Chapter 6

Two times a week right unilateral electroconvulsive therapy in depressed patients: effects on retrograde autobiographical memory and executive function

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Abstract

Background: To evaluate the changes in retrograde amnesia for (auto)biographical memory and executive functioning of depressed patients treated with right unilateral electroconvulsive therapy (ECT).

Methods: Retrograde amnesia and executive functioning were monitored before ECT and one week, 3 and 6 months after the last ECT session. The group of patients receiving ECT at any time during the follow up was compared to the group of patients not receiving any ECT after the index episode. Level of cognitive performances was compared with normative data of a representative normal population.

Results: One week post ECT biographical memory (public events) improved, autobiographical memory did not change and executive functioning declined. Compared to the pre-ECT condition, cognitive performance improved but the performance of the patients still receiving ECT did not change during 6 months follow up. Compared to a representative normal population, cognitive performances one week after ECT were borderline to impaired. After six months, cognitive performance improved to low average levels whereas performance in the group still receiving ECT remained borderline to impaired.

Conclusion: Six months after finishing ECT, (auto)biographical memory and executive functioning improved, but compared to a representative normal population, cognitive performance of remitted patients was still below average level.
Introduction

Cognitive disturbances are among the most frequently reported side effects of electroconvulsive therapy (ECT) (1-6). Especially retrograde amnesia for (auto)biographical events is frequently and furiously debated. Retrograde amnesia is characterized by loss of information or inability to recall information stored before the ECT course. Patients, families and some clinicians experience the loss of autobiographical memories as a serious and harmful effect of an otherwise safe and clinically effective treatment for severe depression (7).

There are conflicting reports about the extent, persistence and course of retrograde amnesia for (auto)biographical events after ECT (1, 6). There are several explanations for these equivocal findings. Firstly, only a minority of the studies take the pre-depression cognitive status into account (1). Most of the research compares cognitive performance just before ECT, when the depression is most severe, with performance after ECT when mood and, as a consequence, cognitive performances have often improved considerably. Secondly, there is a lack of studies which use normative data of either healthy volunteers or depressed patients not treated with ECT (8, 9). And thirdly, follow up studies are scarce. Lastly, there is a lack of studies using reliable assessment instruments.

The extent of cognitive side effects is influenced by techniques used in the administration of ECT (1). Bitemporal ECT is reported to result in more pronounced cognitive side effects than right unilateral (RUL) ECT (10-12). Contradictory results have been found in studies exploring the level of retrograde amnesia by using ultrabrief pulse (UBP) ECT (<0.5 ms) versus brief pulse (BP) ECT (0.5-2.0 ms) (13-15).

In the present study, retrograde amnesia for (auto)biographical events of patients with a major depressive disorder - all treated with RUL ECT - was assessed before the start of ECT (baseline), and one week, 3 and 6 months after the last ECT session. We also monitored executive functioning, in clinical practice a very important cognitive domain for daily living. As ECT affects both temporal and frontal lobes, it seems logical that its effects are not limited to amnesia, but involves both memory and non-memory functions such as executive functioning (16).

Cognitive changes after index ECT depend largely on whether or not a patient is still receiving ECT or restarts a new course. We compared the group of patients receiving (RUL or bilateral (BL)) ECT at any time during follow up to the group of patients not receiving ECT during follow up. Most follow up studies only concentrate on the group without ECT during follow up (17, 18) or do not clearly describe whether patients who received ECT during follow up are included in their follow up analysis or not (14, 19-23).
Aims of the study
We have studied to what extent retrograde amnesia and executive functioning have changed from baseline to one week after the last ECT. Whether or not we could detect differences in cognitive change between the ECT group and non-ECT group during follow up. What the level of cognitive performance of the participants treated with ECT is. All compared with the normative data of a representative sample.

Methods

Study design and data source
From April 2007 to March 2011 we conducted a prospective, double blind, randomized multicenter trial evaluating the efficacy and cognitive side effects of BP and UBP RUL ECT. At three and six months after the randomized phase, naturalistic follow up assessments were performed. Patients were recruited from three ECT centers: Parnassia (The Hague) and GGZ Delfland (Delft) in The Netherlands and the University Psychiatric Center KU Leuven, campus Kortenberg (Kortenberg) in Belgium. The institutional review boards (IRBs) of these hospitals approved the study, conducted according to the Declaration of Helsinki. The study was registered in the Netherlands National Trial register number NTR1304. Data collection was done by or under supervision of the authors by extensively trained physicians, nurses, neuropsychologists and research assistants.

Study population
All in- and outpatients of 18 years and older suffering from a major depressive disorder or bipolar depression (with or without psychosis) according to DSM-IV criteria (24) who were referred for ECT treatment, were screened for inclusion in a randomized controlled trial (15). Patients who received both pre- and post-ECT cognitive assessments were included in the present study. The diagnosis of depression was confirmed by an experienced psychiatrist (HPS, KK, PS, FB) using the Mini-International Neuropsychiatric Interview (MINI) (25, 26). Patients with a history of schizophrenia, schizoaffective disorder or who were diagnosed with dementia were excluded. All eligible patients were asked to participate and baseline assessments were done after providing informed consent.
Treatment
Patients were randomized to treatment with either BP (pulse width of 1.0 ms) or UBP (pulse width of 0.3 ms) RUL ECT for the maximum of the double blind study period of six weeks (15). All patients received ECT twice weekly according to the guidelines of the National Psychiatric Association (27). In accordance with routine clinical practice, psychotropics and somatic medications were kept on a stable dosage during ECT. Lithium was kept at plasma levels of 0.40 – 0.80 mmol/L. Three days prior to ECT Benzodiazepines were tapered to a maximum of 10 mg diazepam equivalents. Etomidate (± 0.25 mg/kg) and succinylcholine (1-2 mg/kg) were used as anesthetic and muscle relaxant, respectively. Seizures were induced with a square-wave BP or UBP bidirectional stimulus delivered by a constant current device (spECTrum 5000 Q MECTA inc., Tualatin, Oregon, USA) and a maximum stimulus level of 1152 mC using RUL d’Elia electrode placement (28). Seizure threshold was determined using empirical dose titration. The first and successive treatment sessions were then continued with a stimulus eight times the seizure threshold. Patients were treated until they achieved sustained remission, defined as a Montgomery Åsberg Depression Rating Scale (MADRS)(29) score < 10 at two consecutive weekly assessments. The ECT was switched to bilateral electrode placement when the clinical condition worsened or after 12 unilateral treatments without sufficient effect, despite adequate seizures. After finishing the ECT-course either continuation-ECT or prophylactic drug treatment was started.

Assessments
Demographic features
At baseline socio-demographic and clinical data were collected: age, gender, marital status, in/out patient status, age of onset, duration of the index major depressive episode, psychosis, polarity, number of previous admissions, history of ECT treatment and medication. Subject’s level of education was defined according to the scoring system of (30) (range 1-7; 1=less than 6 years education, 2=6 years, 3=7-8 years, 4=9 years, 5=10-14 years, 6=more than 14 years, 7=University).

Evaluation of cognitive outcome
Apart from the extensive clinical evaluation, described elsewhere (15), four cognitive assessments were obtained: a week before the first ECT (pre-ECT), one week after finishing the treatment course, and after a follow up of three and six months. In the follow up evaluation, two groups of patients were compared: the group of patients
receiving ECT at any time in the follow up (RUL or bilateral (BL)) and the group of patients not receiving any ECT during follow up. Cognitive assessment was performed by a neuropsychologist or supervised trainee neuropsychologist, both blind to the treatment condition.

A reliable assessment of retrograde amnesia would require that all memories are recorded before and after treatment, since this is not feasible, retrograde amnesia can only be assessed partially and in retrospect by testing the patient’s knowledge of public and personal events. A validated test, Kopelman’s Autobiographical Memory Interview (AMI) (31, 32), was used to assess retrograde amnesia for autobiographical memory (personal events). This interview is a reliable and standardized test to assess personal remote memory. The AMI measures personal semantic memories and autobiographical incidents from different time periods: childhood (ages 0–18), early adulthood (ages 19–30), and recent (within the past 5 years). The personal-semantic questions quiz facts from the past life, relating to childhood (e.g. names of schools or teachers), early adult life (e.g. name of first employer, date and place of wedding), and more recent facts (e.g. holidays, journeys, and previous hospitalizations). Scores of 0, ½, 1, 2 or 3 were awarded according to criteria from the manual. Each period had a maximum score of 21 points. In relation to the autobiographical incident questions subjects were asked to relate incidents that occurred during each of the three time periods and to give temporal and spatial contextual information for each incident described. Each incident was scored out of a possible score of 3, based on the descriptive richness and specificity in time and place of the response. The maximum score per time period was 9.

The Amsterdam Media Questionnaire (AMQ) (32) was used to assess retrograde amnesia for biographical memory (impersonal events). This test is a public events questionnaire consisting of 40 open-ended questions about news events that occurred during the 1970s, 1980s, 1990s and 2000s (ten questions for each decade). One point was awarded for correct answers, zero points for incorrect answers.

Two different verbal fluency tests (Word fluency - animals & professions and Letter fluency - "D", "A", "T") (33) were used to monitor executive functioning. In both tests subjects generated as many words as possible from a category (semantic and phonemic) in 60 seconds. When suffering from executive function deficits, subjects may perform better on Word fluency tests but show lesser performance on Letter fluency tests since this task requires organizing concepts in a novel way.

For the personal and impersonal biographical memory evaluation and evaluation of executive functioning, the total scores of the AMI, AMQ and the two verbal fluency
tests were used as the primary outcome measures. The subscores of the AMI were used to evaluate the temporal gradient of RA. Normative data of the AMI, Word fluency and Letter fluency have been used to compare the level of performance between the depressed patients treated with ECT with the performance of a representative normal population, based on age and education.

**Statistical analysis**

The demographic and clinical characteristics of the patients that dropped out for cognitive follow up assessment were compared with the group of patients that completed the follow up cognitive assessment. Nonparticipants tend to be more seriously ill compared to participants and their exclusion may introduce bias. Next, we compared the group of patients receiving ECT during follow up with the group of patients who did not receive ECT during follow up for possible differences in demographic and clinical characteristics. We used two-tailed t tests, Mann-Whitney U tests, Pearson's chi-square tests or Fisher's Exact tests where appropriate.

To examine change in performance in cognitive function one week post-ECT and during follow up, repeated measures analysis of covariance (ANCOVA) were performed. Age, education, baseline MADRS, MADRS change and the number of ECT sessions patients received were entered as covariates, to examine the extent to which changes in cognitive functioning were related to these variables. The mean raw scores of each test were calculated together with the standard deviation and range of performance to describe the cognitive changes during ECT.

In order to quantify clinical relevance, we calculated the effect sizes (Cohen's d) of the one week post-ECT and follow up cognitive outcomes. A negative effect size indicates that the cognitive performance after ECT was worse compared to pre-ECT. Effect sizes are interpreted as suggested by Cohen (34): 0.2 – 0.5 is considered a small effect, 0.5 – 0.8 a medium effect and ≥ 0.8 a large effect.

Results were considered statistically significant at a p-value lower than 0.05. Adjustment for multiple comparisons with Bonferroni was done. We used IBM SPSS Statistics for Windows, version 20 for all statistical analyses.

To explore the level of the cognitive performance of the depressed patients treated with ECT, cognitive outcome pre-ECT, post-ECT and at follow up, were compared with normative data (defined as z-scores) of a representative normal population. Z-scores are interpreted as: 0 to -0.67 = average; -0.68 to -1.33 = low average; -1.34 to -2.00 = borderline; > -2.00 = impaired.
Chapter 6

Results

Clinical and demographical characteristics
Of the 116 randomized patients, 87 completed the acute treatment phase and, of these, 76 received both pre- and one week post-ECT cognitive assessments (Figure 1). Their clinical and treatment characteristics are shown in Table 1. Of the 76 patients entering the naturalistic follow up phase, 31 patients (40.1%) were lost to long term follow up and did not complete cognitive assessment. In this dropout group 13 patients were lost to follow up because they had to travel to long and/or were unable to complete the tests. There was no difference in demographic and clinical characteristics between the dropout group and the group that completed the follow up cognitive assessments (data not shown), except for their cognitive scores pre-ECT. The dropout group had a statistically significant higher mean score on the AMI incidents ($p=0.02$) and AMQ ($p=0.04$).

In the follow up group ($n=45$) 24 patients received ECT (12 BL, 12 RUL) during follow up and 21 did not. The group that received ECT during follow up had a longer duration of the current depressive episode, a higher MADRS score after index ECT and follow up and received more ECT sessions during the RCT, than the group who had no ECT during follow up (Table 1).

Cognitive assessments

Cognitive effects one week post-ECT
Improvement of cognitive functioning one week after the index ECT compared with baseline was statistically significant for the AMQ (retrograde amnesia for biographical memory - public events) (Table 2). A statistically significant decrease was found for Letterfluency (executive functioning). All effect sizes were small. No change was found on the AMI (retrograde amnesia for biographical memory - personal events) and Wordfluency. The number of ECT's during the RCT was significantly associated with the change in score for the AMI incidents ($r=-.96, p=0.006; 95\%: CI -1.61 to -0.30$) and the change in the AMI total score ($r=-2.47, p<0.001; 95\%: CI -3.65 to -1.30$). A higher number of treatment sessions thus seems to predict a lower score on retrograde amnesia for autobiographical memory (personal events).
Figure 1 Participant flow randomized controlled trial and follow up

Intention-to-treat (ITT) sample started with right unilateral ECT (n = 116)

ECT completed with pre-ECT cognitive assessment (n = 87)

Dropped out (n = 11)
- Switch to bilateral: n = 1
- Assessment problems: n = 1
- Medical reason/complication: n = 1
- Withdrawal consent: n = 5
- Reason unknown: n = 3

Dropped out (n = 29)
- Switch to bilateral: n = 7
- Medical reason/complication: n = 6
- Confusion/delirium: n = 6
- Violation of protocol: n = 4
- ECT refusal: n = 2
- Withdrawal consent: n = 1
- Assessment problems: n = 1
- Attempted suicide: n = 1
- Switch to 3x weekly: n = 1
- Mania: n = 1

1 week post-ECT cognitive assessment (n = 76)

Dropped out (n = 31)
- Medical reason/complication: n = 2
- Withdrawal consent: n = 8
- Reason unknown: n = 7
- Suicide: n = 1
- Logistic problems: n = 13

3 months & 6 months post-ECT cognitive assessment (n = 45)

ECT in follow up: n = 24
No ECT in follow up: n = 21
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>post-ECT group (n=76)</th>
<th>post-ECT follow up group</th>
<th>post-ECT follow up group (n=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (sd; range)</td>
<td>60.6 (15.5; 26-90)</td>
<td>67.6 (12.0; 45-82)</td>
<td>59.5 (16.2; 26-90)</td>
<td>0.07</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>51 (67.1)</td>
<td>16 (76.2)</td>
<td>18 (75)</td>
<td>1.00</td>
</tr>
<tr>
<td>Education level, median (interquartile range)</td>
<td>4 (2)</td>
<td>5 (2)</td>
<td>5 (2)</td>
<td>0.93</td>
</tr>
<tr>
<td>Previous depression, n (%)</td>
<td>56 (73.7)</td>
<td>18 (85.7)</td>
<td>16 (66.7)</td>
<td>0.18</td>
</tr>
<tr>
<td>Current episode (months), mean (sd; range)</td>
<td>23.9 (48.1; 1-324)</td>
<td>8.0 (7.9; 1-36)</td>
<td>23.8 (26.4; 1-120)</td>
<td>0.009</td>
</tr>
<tr>
<td>Unipolar, n (%)</td>
<td>64 (84.2)</td>
<td>18 (85.7)</td>
<td>20 (83.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Psychotic, n (%)</td>
<td>28 (36.8)</td>
<td>10 (47.6)</td>
<td>8 (33.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>Early onset depression (&lt;55), n (%)</td>
<td>54 (71.1)</td>
<td>12 (57.1)</td>
<td>18 (75)</td>
<td>0.23</td>
</tr>
<tr>
<td>MADRS mean (sd; range)</td>
<td>29.96 (9.0; 5-51)</td>
<td>28.9 (10.1; 5-51)</td>
<td>31.9 (7.5; 18-47)</td>
<td>0.25</td>
</tr>
<tr>
<td>Baseline</td>
<td>11.2 (10.8; 0-39)</td>
<td>11.0 (1.3; 0-4)</td>
<td>17.6 (12.0; 0-36)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Follow up 3 months</td>
<td>1.8 (5.1; 0-21)</td>
<td>1.8 (5.1; 0-21)</td>
<td>15.3 (15.3; 0-40)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Follow up 6 months</td>
<td>22 (28.9)</td>
<td>10 (47.6)</td>
<td>5 (20.8)</td>
<td>0.11</td>
</tr>
<tr>
<td>History of ECT, n (%)</td>
<td>34 (44.7)</td>
<td>11 (52.4)</td>
<td>8 (33.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>Brief pulse, n (%)</td>
<td>9.6 (2.8; 4-12)</td>
<td>7.8 (2.8; 4-12)</td>
<td>10.5 (2.4; 4-12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Number of index ECT treatments, mean (sd; range)</td>
<td>43 (56.6)</td>
<td>19 (90.5)</td>
<td>9 (37.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Remission after index ECT (MADRS &lt; 10), n (%)</td>
<td>43 (56.6)</td>
<td>19 (90.5)</td>
<td>9 (37.5)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

MADRS = Montgomery Åsberg Depression Rating Scale; Two-tailed t test, Chi-square or Mann-Whitney U test, where appropriate

**Follow up: cognitive effects three and six months post-ECT**

The course of the follow up cognitive trajectory differed between the patients that received ECT and those that did not. The group that received ECT at any time during follow up showed no significant cognitive change after three and six months post-ECT compared to pre-ECT performance (Table 3; Figure 2). The group that did not receive ECT during follow up showed an improvement in cognitive functioning three and six months post-ECT compared to pre-ECT performance (Table 3). These improvements were statistically significant for the AMI total score, AMI incidents, AMQ and Letterfluency (Figure 2). Significant improvement for Wordfluency Animals and Wordfluency Profession was found only at three months post-ECT (Figure 2). In both follow up groups, no association was found between the cognitive performances and age, total amount of ECT’s (index-period) and MADRS score.
Table 2: Cognitive assessment scores pre- and one week post-ECT¹ (n=76)

<table>
<thead>
<tr>
<th>Assessment</th>
<th>n</th>
<th>Pre-ECT</th>
<th>Post-ECT</th>
<th>p-value</th>
<th>Cohen's d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (sd)</td>
<td>Range</td>
<td>Mean (sd)</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth</td>
<td>74</td>
<td>15.2 (4.9)</td>
<td>3 – 21</td>
<td>15.9 (4.4)</td>
<td>1.5 – 21</td>
</tr>
<tr>
<td>Adulthood</td>
<td>74</td>
<td>16.8 (3.9)</td>
<td>4.5 – 22</td>
<td>17.5 (3.7)</td>
<td>4.5 – 21</td>
</tr>
<tr>
<td>Recently</td>
<td>74</td>
<td>16.7 (3.6)</td>
<td>7 – 23</td>
<td>16.3 (4.0)</td>
<td>4.5 – 21</td>
</tr>
<tr>
<td>Incidents</td>
<td>74</td>
<td>10.9 (7.7)</td>
<td>0 – 27</td>
<td>10.4 (6.8)</td>
<td>0 – 24</td>
</tr>
<tr>
<td>Total score</td>
<td>74</td>
<td>59.8 (16.5)</td>
<td>19.5 – 90</td>
<td>59.4 (16.0)</td>
<td>15 – 85</td>
</tr>
<tr>
<td>AMQ</td>
<td>69</td>
<td>20.3 (9.9)</td>
<td>1 – 41</td>
<td>21.5 (9.7)</td>
<td>0 – 40</td>
</tr>
<tr>
<td>Word fluency</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>70</td>
<td>14.8 (5.8)</td>
<td>3 – 33</td>
<td>13.7 (5.6)</td>
<td>4 – 32</td>
</tr>
<tr>
<td>Profession</td>
<td>70</td>
<td>10.8 (5.2)</td>
<td>0 – 27</td>
<td>10.2 (4.5)</td>
<td>0 – 28</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>71</td>
<td>27.1 (14.4)</td>
<td>2 – 65</td>
<td>23.7 (13.7)</td>
<td>2 – 65</td>
</tr>
</tbody>
</table>

AMI = Autobiographical Memory Interview; AMQ = Amsterdam Media Questionnaire

All repeated measures are adjusted for age, education, baseline MADRS, MADRS change and total amount ECTs as covariates

¹ Adjustment for multiple comparisons: Bonferroni

**Comparison with norm groups**

**Pre-ECT**

When we compared the cognitive performance in the groups before ECT started with available norms, the results showed that the performance levels for both follow up groups varied from borderline to impaired for all cognitive functions, except for Letter fluency (Figure 2). There was a significant difference between the two groups on this test. The group without ECT during follow up had a borderline performance before ECT started, whereas the group with ECT had an average performance.

**One week post ECT**

One week after the ECT course the level of cognitive performance had not changed compared with norms to pre-ECT performance. The performance levels for both groups after ECT were still in the range from borderline to impaired on all cognitive functions, except for the performance on Letter fluency. The performance of the group with ECT during follow up was lowered from average to borderline.
Figure 2: All cognitive assessments: mean-scores and Z-scores pre-ECT, one week post-ECT, 3 months post-ECT and 6 months post-ECT (n=45)
RUL ECT: effects on retrograde autobiographical memory and executive function
Table 3  Cognitive assessment scores post-ECT, follow up 3 and 6 months (n=45), with and without ECT in follow up¹

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Non-ECT group (n=21)</th>
<th>ECT group (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-ECT (T0)</td>
<td>3mth post-ECT²</td>
</tr>
<tr>
<td>AMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Youth</td>
<td>Mean (sd)</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td>13.6 (5.1)</td>
<td>4.5 – 21</td>
</tr>
<tr>
<td></td>
<td>Adulthood</td>
<td></td>
</tr>
<tr>
<td></td>
<td>17.4 (3.5)</td>
<td>8 – 22</td>
</tr>
<tr>
<td></td>
<td>Recently</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.9 (3.8)</td>
<td>8.5 – 20</td>
</tr>
<tr>
<td></td>
<td>Incidents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.7 (6.2)</td>
<td>1 – 21</td>
</tr>
<tr>
<td>Total score</td>
<td>55.1 (15.5)</td>
<td>28.5 – 84</td>
</tr>
<tr>
<td>AMQ</td>
<td>16.7 (8.8)</td>
<td>2 – 37</td>
</tr>
<tr>
<td>Word fluency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animals</td>
<td>13.5 (4.2)</td>
<td>8 – 21</td>
</tr>
<tr>
<td>Profession</td>
<td>9.6 (5.2)</td>
<td>0 – 19</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>22.7 (8.4)</td>
<td>5 – 60</td>
</tr>
</tbody>
</table>

AMI = Autobiographical Memory Interview; AMQ = Amsterdam Media Questionnaire

All repeated measures are adjusted for age, education, baseline MADRS, MADRS change and total amount ECTs as covariates

¹ Adjustment for multiple comparisons: Bonferroni
² Cognitive assessments three months post-ECT
³ Cognitive assessments six months post-ECT
Follow up three and six months
After three and six months follow up, the performance levels of the group without ECT during follow up improved to low average levels whereas the performance levels of the group with ECT during follow up did not change, varying from borderline to impaired levels except for Letterfluency (low average level).

Discussion
To the best of our knowledge, this is the first study comparing the cognitive trajectory over the course of six months between a group patients receiving ECT at any time during follow up and a group of patients without ECT during follow up. The use of normative data to compare the level of performance of the depressed patients treated with ECT with the performance of a representative normal population is limited in the field of ECT related cognition research.

Retrograde autobiographical memory
In most studies retrograde autobiographical memory performance was found to deteriorate after an ECT-course (9, 13, 14, 17, 21, 35, 36). Consistent with other studies (18, 19, 37), our results did not show any decrease one week post-ECT relative to pre-ECT baseline. During follow up (3 and 6 months) we demonstrated significant improvement in retrograde autobiographical memory compared to pre-ECT performance. These positive changes over time after finishing the ECT course were also found in most other follow up studies (9, 17, 18, 35, 36) but not in the studies of Sackeim et al. (14, 21). No improvement or decrease within 6 months post-ECT follow up was found.

Treatment parameters and differences influencing retrograde autobiographical memory
Treatment parameters influence retrograde autobiographical memory strongly (10-12). The number of ECT treatments is one of the treatment parameters associated with the retrograde autobiographical memory performance (21). With a higher number of treatments it might be expected to find more deterioration. In the study of Sienaert et al. (18) however, no decline after ECT was found after a mean number of 12.3 treatments whereas McCall (35) described a decline after a mean of 5.8 treatments. This does suggest that a higher number of ECT treatments does not account for deterioration per se.
The treatment schedule is another treatment parameter relating to the retrograde autobiographical memory performance. Studies that treat patients 3 times a week find decreasing autobiographical memory performance (9, 13, 14, 21, 35) with one exception in the study by Mayur et al. (19).

Another methodological explanation for the contrasting results in the literature is the use of different instruments to assess autobiographical memory. Studies that found a decrease in performance used questionnaires and interviews that evaluated the percentage consistency of autobiographical memory at a certain time based on baseline performance (e.g. the Colombia University Autobiographical Memory Interview (CUAMI) (38). Instruments based on measuring consistency cannot capture any improvement in autobiographical memory. Therefore follow up performance is always inferior to baseline performance (39). Studies that found improvement or no decrease, like ours, used another assessment instrument, (e.g. Autobiographical Memory Interview of Kopelman et al. (Kopelman AMI) (31)). This instrument is not based on percentage consistency of memory-scores, implying that also improvement in autobiographical memory performance can be assessed over time. At this moment, the use of the CUAMI and the Kopelman AMI is hotly debated (39-42). In our opinion these two instruments measure two important but different concepts and should be both assessed. The percentage consistency of autobiographical memory as well as the opportunity to improve in autobiographical memory performance is clinically valuable.

**Executive functioning**

In our study we used Letter fluency as a reflection of executive functioning. Our finding that executive functioning significantly declined after the ECT course is consistent with literature (4, 13, 37). After six months, the performance of the patients that did not receive ECT significantly improved to pre-ECT level. On this basis we conclude that executive functioning seems sensitive to ECT effects; however more research is necessary to underline our findings.

**Differences between non-ECT and ECT group during follow-up**

During follow up, the cognitive trajectories differed between the non-ECT and ECT groups. The cognitive performances of the non-ECT group improved and the performances of the ECT group did not change compared to pre-ECT level. These differences were not attributable to differences in age, total amount of ECT’s (index-
period) or MADRS score. Differences in the long-term cognitive outcome were related to whether or not the patients received ECT during follow up supporting the conclusion that ECT has an impact on cognitive performance. On top of this it also shows that cognitive improvement begins when ECT has been stopped. In other words, it is not a result of remitted depression only. Our data corroborate the findings of a study with a comparable design (9). They showed that at 2-month follow up, the recall of retrograde autobiographical memory of their non-ECT follow up group did improve, contrary to the group who received a second ECT course during follow up. Other follow up studies only included the group without ECT during follow up (17, 18) or did not state clearly in their analysis whether patients received ECT during follow up or included ECT as a covariate in their follow up analysis (14, 19, 21-23).

**Comparison with norm groups**
The improvement of the non-ECT group during follow up does not automatically imply a return to premorbid levels. In our study, normative data showed that the cognitive performance varied from borderline to impaired before ECT started. As expected, compared to a representative normal population, cognitive performance of depressed patients is poor. In both follow up groups (non-ECT and ECT) no change in cognitive performance was shown directly after the ECT course was ended. Despite remission of the depression, performances on most cognitive assessments were still borderline to impaired. After six months the performance in the non-ECT group improved to low average levels whereas the performance in the ECT group remained unchanged. However, cognitive functioning in the remitted non-ECT group still showed poorer performance compared to a representative normal population. Thus we must be careful in the interpretation of this improvement. Significant improvement of cognitive performances in remitted patients must not lead to the conclusion that cognitive performance after ECT is normalised. Persistent cognitive dysfunction in remitted depression is not uncommon. Studies in drug-free euthymic patients after remission of their depression showed residual executive dysfunction in young, middle-aged, and elderly people (43-45). This should be taken into account when interpreting changes in cognitive performance after ECT, even when improving.

**Relationship between cognitive improvement, depression and ECT**
In our study, the magnitude of clinical improvement of depression was not associated with improvement of cognitive performance at any time point during ECT, in line with other ECT studies (9, 37, 46, 47). Our results showed that cognitive performance
started to improve after the end of the ECT course when patients had already achieved remission. Improvement of autobiographical and executive functions and remission of depression seem to be independent phenomena. This might be surprising because depressed patients commonly have impairments in different cognitive domains (48, 49) and mixed-age population studies concluded that neurocognitive performance is positively correlated with improvement in depression (50, 51). Bayless et al. (52) suggest that not severity but the negative symptoms of a depressive episode are related to cognitive dysfunction.

Limitations
A naturalistic follow up has its limitations, since there are factors like social support, medical comorbidity, and psychotherapy which can influence for example risk of relapse after ECT and therefore the trajectory of cognitive performance. We did not control for other confounders as e.g. psychotropic medication. Recruitment rates in cognitive testing are discussed as a major limitation in ECT studies, since patients with the highest risk for cognitive side effects are not able to participate, limiting the capacity to generalize findings (47). In our study the recruitment rate of 87% was high (76/87), but may still limit the generalizability of our findings to the group of patients (13%) who were not able to perform cognitive assessments before or after ECT treatment. Another limitation is that 40.1% of the recruited patients were lost to follow up cognitive assessment. Their exclusion might bias our results. Our lost participants did not differ in demographic, clinical and cognitive characteristics. The finding that our non-ECT group during follow up seems to have improved is probably not representative for all patients individually. Recently Dybedal (37) demonstrated that, although a mean score of a group can demonstrate stable or improved performance, 40% of the patients showed a significant decline in neuropsychological functioning, at an individual level. Looking into cognitive impairment of individual patients was beyond the scope of this study.

In conclusion six months after finishing ECT, (auto)biographical memory and executive functioning of severely depressed patients were improved, but compared to a representative normal population, cognitive performance of remitted patients is still below average level.
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