Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: cognitive side-effects

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Abstract

Objective: The cognitive side-effects of bifrontal (BF) and right unilateral (UL) ultra-brief pulse (0.3 ms) electroconvulsive therapy (ECT) were compared, in the treatment of patients with a depressive episode.

Method: Neuropsychological functioning in patients with a medication refractory depressive episode, that were treated with a course of BF ultra-brief ECT at 1.5 times seizure threshold (ST) or UL ultra-brief ECT at 6 times ST, by random assignment, was assessed before treatment, and 1 and 6 weeks after the treatment course, by a blinded rater.

Results: Of the 64 patients that were included, 32 (50%) received BF ECT, and 32 (50%) received UL ECT, by random assignment. Neuropsychological testing 1 and 6 weeks after treatment was performed by 30 (93.75%) and 19 (59.37%) patients, respectively, in the BF-group and 29 (90.62%) and 20 (62.50%), respectively, in the UL-group. There was no deterioration in any of the neuropsychological measures. Patients rated their memory as clearly improved after treatment. There were no significant differences between the patients given BF ECT and those given UL ECT.

Conclusions: Ultra-brief ECT, used either in combination with a UL electrode position and a stimulus of at least 6 times ST, or a BF electrode position with a stimulus of 1.5 times ST, are effective antidepressant techniques, that do not have a deleterious effect on cognitive function.

Keywords: Electroconvulsive therapy, Cognitive function, Depressive disorders, Pulse width, Bifrontal ECT, Unilateral ECT

1. Introduction

Electroconvulsive therapy (ECT) is a powerful acute treatment for severe and resistant depression (UK ECT Review Group, 2003). Patients rate the cognitive side-effects of ECT as the most troublesome (Rose et al., 2003), and the notion that cognitive side-effects are an inevitable consequence of this treatment, hampers its widespread acceptance in the general public and the psychiatric community. The extent of cognitive side-effects has been shown to be dependent upon techniques used in the administration of ECT (Fraser et al., 2008). There has been general agreement that with bitemporal ECT, cognitive side-effects will be most pronounced (Prudic, 2008; Sackeim et al., 1993). With right unilateral (UL) ECT, these side-effects can be diminished, while maintaining efficacy, if a stimulus dose of at least 6 times the initial seizure threshold (ST) is used (Sackeim et al., 2000). Bifrontal (BF) ECT has been adopted by clinicians striving to optimize the efficacy/side effect profile of ECT (Loo et al., 2006), in view of the fact that it exhibits an equal antidepressant efficacy than bitemporal ECT, and has few cognitive side-effects, although this technique is less well studied (Crowley et al., 2008). A major step in the reduction of cognitive side-effects, was the use of a square-wave brief pulse stimulus, thereby reducing the excess energy of sine wave ECT. What the optimal pulse width is, however,
remains unresolved. Standard pulse width ECT (i.e. 0.5–2 milliseconds (ms)) still delivers excess energy, since the shortest duration of an electrical stimulus necessary to stimulate a neuron at minimum strength required for a threshold response is 0.1 to 0.2 ms (Prudic, 2008). It has been suggested that the use of a stimulus with an ultra-brief pulse width (i.e. 0.3 ms) is substantially more efficient in seizure induction, as compared to a stimulus with a standard pulse width, thus needing less energy (Sackeim et al., 2008, 2009a; Loo et al., 2007). This might further minimize cognitive side-effects (Kim et al., 2007; Sackeim, 2004; Sackeim et al., 2001; Prudic, 2008). Early research showed less retrograde amnesia with ultra-brief pulse ECT as compared to brief pulse or sine wave ECT (Cronholm and Ottosson, 1963a; Valentine et al., 1964). Pisvej et al. (1998) used ultra-brief (0.2–0.4 ms) UL ECT in patients with schizophrenia and reported similar cognitive results to those obtained with standard pulse width ECT. In a non-randomized study, 30 patients were treated with ultra-brief UL ECT, and compared retrospectively with 30 patients who received standard pulse UL ECT. After 6 treatments, ultra-brief ECT incurred less cognitive side-effects than standard pulse UL ECT (Loo et al., 2007). In a recent randomized study with 90 patients, Sackeim et al. (2008) have shown that ultra-brief ECT markedly reduces the acute, short-term and long-term cognitive side-effects. Patients receiving ultra-brief UL ECT did not show a deterioration in any of the neuropsychological measures tested. Moreover, the pulse width proved to be of greater importance than the electrode position used.

This study compares the cognitive effects of BF ECT and UL ECT in patients with a major depressive episode, using an ultra-brief pulse width.

2. Methods

2.1. Study population

Patients with DSM-IV-defined major depressive disorder, either bipolar or unipolar, with or without psychotic symptoms, with an age of 18 years or older, who were referred for ECT, had a minimum baseline score of 18 on the 17-item Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and were able to complete neuropsychological testing, were eligible for study inclusion. Exclusion criteria included schizophrenia, neurological illness, cognitive disorder, substance abuse or dependence within the previous year, or ECT within the past 6 months. Patients provided written informed consent, and the study was approved by the Ethical Committee of the University Hospital of the Catholic University of Leuven.

2.2. Treatment

Patients were withdrawn from antidepressants at least 3 days before starting ECT. Lorazepam up to 4 mg/day or clopiapine up to 40 mg/day was allowed if needed for agitation or anxiety. The patients received BF or UL ECT by random assignment. Anesthetic medications consisted of glycopyrrolate (0.2 mg), methohexital (1.0 mg/kg) or etomidate (0.2 mg/kg), and succinylcholine (1.0 mg/kg), all given intravenously. For BF placement, each electrode was placed 5 cm above the outer angle of the orbit on a line parallel to the sagittal plane (Letemendia et al., 1993). The d'Elia placement was used in UL ECT (D'Elia, 1970). Treatment was given two times a week with a square-wave, brief-pulse, constant-current device (MECTA SR1; Lake Oswego, OR, U.S.A.). At the first treatment, the subject’s ST was established by empirical titration. Subsequent treatments were given at 1.5 times the ST for BF placements, and 6 times the ST for UL placements. Stimulus train duration was the longest, stimulus frequency the lowest allowed for the dose selected. After finishing the ECT-course, at the discretion of the treating psychiatrist, either continuation-ECT or prophylactic drug treatment was started.

2.3. Evaluation of outcome

Apart from the extensive clinical evaluation, described elsewhere (Sienaert et al., 2009a), the neuropsychological assessment was obtained at baseline and at 1 and 6 weeks after finishing the treatment course, by a research psychologist, blinded for the treatment condition. Patients receiving continuation-ECT had their first continuation treatment after the 1 week post treatment evaluation, and did not participate in the 6 week post treatment evaluation. The following tests were used to test several domains of cognitive functioning: Mini Mental State Examination (MMSE) (global cognitive function) (Folstein et al., 1975), Rey Auditory Verbal Learning Test (RAVLT) (verbal learning, retention) (Rey, 1964; Spreen and Strauss, 1998), Continuous Performance Test (CPT) (attention) (Rosveld et al., 1956), Wisconsin Card Sorting Test (WCST) (executive function) (Spreen and Strauss, 1998), Trail Making Test (TMT) (attention and executive function) (Spreen and Strauss, 1998), Letter Number Sequencing Test (LNS) (working memory) (Spreen and Strauss, 1998; Wechsler, 2004), and the Autobiographical Memory Interview (AMI) (episodic autobiographical memory) (Kopelman et al., 1989). This way, four major cognitive domains were tested: attention (CPT, TMT-A), executive function/working memory (LNS, TMT-B, WCST-C), anterograde episodic memory (RAVLT A1-5, RAVLT A7) and episodic autobiographical memory (AMI). Subjective memory function was assessed with the self-rated Squire Subjective Memory Questionnaire (SSMQ) (Squire et al., 1979). To assure that patients receiving BF or UL ECT were comparable in terms of intellectual ability, their premorbid ability was estimated using the Wechsler Adult Intelligence Scale–Vocabulary Subtest (Wechsler, 2004). Postictal orientation recovery was assessed after every treatment session. At 5, 15 and 30 min following the resumption of spontaneous respiration, the patient was asked to state his or her name, date of birth, age, where he or she was, and the day of the week. Recovery of orientation was defined as a correct response to four of the five questions (Sobin et al., 1995). Patients who failed to meet this criterion within 30 min were given a score of 31. For each patient, the mean time to recovery of orientation across sessions was calculated.

2.4. Statistical analysis

Baseline comparisons between patients given BF and UL ECT were analyzed with standard descriptive tests: chi-square tests (or exact tests) for categorical variables and t tests (or Wilcoxon two-sample test) for continuous variables. To examine differences between BF and UL ECT in cognitive function at baseline, and 1 and 6 weeks after the treatment course,
repeated measures analysis were performed with mixed effect models (Guerguieva and Krystal, 2004) in two steps. In a first step, mixed models with cognitive variables as criteria and electrode position and measurement time as predictors were estimated to simply evaluate cognitive functioning after the treatment course. In a second step, HDRS scores and the number of ECT sessions patients received were entered as time-varying and time-invariant covariates, respectively, to examine the extent to which changes in cognitive functioning were related to changes in depression and to the number of ECT sessions. Different alternative specifications of the error-covariance structure were considered including the ‘compound symmetry’ (CS), ‘Huynt–Feldt’ (HF), and the ‘unstructured’ (UN) form as suggested by Wolflinger and Chang (1998). For each model, an optimal error-covariance structure was selected on the basis of Akaike’s information criterion (AIC) (Wolflinger, 1993, 1997); this allows to choose an error-covariance structure with optimal balance between model fit and model complexity. All analyses were done with the PROC MIXED procedure of the Statistical Analysis Software (SAS) version 9.

3. Results

3.1. Participant flow

Of 81 patients that were randomized to the clinical trial (Sienaert et al., 2009a), 64 patients completed a whole course of ECT and were included in this cognitive study. Thirty-two patients (50%) received BF ECT, and 32 (50%) received UL ECT. Neuropsychological testing 1 week after treatment was completed by 30 (93.75%) patients in the BF-group and 29 (90.62%) in the UL-group. Testing 6 weeks after treatment was performed by 20 (62.50%) patients in the BF-group, and 21 (65.62%) in the UL-group. Five patients (BF: N = 2, 6.25%; UL: N = 3, 9.37%) refused further neuropsychological testing at 1 week after the treatment, another 2 (6.25%) in each group refused testing at 6 weeks. One patient did not state a reason for refusing further testing; 8 patients were discharged by the time of the neuropsychological assessment, 3 of which were referred to another hospital for psychotherapeutic treatment. All these patients refused further testing because of ‘practical inconvenience’. Continuation-ECT was started in 8 patients (25.00%) in the BF-group and 6 patients (18.75%) in the UL-group. These patients were not tested at 6 weeks after treatment. Patients who performed neuropsychological testing at all time points did not differ in baseline HDRS-score, baseline scores on cognitive measures, history of past ECT and number of previous hospitalizations from patients not having the testing at 6 weeks after ECT. Patients in the BF- and UL-groups did not differ in age, or the distributions of gender, history of past ECT, number of previous hospitalizations and number of days free of antidepressants, but differed in the presence of psychotic symptoms (BF: N = 13, 40.63%; UL: N = 4, 12.50%; χ²(1) = 6.49; p = 0.01). In the BF-group, more patients received methohexital as an induction agent (N = 24, 75%; UL: 16, 50%; χ²(1) = 4.27; p = 0.04).

3.2. Clinical and treatment characteristics

Clinical and treatment characteristics are shown in Table 1. As expected, patients in the UL-group had a lower ST than patients in the BF-group, 38.40 ± 24.92 mC and 89.35 ± 70.44 mC, respectively (p < .0001). Since they were treated at 6 times ST, as expected, patients in the UL-group also had a longer train duration 7.98 ± 0.09 s; BF: 7.60 ± 0.68 s; p = .0005), a higher frequency (65.77 ± 28.20 Hz; BF: 46.90 ± 28.85 Hz; p = .0015), and a higher final treatment dose (311.55 ± 206.74 mC; BF: 213.71 ± 155.31 mC; p = .01). There were no group differences in the number of treatment sessions in the treatment course (t(62) = 1.35; p = .18). Scores on the Vocabulary Subtest of the Wechsler Adult Intelligence Scale, assessing premorbid intellectual function, did not differ between the two treatment groups (BF: 10.94; UL: 10.81; t(53) = −.05; p = .96) (Table 1).

3.3. Efficacy

Response criteria were met by 78.13% of patients (N = 50). Remission (HRSD-score ≤ 10) was achieved by 65% of patients (N = 42). There was no significant difference in response and remission rates between the two treatment groups. HRSD-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bifrontal N = 32 (50%)</th>
<th>Unilateral N = 32 (50%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.14 ± 10.79</td>
<td>54.40 ± 13.11</td>
<td>.56</td>
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<tr>
<td>Sex (Female)</td>
<td>19</td>
<td>23</td>
<td>.29</td>
</tr>
<tr>
<td>HDRS-score, baseline</td>
<td>30.25 ± 6.46</td>
<td>29.03 ± 5.18</td>
<td>.41</td>
</tr>
<tr>
<td>HDRS-score, 6 weeks after ECT</td>
<td>11.60 ± 7.70</td>
<td>9.55 ± 6.30</td>
<td>.41</td>
</tr>
<tr>
<td>Premorbid intellectual functioning</td>
<td>10.85 ± 3.16</td>
<td>10.89 ± 2.86</td>
<td>.96</td>
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<tr>
<td>Previous hospitalizations (no.)</td>
<td>3.87 ± 2.70</td>
<td>3.65 ± 3.12</td>
<td>.50</td>
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<tr>
<td>Age of First Hospitalization (year)</td>
<td>45.82 ± 14.33</td>
<td>43.30 ± 15.18</td>
<td>.51</td>
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<tr>
<td>Days free of antidepressants</td>
<td>8.83 ± 4.35</td>
<td>7.06 ± 4.40</td>
<td>.06</td>
</tr>
<tr>
<td>Seizure threshold (mC)</td>
<td>89.35 ± 70.44</td>
<td>38.40 ± 24.92</td>
<td>&lt;.0001</td>
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<tr>
<td>Frequency (Hz)</td>
<td>46.90 ± 28.85</td>
<td>28.20 ± 34.95</td>
<td>&lt;.0005</td>
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<tr>
<td>Train duration (s)</td>
<td>7.60 ± 0.68</td>
<td>5.86 ± 0.94</td>
<td>.005</td>
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<tr>
<td>Final treatment dose (mC)</td>
<td>213.71 ± 155.31</td>
<td>311.55 ± 206.74</td>
<td>.01</td>
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<tr>
<td>Motor seizure duration – first treatment</td>
<td>58.74 ± 19.82</td>
<td>62.19 ± 34.37</td>
<td>.63</td>
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<tr>
<td>Motor seizure duration – last treatment</td>
<td>41.17 ± 12.56</td>
<td>37.07 ± 10.24</td>
<td>.17</td>
</tr>
<tr>
<td>EEG seizure duration – first treatment</td>
<td>91.52 ± 45.16</td>
<td>98.81 ± 46.78</td>
<td>.53</td>
</tr>
<tr>
<td>EEG seizure duration – last treatment</td>
<td>58.79 ± 16.52</td>
<td>55.37 ± 14.96</td>
<td>.41</td>
</tr>
<tr>
<td>Number of treatment sessions</td>
<td>13.72 ± 4.50</td>
<td>12.34 ± 3.59</td>
<td>.18</td>
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</tbody>
</table>

a Wechsler Adult Intelligence Scale-Vocabulary Subtest-score (normative data 10 ± 3).
scores (Table 1) decreased significantly over time in both groups (main effect time: $F(3,62) = 145.54, p < .0001$). Additional details on efficacy are described elsewhere (Sienaert et al., 2009a).

### 3.4. Neuropsychological test scores

Neuropsychological test scores are shown in Table 2. The treatment groups were comparable in baseline neuropsychological measures. In both groups, apart from normal MMSE-scores, deficits in verbal learning and memory, attention (on the CPT-task), and executive functioning (on the WCST-C) were detected at baseline. Patients in the BF-group showed more pronounced deficits in delayed recall of verbal information ($5.58 \pm 0.59$) and the divided attention and set-shifting as measured with the TMT-B (122.73 ± 0.11). Baseline scores on the AMI in the RUL-group (63.35 ± 2.43) were within the normal range. Neither the BF-group nor the RUL-group did show a further impairment on any of the cognitive measures obtained at 1 and 6 weeks after the treatment course. All neuropsychological measures improved over time. After the Bonferroni-correction (adjusted for the number of cognitive variables involved in the study), statistically significant effects of time could be detected for MMSE-scores ($p < .001$), verbal learning ($p < .0001$), delayed recall ($p < .001$), attention (on the CPT-task) ($p < .05$), executive function (on the WCST-C) ($p < .05$), and subjective memory complaints ($p < .001$) (Table 2). The changes of neuropsychological measures over time did not differ between both treatment groups (no effect of electrode position; no effect of the interaction electrode position and time). Additional analyses, controlling for potentially confounding variables like the presence of psychotic symptoms and the anesthetic used, resulted in the same conclusions as mentioned above (data not shown).

Next, it was examined to what extent the changes in neuropsychological measures were related to changes in depression and to the total number of treatment sessions patients had received (Table 3). An effect of time remained detectable for verbal learning ($p = .01$), delayed recall ($p = .01$), attention on the CPT-task ($p = .0005$), executive function on the WCST-C ($p = .03$), and autobiographical memory ($p = .02$). Apart from that, this analysis produced an effect of HRSD-change on verbal learning ($p = .04$), delayed recall ($p = .06$), attention on the CPT-task ($p = .004$), and subjective memory complaints ($p < .0001$), and an effect of the total number of treatment sessions on verbal learning ($p = .05$), delayed recall ($p = .01$), attention on the TMT-task ($p = .009$), and autobiographical memory ($p = .02$). Thus, a more robust improvement in depression-scores tends to predict a more pronounced improvement in verbal learning, delayed recall, and attention, and a stronger decrease in subjective memory complaints. A higher number of treatment sessions seems to predict lower scores on verbal learning, delayed recall, attention, and autobiographical memory. Since a high number of variables were entered in this analysis, a more conservative Bonferroni-correction (adjusted for the number of cognitive variables involved in the analysis), was again carried out. After the Bonferroni-correction, the most robust finding remains that changes in depression severity had a highly significant effect on the subjective cognitive function (SSMQ) ($p < .001$) with higher depression-scores predicting a lower score on subjective

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**Table 2**

<table>
<thead>
<tr>
<th>Cognitive domain (measure)</th>
<th>normative data</th>
<th>Baseline</th>
<th>Post1</th>
<th>Post6</th>
<th>Baseline</th>
<th>Post1</th>
<th>Post6</th>
<th>Baseline</th>
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<th>Post6</th>
<th>Baseline</th>
<th>Post1</th>
<th>Post6</th>
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<tbody>
<tr>
<td>Global cognitive function (MMSE)</td>
<td>26.9 (3.0)</td>
<td>29.2 (2.7)</td>
<td>27.8 (2.9)</td>
<td>28.9 (3.0)</td>
<td>30.2 (3.3)</td>
<td>31.7 (3.7)</td>
<td>32.1 (3.5)</td>
<td>32.4 (3.7)</td>
<td>32.7 (3.9)</td>
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<tr>
<td>Delayed recall (RAVLT A7), 10.4 (3.1)</td>
<td>5.58 (1.0)</td>
<td>7.21 (1.0)</td>
<td>8.49 (1.1)</td>
<td>9.65 (1.2)</td>
<td>10.47 (1.3)</td>
<td>11.14 (1.4)</td>
<td>11.35 (1.5)</td>
<td>11.57 (1.6)</td>
<td>11.78 (1.7)</td>
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<td>Attention (CPT), 1.6 (0.6)</td>
<td>0.63 (0.15)</td>
<td>0.60 (0.16)</td>
<td>0.68 (0.17)</td>
<td>0.79 (0.18)</td>
<td>0.86 (0.19)</td>
<td>0.93 (0.20)</td>
<td>0.94 (0.21)</td>
<td>0.95 (0.22)</td>
<td>0.96 (0.23)</td>
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<td>Working memory (LNSA), 10 (3)</td>
<td>7.58 (0.70)</td>
<td>8.49 (0.71)</td>
<td>9.42 (0.73)</td>
<td>10.47 (0.75)</td>
<td>11.42 (0.77)</td>
<td>12.37 (0.79)</td>
<td>13.32 (0.81)</td>
<td>14.37 (0.83)</td>
<td>15.42 (0.85)</td>
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<tr>
<td>Executive function (TMT-B), 79.6 (22.9)</td>
<td>122.73 (0.11)</td>
<td>112.17 (0.12)</td>
<td>104.58 (0.14)</td>
<td>98.49 (0.12)</td>
<td>104.58 (0.12)</td>
<td>100.48 (0.14)</td>
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<td>Executive function (WCST categories), 3.4 (1.3)</td>
<td>2.31 (0.37)</td>
<td>2.82 (0.37)</td>
<td>3.51 (0.40)</td>
<td>4.26 (0.41)</td>
<td>4.81 (0.44)</td>
<td>5.36 (0.47)</td>
<td>6.01 (0.50)</td>
<td>6.66 (0.53)</td>
<td>7.31 (0.56)</td>
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<td>Autobiographical memory (AMI), 62-90</td>
<td>63.19 (2.49)</td>
<td>67.11 (2.0)</td>
<td>62.58 (2.0)</td>
<td>61.59 (2.0)</td>
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<tr>
<td>Subjective cognitive function (SSMQ)</td>
<td>34.74 (3.54)</td>
<td>12.02 (5.02)</td>
<td>30.06 (5.07)</td>
<td>28.01 (5.13)</td>
<td>26.06 (5.20)</td>
<td>24.01 (5.27)</td>
<td>22.06 (5.34)</td>
<td>20.01 (5.41)</td>
<td>18.06 (5.48)</td>
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*Analysis was performed on ln (TMT-A) and ln (TMT-B); for ease of interpretation, exp of the estimated means are reported; $\#$ Bonferroni-correction adjusting for the number of dependent variables being tested; $\$ F$-value was significant after Bonferroni-correction ($p < .05$).
memory complaints. There was also a small, though significant effect of HRSD on CPT-scores ($p < .05$), with higher depression-scores resulting in lower attention scores. There was no effect of electrode position on any of the measures examined.

Subjective memory complaints, as measured by the SSMQ, improved significantly over time (Table 2). There was no effect of electrode position (Table 2), nor was there an effect of changes in scores on the RAVLT ($F(48) = 0.06; p = .80$), WCST ($F(48) = 0.12; p = .73$), LNSA ($F(48) = 0.20; p = .66$) and AMI ($F(48) = 1.60; p = .21$). Changes in scores on the CPT had an effect on changes in SSMQ ($F(48) = 8.16; p = .006$).

Concerning the mean time to recovery of orientation, there was no statistically significant difference between groups (BF: $17.7 min \pm 6.47 min$; RUL: $20.23 min \pm 6.55 min$; $t(60) = −1.53; p = .13$), which was confirmed using survival analyses (Kaplan–Meyer, Cox regression models). Since time to recovery of orientation has been shown to predict changes in autobiographical memory scores (Sobin et al., 1995), this was also examined. Mean time to recovery of orientation did not predict changes in the autobiographical memory scores ($F(48) = 2.30; p = .11$).

4. Discussion

This study further demonstrates the cognitive safety of ultra-brief pulse ECT, when used with BF or UL electrode position. Whereas in most studies, cognitive function decreases during and immediately after ECT, to increase to at least pretreatment levels after several months (Schat et al., 2007; Ingram et al., 2008; Porter et al., 2008; Lisanby et al., 2000), in this study patients did not show deterioration of any neuropsychological measure relative to baseline. On the contrary, changes in neuropsychological measures pointed to an improvement of cognitive function over time. These results corroborate the findings of previous reports showing the cognitive safety of high-dose ultra-brief UL ECT (Sackeim et al., 2008; Loo et al., 2007), and provide the first data for the cognitive safety of ultra-brief BF ECT, at 1.5 times ST. Both techniques studied, are effective antidepressant techniques (Sienaert et al., 2009a). Sackeim et al. (2008) found bilateral, i.e. bitemporal, ECT with an ultra-brief stimulus at 2.5 times ST. Apart from the difference in electrode position as such, this might add to a difference in cognitive side-effects (Kellner, 2009).

Impairment in different cognitive domains, such as attention, executive function, learning and memory capacity, is common in major depression (Castaneda et al., 2008; Porter et al., 2003; Marvel and Paradiso, 2004), and this is a key confounder affecting assessments comparing pre- and post-ECT memory performance (Fraser et al., 2008). Greater symptom severity seems to be associated with increased cognitive impairment (Marvel and Paradiso, 2004). A treatment improving depression is thus supposed to improve cognitive dysfunction. In this study, cognitive impairment at baseline was substantial, and comparable to other studies in major depression (e.g. Airaksinen et al., 2004) or melancholic
depression (e.g., Austin et al., 1999). Further analysis, controlling for depressive symptomatology at all time points, indicated that the improvement seen in attention, and, to a lesser extent, anterograde memory, correlates with an improvement of the depression. After treatment, however, mild cognitive impairment (score below average on retrieval of verbal information, divided attention and set-shifting-tasks) was still detectable, corroborating the findings of several studies that cognitive deficits persist after remission, indicating that some types of cognitive deficits might represent trait rather than state characteristics (Marvel and Paradiso, 2004). The fact, however, that apart from the changes in the neuropsychological measures attributable to changes in depression, an effect of time remained detectable, indicates that a course of ultra-brief pulse BF or UL ECT did not impair attention and anterograde memory.

A possible drawback of ultra-brief ECT is that it might require a higher number of treatment sessions to yield the same antidepressant efficacy as standard pulse ECT (Cronholm and Ottoisson, 1963b; Robin and De Tissere, 1982; Loo et al., 2007; Sienaert et al., 2009a). A higher number of treatments sessions is generally associated with more pronounced cognitive side-effects (Sackeim et al., 2007; Fraser et al., 2008). In this study, a non-significant tendency for a higher number of treatment sessions predicting a less pronounced increase in verbal learning, delayed recall, and attention, and a more pronounced decrease in autobiographical memory scores, was detectable. The power of this study is perhaps too low to detect more significant influences of the number of treatment sessions on cognitive changes.

Evidence suggests that autobiographical memory impairment does occur as a result of ECT (Fraser et al., 2008), that it can persist for longer periods of time after treatment (Squire and Slater, 1983; Sackeim et al., 2008) and that it is clinically the most concerning to patients (Rose et al., 2003; Fraser et al., 2008). It has been shown that patients who manifest global cognitive impairment, as measured with the MMSE, and patients who experience prolonged postictal disorientation, are more prone to autobiographical memory impairment (Sobin et al., 1995). In this study, autobiographical memory did not show a significant impairment, and mean time to recovery of orientation did not predict changes in autobiographical memory scores. Measurement of the mean time to reorientation in this study was, however, not continuously, but at 3 time points after treatment. This undoubtedly contributes to the higher time to reorientation as compared to the time to reorientation reported in the Sackeim et al.-study.

A limitation of this study, as in other studies on cognitive side-effects of ECT, is the lack of information about the participants’ premorbid memory performance. In the absence of this information, Fraser et al. (2008) suggest to routinely control premorbid intellectual ability. In this study, participants presumably had normal premorbid memory function, since scores on the vocabulary subtest of the Wechsler Adult Intelligence Scale yielded values within the normal range in both treatment groups. These scores are generally unaffected by depression, and are thought to be highly correlated with premorbid memory function (Williams, 1997).

Patients rated their memory after treatment significantly better than before treatment. Our results convincingly show that this perceived improvement of memory function, is largely explained by an improvement of the depression. It has already been shown repeatedly that cognitive complaints correlate with mood, while there is often no correlation with objective neuropsychological measures (Prudic et al., 2000). Apart from the finding that a higher improvement in attention on the CPT correlated with a higher decrease in subjective memory complaints, we also failed to detect a correlation between changes in neuropsychological test scores and subjective complaints.

The reasons why the use of an ultra-brief pulse width reduces the cognitive side effect burden of ECT remain elusive. It is possible that a reduction in pulse width changes the size and geometry of the neuronal population engaged in the ictal process (Sackeim et al., 2008), or that a shorter pulse width preferentially activates some specific neuronal elements over others (McIntyre, 2008). It has been convincingly shown that reducing pulse width increases electrical efficiency. Patients treated with ultra-brief pulse ECT have lower ST than reported with standard pulse width ECT (Sackeim et al., 2008; Loo et al., 2007; Sienaert et al., 2009a). As a result, patients can have therapeutic seizures at relatively low absolute doses. This superior electrical efficiency as compared to standard pulse ECT is perhaps an important reason for the beneficial side effect profile of ultra-brief pulse ECT.

A major limitation of this study is the rather small sample size, not allowing to conclude that, although no differences could be detected, BF and UL ECT have identical safety profiles. Another limitation lies in the fact that after finishing the course of ECT, patients were further treated with pharmacological agents. It is unsure to what extent this might have influenced the results.

The results of this study should be interpreted with caution, since only 59 of 81 patients (72.8%) that were initially randomized completed post-ECT neuropsychological testing. It could be argued that the patients who dropped out might have had more cognitive adverse effects. The reasons for drop-out were described in detail elsewhere (Sienaert et al., 2009a). Eight patients dropped out because of violation of protocol, and 9 withdrew consent during the treatment course. None of these patients, however, stated cognitive side-effects as the reason for withdrawing consent. Of the 9 patients refusing further post-ECT testing, 8 stated ‘practical inconvenience’ as the main reason. Although it seems unlikely that patients experiencing pronounced cognitive adverse effects would refuse neuropsychological testing, since this assessment would address their concerns, it can, however, not be ruled out that cognitive side-effects might have been a reason for refusing further participation in the testing.

Finally, interpreting the results of studies on the cognitive effects of ECT should take into account the methodology of the cognitive assessment (Rose et al., 2003; Sienaert et al., 2009b). Assessing patients early after the treatment course, may underestimate the impairments experienced by patients after discharge, and cognitive tests used may not actually measure the impairments that distress patients (Robertson and Pryor, 2006).

Research has put an overzealous emphasis on cognitive deficits during ECT (Fink, 2007; Loo, 2008), adding to the negative image of this highly effective treatment. Nevertheless, patients’ memory complaints should be acknowledged, and continued efforts to minimize cognitive side-effects of ECT...
should continue. This, and other recent studies, show that it is possible to practice ECT in an effective way, without a clinically significant influence on cognitive function. These findings, however, need further replication in larger trials, before adopting ultra-brief pulse ECT as a routine clinical practice (Coffey, 2008; Kellner, 2009). Ultrabrief stimulation, according to Lerer and Isserles (2008), could turn out to be a pivotal step in an exciting cascade of events that may alter the biological treatment of depression.

5. Conclusion

Ultrabrief pulse ECT, used either in combination with a UL electrode placement and a stimulus of 6 times the initial ST, or a BF electrode placement with a stimulus of 1.5 times ST, are effective antidepressant techniques, that do not have a deleterious effect on the cognitive measures used in this study.

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Conflict of interest

The authors declare no conflict of interest.

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