients started with right unilateral (RUL) electrode placement, except when clinicians decided to start with bifrontotemporal (BL) placement immediately. An empirical, age-adjusted, titration method was used to estimate the seizure threshold (ST) and the personalized dose was set at 6 and 2.5 times ST for RUL and BL ECT, respectively. In case of six ineffective RUL-sessions, patients switched to BL-sessions. After reaching remission, or when no further improvement was seen within two weeks, the ECT-course was terminated. The total number of administered ECT-sessions was registered for each patient.

2.5. Statistical analysis

Data analyses were performed from February to June 2020. Data of both groups (EMR-ECT and CMR-ECT) were analyzed for baseline characteristics using two-sample *t*-tests, χ^2 – tests, or Mann-Whitney *U* tests as appropriate. Changes in DAS-scores, HDRS-scores, and MMSE-scores between baseline and post-ECT were analyzed using paired t-tests. To analyze whether post-ECT DAS-scores differed between EMR-ECT and CMR-ECT, multiple regression analyses were conducted with corrections for baseline DAS-score, sex and age. Correlation analyses were performed to test for associations between baseline and post-ECT HDRS- and DAS-scores with Bonferroni correction for multiple comparisons. Simple mediation models were applied to test for causal relations amongst these variables, by using the PROCESS (v3.4) plugin for SPSS with 5000 bootstraps, and correcting for treatment group, sex and age. All analyses were conducted using SPSS 25 (IBM, Armonk, NY) and were two-sided with p ≤ 0.05 denoting statistical significance.

3. Results

Seventy-two patients were pseudo-randomly assigned to treatment groups in the study. Six patients dropped-out (for more details see (Scheepens et al., 2020)) and DAS-scores of seven patients were missing. The final sample consisted of 59 patients of which 30 received EMR-ECT and 29 CMR-ECT. At baseline, no significant differences were found between the groups regarding age, sex, IQ, level of treatment resistance (i.e., DM-TRD-score), HDRS-score, DAS-score, MMSE-scores, final electrode placing or total of ECT-sessions (see Table 1). Post-ECT, the mean HDRS-score of the whole sample (15.10 ± 8.65 [SD]; n = 59) was lower compared to baseline (24.83 ± 5.91 [SD]; t (58) = 7.6; p < 0.001, Cohen's d_z = 1.0). After the ECT-course, out of 59 patients, 25 (42.4%) patients fulfilled criteria for response and 15 (25.4%) for remission. There was no significant change in MMSE-scores (t (52) = −0.1; p = 0.89, Cohen's d_z = −0.02).

3.1. Changes in DAS-score after ECT and effect of experimental intervention

The mean post-ECT DAS-score (98.73 ± 32.35 [SD]; n = 59) was lower than the mean baseline DAS-score (113.83 ± 34.99 [SD]; t (58) = 3.9; p < 0.001, Cohen's d_z = 0.51). Multiple regression analysis showed no significant effect of EMR-ECT on post-ECT DAS-scores, corrected for age, sex and baseline DAS-scores (EMR-ECT versus CMR-ECT; β = −0.04; p = 0.72, semipartial r^2 = −0.04).

Table 1
Patient and treatment characteristics for emotional memory reactivation electroconvulsive therapy (EMR-ECT) and neutral memory reactivation electroconvulsive therapy (CMR-ECT); responders to ECT showed ≥50% decrease of symptom severity on the Hamilton Depression Rating Scale (HDRS) and remitters showed to score ≤ 7 on the HRSD after the ECT-course.

	Total sample (N = 59)*	EMR-ECT (N = 30)	CMR-ECT (N = 29)	p-Value
Patient characteristics				
Age, mean (±SD)	49.03 [±12.25]	49.80 [±11.56]	48.24 [±13.09]	0.63[a]
Female, % (N)	59.3 (35)	60.0 (18)	58.6 (17)	0.91[b]
IQ, mean (±SD)[d]	97.78 [±14.84]	97.00 [±14.5]	98.62 [±15.41]	0.69[a]
DM-TRD, mean (±SD)	14.98 [±2,94]	15.05 [±3.10]	14.91 [±2.83]	0.86[a]
Baseline ECT HDRS, mean (±SD)	24.83 [±5.91]	25.69 [±5.68]	23.95 [±6.11]	0.26[a]
Post-ECT HDRS, mean (±SD)	15.10 [±8.65]	15.74 [±8.74]	15.02 [±8.70]	0.95[a]
Baseline ECT MMSE, mean (±SD)[e]	28.66 [±1.81]	28.87 [±1.36]	28.43 [±2.20]	0.36[a]
Post-ECT MMSE, mean (±SD)[f]	28.65 [±1.92]	28.93 [±1.17]	28.37 [±2.45]	0.29[a]
Baseline ECT DAS, mean (±SD)	113.83 [±34.99]	114.88 [±39.22]	112.76 [±30.66]	0.82[a]
Post-ECT DAS, mean (±SD)	98.73 [±32.35]	97.93 [±32.43]	99.55 [±33.01]	0.85[a]
Response rate, % (N)	42.4 (25)	40.0 (12)	44.8 (13)	0.71[b]
Remission rate, % (N)	25.4 (15)	23.3 (7)	27.6 (8)	0.71[b]
Treatment characteristics				
Final electrode placing is RUL, % (N)	67.8 (40)	63.3 (19)	72.4 (21)	0.46[b]
Total ECT-sessions, mean (±SD)[e]	14.21 [±6.96]	15.14 [± 7.30]	13.28 [±6.61]	0.40[c]

SD = standard deviation; IQ = intelligence coefficient; DM-TRD = Dutch Measure of quantification of Treatment Resistance; DAS = dysfunctional attitude scale; RUL = right unilateral electrode placement; MMSE = Mini-Mental State Examination.

[a] Two-sample t-test.
[b] Chi-squared test.
[c] Mann-Whitney U test.
[d] N = 54.
[e] N = 58.
[f] N = 54.

3.2. Relationship between changes in cognitive schemas and depression severity

Correlation analyses revealed positive correlations between baseline and post-ECT DAS-scores ($r = 0.61$; $p < 0.01$, corrected), baseline DAS-scores and baseline HDRS-scores ($r = 0.39$; $p < 0.05$, corrected), baseline DAS-scores and post-ECT HDRS-scores ($r = 0.38$; $p < 0.05$, corrected) and post-ECT DAS-scores and post-ECT HDRS-scores ($r = 0.41$; $p < 0.01$, corrected) (see Table 2). To clarify whether improvement of cognitive schemas could be explained by improvements in depression severity, or vice versa, we conducted two path analyses that were corrected for sex, age and treatment group (EMR-ECT versus CMR-ECT). In the first mediation model, we tested whether the ECT-related reduction in DAS-scores was mediated by improved post-ECT HDRS-scores. This model failed to detect a significant indirect effect of baseline DAS-scores on post-ECT DAS-scores through post-ECT HDRS-scores. In contrast, the second model revealed a significant indirect effect of baseline DAS-scores on post-ECT HDRS-scores through post-ECT DAS-scores (see Fig. 1). To ascertain this effect was related to the improvement in HDRS-scores, we repeated the analysis with the change in HDRS-scores as dependent variable, which also appeared significant ($\beta = 0.07$, 95% CI [0.0079, 0.1338], $p < 0.05$). Together, this indicated that mood improvement was mediated by improvement of negative cognitive schemas.

4. Discussion

In this prospective study, we provide evidence suggesting that the negative cognitive schemas can be altered by an ECT-course. Our results suggest that these benefits include change in cognitive schemas which precede mood-inducing effects. Path analyses indicate that the reduction of negative schemas mediate the improvement of depressive symptomatology. An additional emotional memory reactivation intervention prior to each ECT-session did not enhance the reduction of negative cognitive schemas. To our knowledge, this is the first study to explore the clinical effect of ECT on negative schemas in patients suffering from MDD.

4.1. Cognitive change pivotal for symptom change after ECT?

Despite many attempts to understand the mechanisms by which antidepressive treatments achieve their effects, consensus has not emerged regarding the dynamics of therapeutic procedures, psychological and or biological mechanisms, and symptom improvement (Lorenzo-Luaces et al., 2015). ECT is believed to achieve a therapeutic alteration of brain activity by the use of electrical currents that pass through the brain and produce a seizure. This seizure activity transduce into clinical benefits through different hypothesized mechanisms in the brain (Jiang et al., 2017). Our results suggest that these benefits include effective change in cognitive schemas which precede mood inducing effects.

In specific treatments (e.g., cognitive behavioral therapy [CBT] (Harmer and Cowen, 2013)), change of negative schemas is a direct focus (Cristea et al., 2015). Actually, cognitive change may be essential for overall clinical improvement, since non-responders after antidepressive treatment fail to manifest cognitive change (Simons et al., 1984). In our current study, the mediation model suggests that cognitive change precedes improvement of depressive symptoms. Therefore, our results support the hypothesis that cognitive change may be crucial for symptom change, regardless of how it is achieved (Lorenzo-Luaces et al., 2015). Though in the causal chain ECT most likely first affects brain function, as ECT consists of the induction of seizures that eventually give rise to clinical benefits. Our results suggest that ECT may first affect the neural mechanisms that underlie cognitive schemas before normalizing the neural mechanisms related to negative mood.

Table 2
Correlations of Dysfunctional Attitude Scale (DAS) and Hamilton Depression Rating Scale (HDRS), measured before (baseline) and after (post) a course of electroconvulsive therapy (ECT).

	Post-ECT DAS	Baseline-ECT HDRS	Post-ECT HDRS
Baseline-ECT DAS	0.61**	0.39*	0.38*
Post-ECT DAS	–	0.11	0.41**
Baseline-ECT HDRS	–	–	0.13

* $p < 0.05$, Bonferroni corrected.
** $p < 0.01$, Bonferroni corrected.

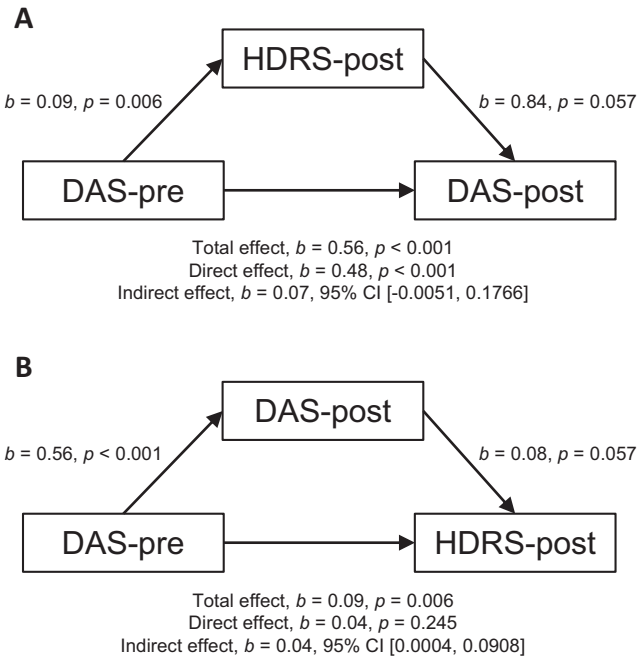

Fig. 1. Mediation models testing the interrelatedness between improvements in mood and cognitive schemas. A) No significant indirect effect of baseline Dysfunctional Attitude Scale (DAS-) scores on post-ECT DAS-scores through post-ECT Hamilton Depression Rating Scale (HDRS-)scores. B) A significant indirect effect of baseline DAS-scores on post-ECT HDRS-scores through post-ECT DAS-scores.

4.2. Is cognitive change a working mechanism of ECT?

Although ECT is effective for patients with severe MDD, half of patients do not benefit (Heijnen et al., 2010) and relapse rates are high with percentages varying depending on using prophylaxis (Sackeim et al., 2001). Therefore, in our RCT it was tested whether an experimental intervention (EMR-ECT) could increase and speed-up response, but this proved not be the case (Scheepens et al., 2020). In our sample, 42% and 25% of the patients reached criteria for 'response' and 'remission' after the ECT-course, respectively, which is comparable to the response rate of other studies (Prudic et al., 2004). The putative working mechanisms of ECT still remain unclear, though our study suggests – for the first time - that ECT may have the ability to remediate negative schemas in patients. It is assumed that verbal treatments - like CBT - changes the patients' thinking which mediates the antidepressive effects (Dobson and Dozois, 2010). Our results suggest that a non-cognitive and non-verbal neurostimulation treatment (i.c., ECT) as well may act on change of negative thinking and – therewith – mediates the antidepressive effects.

4.3. Cognitive change essential to prevent relapse after ECT?

After a successful ECT-course, relapse rates for depression are substantial, especially when no prophylaxis is used (Sackeim et al., 2001). It is still unknown whether change of cognitive schemas after ECT may decrease the patients' risk to relapse. After treatment with CBT, patients showed less cognitive reactivity to mood challenges in comparison to pharmacotherapy; even after years, the patients' reaction to a mood induction procedure was predictive of depressive relapse, which highlights the preventive effects of change of negative schemas (Segal et al., 1999). Also, accumulating evidence was found that cognitive interventions following remission can be useful in preventing relapse/recurrence in patients with recurrent depression (Bockting et al., 2005). The ability of ECT to change negative schemas may be less profound than of CBT, and this difference may be associated with higher relapse rates in ECT compared to CBT (Segal et al., 1999). Future studies should determine whether cognitive reactivity to the patients' mood condition changes after ECT, and whether this phenomenon is related to depression relapse at follow-up. Hopefully, with increased insights more sufficient relapse prevention after ECT can be developed.

4.4. Limitations

This study had several limitations. Despite that ECT-patients did not receive specific additional psychotherapeutic interventions, non-specific factors during the ECT-course like depression treatment programs (focusing on activation or other supportive components) might have influenced the post-ECT DAS-scores. Pharmacotherapy was kept constant during the ECT-course and was therefore not expected to have influenced the DAS-scores, although medication might have augmented the effect of ECT on the DAS-scores. Importantly, the study did not include a waitlist control group. We can therefore ascertain whether changes in DAS-scores could have occurred spontaneously or reflect repeated testing. But as ECT patients are severely ill and often suicidal, a waitlist control group could be considered unethical.

The two treatment groups in this RCT showed no difference in outcome data regarding the DAS-scores and HDRS-scores. It was unfortunately impossible to ascertain whether the emotional memory reactivation actually activated or have influenced the underlying negative schemas in the EMR-ECT-group. We did not measure the change in autobiographical memory before and after ECT-course, because this would have interfered with the objective of the study to weaken negative autobiographical memories. However, the research assistants typically noticed emotional reactions when the patients listened to the retrieval of their personal negative experiences. Although these emotional responses suggested that negative schemas were activated, this appeared not sufficient to influence the impact of ECT on DAS-scores.

It remains unclear whether the changes in negative schemas are specific these cognitions or are a consequence of a generic change in cognition. The results showed no significant change in MSSE-scores, suggesting that there were no large changes in cognitive functioning. However, the MSSE is a very broad instrument that can only detect cognitive impairment. Whether more subtle changes in cognition after ECT that have been reported in the literature such as autobiographical memory impairments are related to the changes in negative schemas remains unknown (Verwijk et al., 2012).

In this RCT, the response rate was lower than expected. However, the DM-TRD scores were considerably higher than for other treatment-resistant MDD groups (Peeters et al., 2016; van Dijk et al., 2019). Also, we excluded patients with a higher chance of successful ECT, such as age $>$ 70 years and presence of psychotic features (Peeters et al., 2016), which may have contributed to the lower response and remission rates. Besides patients with psychotic features, we also excluded patients with a bipolar depression. The exclusion of patients with psychotic symptoms and bipolar depression precludes to the generalization of our results to the entire ECT population. However, whether this restricted patient selection also might have decreased the chance of alteration of negative schemas, remained unknown. Additionally, we did not evaluate the presence of personality disorders, because often we were not able to diagnose personality disorders due to the active depressive episode. Negative cognitive schemas, though, may also be interpreted as trait factor attributed to underlying personality disorders and current MDD may amplify such negative schemas (Dozois et al., 2009; Kunst et al., 2020). It may therefore be possible that changes in negative schemas may have been different in patients with compared to without comorbid personality disorders.

Our results suggest that change in cognitive schemas may lead to change in depressive symptoms, rather than the reverse. However, our conclusion about this causal pathway is based on observational data and mediation analysis, which can be used to *test* casual relationships but can actually never *proof* causality (Pearl, 2010). Future studies may provide further evidence for a causal relation by measuring DAS-scores on multiple occasions during the ECT-course and not only at baseline and after the last ECT-session.

5. Conclusion

A course of ECT improved negative cognitive schemas in severely depressed, treatment-resistant patients. The modification of negative schemas appeared to mediate the improvement of depressive symptomatology. Our results support the notion that cognitive change is important for the reduction of depressive symptoms, and possibly regardless of how this is achieved.

Declaration of competing interest

All authors report no conflict of interest.

Acknowledgements

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Role of funder/sponsor

The sponsor had no role in the design and conduct of the study; in the collection, management, analysis, and interpretation of the data; in the preparation, review, or approval of the manuscript; nor in the decision to submit the manuscript for publication.

Access to data and data analysis

DSS and GAvW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Non-author contributions

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