Bilateral bispectral index monitoring during and after electroconvulsive therapy compared with magnetic seizure therapy for treatment-resistant depression

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Editor’s key points

- Bispectral index (BIS) monitoring was used to standardize anaesthetic depth before electroconvulsive and magnetic convulsive therapy.
- Electrical therapy was mostly applied unilaterally, whereas magnetic therapy was applied bilaterally.
- After magnetic seizure therapy, recovery was more rapid and was associated with higher post-ictal BIS values.
- There were no significant differences in the left- and right-sided BIS values.

Background. Electroconvulsive therapy (ECT) is a highly effective and established treatment for depression. Magnetic seizure therapy (MST) has recently been developed and seems equally effective while associated with fewer side-effects. Both require general anaesthesia, which could be quantified using the bispectral index (BIS). We compared ECT and MST with respect to recovery times, left-sided BIS, and left–right differences in BIS.

Methods. In this prospective, observational study, we enrolled 10 successive patients receiving ECT and 10 patients undergoing MST. Anaesthesia was performed with propofol and monitored with a bilateral BIS sensor. The seizure was elicited when the BIS was within a range from 50 to 60. The time to eye opening was measured and bilateral BIS were recorded for 10 min after seizure induction.

Results. A comparable anaesthetic depth was observed in the ECT and MST groups at baseline [mean (standard deviation, SD) BIS values of 94.1 (4.1) and 95.5 (3.0), respectively] and before seizure induction [mean (SD) BIS values of 52.3 (9.6) and 55.2 (10.3), respectively]. Post-ictally, MST patients opened their eyes significantly earlier than ECT patients [3.0 (1.0) vs 6.7 (1.3) min, P < 0.001]. They showed a significantly higher BIS at 2 min after seizure induction [69.2 (10.1) vs 50.9 (15.9), P = 0.003], and this difference was still present at 10 min after seizure induction [BIS 81.5 (6.5) vs 68.0 (16.4), P < 0.001]. Significant differences between the left and right BIS were observed in neither the ECT nor the MST group.

Conclusions. At a comparable anaesthetic depth, MST is superior to ECT in terms of post-ictal recovery, which is correctly reflected by higher post-ictal BIS values. Unilateral BIS monitoring is sufficient to monitor anaesthetic depth in ECT and MST patients.

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Keywords: anaesthetics i.v.; propofol; consciousness monitors; depressive disorder; treatment-resistant; electroconvulsive therapy

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Electroconvulsive therapy (ECT) has been shown to be highly effective in patients suffering from treatment-resistant depression (TRD).1–3 However, it is associated with cognitive side-effects, especially memory disturbance,4,5 which limits its acceptance among patients. Therefore, an alternative therapy has been developed which elicits the desired seizure not by electric current as in ECT, but by magnetism. This magnetic seizure therapy (MST) was first successfully applied in humans in 20006 and has been subject to several studies since then. So far, MST has been shown to have a comparable antidepressant effect7–10 with no cognitive side-effects.11 Both ECT and MST require muscle relaxation to prevent the patients from seizure-related injuries. General anaesthesia is required to protect the patients against the most unpleasant feeling of complete paralysis; however, the optimal choice of the hypnotic agent and its optimal dosage remain a matter of debate.11–17 Moreover, the depth of anaesthesia has been shown to be relevant, especially before seizure induction: light anaesthesia might result in awareness18 but leads to superior ictal characteristics,19 whereas deep anaesthesia will impede seizure induction—due to the anticonvulsant effect of anaesthetics11—reduce the antidepressant
effect of the therapy,\textsuperscript{20} and increase the risk of cognitive side-effects.\textsuperscript{21}

The EEG-derived bispectral index (BIS) monitor quantifies the depth of anaesthesia,\textsuperscript{22, 23} in terms of its hypnotic component, displayed by a dimensionless number, which ranges from 100 to 0, signifying a complete awake patient or a patient with isoelectric EEG, respectively.\textsuperscript{22, 23} Hence, the BIS decreases as anaesthetic depth increases, with 40–60 being the recommended BIS range for general anaesthesia.\textsuperscript{24} So far, a lower BIS before seizure induction has been shown to correlate with a shorter seizure duration,\textsuperscript{20, 25, 26} a higher number of ECT sessions needed to reach remission,\textsuperscript{20} and a longer awakening time.\textsuperscript{25, 26} Usually, the BIS sensors are placed unilaterally at the left forehead, even though BIS monitoring works equally well when placed at the right side. Relevant BIS differences between the left and right forehead occur rarely, but have been reported in patients with unilateral brain lesions,\textsuperscript{27} during unilateral epilepsy surgery,\textsuperscript{28} and in children at an intensive care unit.\textsuperscript{29}

We hypothesized that (i) patients recover faster from MST when compared with ECT, (ii) which should be reflected by a higher post-ictal BIS in MST patients, and that (iii) BIS differences between the left and right side are more pronounced in the ECT group, since ECT is mostly elicited unilaterally in contrast to the bilateral-induced MST. We therefore performed a prospective, observational study.

Methods

Patients

The study was approved by the regional ethics committee (Ethik-Kommission der Medizinischen Fakultät, Rheinische Friedrich-Wilhelms-Universität, Bonn, Germany; Approval No. 023/05) and registered with ClinicalTrials.gov (Ref: NCT01318018). Generally, patients with depression are judged as being able to give informed consent. Nonetheless, we required—without stipulation by the ethics committee—in addition to the patient’s own written consent the agreement of the closest caregiver and requested a waiting period before signing the informed consent form. Twenty patients suffering from TRD were studied. Inclusion criteria were a depressive episode in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR).\textsuperscript{30} Exclusion criteria were an age <18 yr, pregnancy, signs of delirium, dementia, amnesia, or other cognitive disorders, and also alcohol or substance abuse. For MST, patients with magnetic materials in the head or implanted medical devices, such as cardiac pacemakers, vagus nerve stimulators, cochlear implants, or medical pumps, were furthermore excluded. Patients were recruited from their treating psychiatrist, or were referred from the University Hospital outpatient clinic. In contrast to ECT, not every psychiatrist enrolled patients for MST, since ECT is the usual therapy for TRD. Whenever a patient was enrolled into the MST group, a corresponding ECT patient, who started treatment at the same time, was asked for consent. Ten successive patients undergoing MST were compared with 10 patients receiving ECT.

Anaesthesia

All patients were on antidepressant drugs, however received no specific premedication before ECT or MST. The EEG was continuously and bilaterally recorded using the BIS VISTA\textsuperscript{TM}—bilateral monitor (Covidien Inc., Boulder, CO, USA, Vista V 3.0), and the BIS (V 4.1, 10 s smoothing time) of the left and right side was stored in 1 s intervals on an USB-stick for later analysis. The BIS Bilateral Sensor was applied as recommended by the manufacturer, after the forehead skin had been cleaned with 70% isopropanol to improve skin conductance.

Patients were preoxygenated with 100% oxygen and received 0.5–1 mg cisatracurium i.v. for precurarization and 0.2 mg glycopyrrolate i.v. to reduce salivation. Anaesthesia was induced with propofol i.v. at a predetermined dose of 1.5 mg kg\textsuperscript{-1} body weight. After loss of consciousness, a cuff was placed around the right lower leg and inflated above systolic arterial pressure to prevent the right foot from muscle relaxation. Subsequently, succinylcholine was administered at a predetermined dose of 1 mg kg\textsuperscript{-1} body weight, and the patient was ventilated via a face mask. The seizure was induced, only after the BIS was in the desired range between 50 and 60: to do so, a bolus of 10 mg propofol was given in the case of a BIS above 60. If the BIS was below 50, then we waited until the BIS increased spontaneously to above 50.

A rubber bite block was inserted to prevent dental damage and tongue bite. Patients of the MST group received earplugs to protect against the clicking noise of the MST device. The seizure was induced by electric current (ECT group) or magnetic stimulation (MST group), and its duration was measured according to the recorded raw EEG activity. In addition, the duration of motor seizure activity was assessed according to the movements of the right foot. When the seizure terminated, patients were ventilated again until restoration of spontaneous breathing. The time point, at which the patients opened their eyes, was noted, and the BIS recording was terminated 10 min after seizure induction.

The dosage of propofol and succinylcholine was adjusted in a given patient at the next ECT or MST treatment according to the clinical demands of the previous treatment: if the patient required an additional bolus of propofol, then the dosage was increased by 10 mg at the next time. If the BIS was below 50 thus requiring some waiting time before seizure induction, then the propofol dose was decreased by 10 mg. Additionally, if the patient showed signs of remaining muscle relaxation, then the succinylcholine dose was reduced by 10 mg at the next ECT or MST treatment.

Electroconvulsive and magnetic seizure therapy

The ECT and MST and also its parameter selection are described in detail elsewhere.\textsuperscript{8} In brief, ECT was delivered with a Thymatron IV device (Somatics LLC, Lake Bluff, IL, USA) using a right unilateral or bilateral stimulation (square wave, pulse width 0.5 ms, duration of stimulus 4–8 s) at six or three times the seizure threshold, respectively. The seizure threshold was identified during the first session. MST was performed using a MagPro device (MagVenture A/S, Farum, Denmark) with a
of 0.8 and an $\alpha$ of 0.05, eight patients per group are required to do so, plus two additional patients to correct for possible drop-outs.

The BIS values were analysed offline and averaged over 20 s intervals in order to reduce the BIS fluctuations over time. The BIS was investigated at certain time points, starting at baseline, which was without premedication and before the application of any anaesthetic drug. Further time points were before the application of succinylcholine, before seizure induction, during seizure and every minute thereafter until 10 min after seizure induction. In each patient, multiple (typically three) treatments were recorded and averaged to obtain one data set per patient. Finally, these patient data sets were averaged within the ECT and MST groups and compared by t-test in the case of normal distribution, or Mann–Whitney rank-sum test, otherwise. Data are shown as mean [standard deviation (SD)] in the case of normal distribution, or as median (25%; 75% percentile) otherwise. All statistical tests were performed using SigmaPlot-Software (version 12.3, Systat Software Gmbh, Erkrath, Germany) and significance was assumed at $P<0.05$.

**Results**

Both groups consisted of 10 patients each, with a mean age of 55 (12) (range: 34–72) yr in the ECT group and of 45 (14) (range: 22–72) yr in the MST group. However, this difference in age was not significant ($P=0.094$). Twenty-nine and 35 treatments were recorded in the ECT and the MST groups, respectively. Hence, a median of three treatments per patient was averaged to obtain a characteristic data set for each of the 20 patients. In addition, both groups were comparable with respect to their gender distribution, height, weight, and their anaesthetic dosage (Table 1). In particular, both groups received the same propofol dosage ($\sim 1.5 \text{ mg kg}^{-1} \text{ body weight}$).

**Seizure characteristics**

A bilateral stimulation was performed in all MST patients and in one ECT patient, whereas the remaining nine ECT patients received a right unilateral stimulation.

**Table 1** Characteristics of the ECT and the MST group. Data are expressed as mean (so). Any differences in the shown parameters were not significant

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ECT</th>
<th>MST</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Sex (female: male)</td>
<td>4:6</td>
<td>3:7</td>
<td></td>
</tr>
<tr>
<td>No. of recorded treatments</td>
<td>29</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55 (12)</td>
<td>45 (14)</td>
<td>0.094</td>
</tr>
<tr>
<td>Range (yr)</td>
<td>34–72</td>
<td>22–72</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174 (9)</td>
<td>176 (9)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 (17)</td>
<td>85 (14)</td>
<td></td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>118 (31)</td>
<td>124 (30)</td>
<td></td>
</tr>
<tr>
<td>(mg kg$^{-1}$)</td>
<td>1.47 (0.30)</td>
<td>1.46 (0.29)</td>
<td></td>
</tr>
<tr>
<td>Succinylcholine (mg)</td>
<td>79 (15)</td>
<td>72 (14)</td>
<td></td>
</tr>
<tr>
<td>(mg kg$^{-1}$)</td>
<td>0.99 (0.19)</td>
<td>0.85 (0.16)</td>
<td>0.088</td>
</tr>
</tbody>
</table>

**Table 2** Characteristic time interval in a comparison between the ECT and the MST groups. The ECT and the MST groups consisted of 10 patients each. Data are shown as mean (so) in the case of normal distribution, or as median (25%; 75% percentile) otherwise

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ECT</th>
<th>MST</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure duration, according to EEG (s)</td>
<td>34.6 (28.6; 41.5)</td>
<td>20.5 (17.0; 31.2)</td>
<td>0.023</td>
</tr>
<tr>
<td>Motor activity (s)</td>
<td>27.5 (19.9; 31.6)</td>
<td>21.1 (16.4; 28.2)</td>
<td>N.S</td>
</tr>
<tr>
<td>Recovery time intervals, from seizure induction to restoration of breathing (min)</td>
<td>2.5 (1.9; 3.5)</td>
<td>1.5 (1.2; 1.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>Eye opening (min)</td>
<td>6.7 (1.3)</td>
<td>3.0 (1.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recovery time interval, from propofol application to eye opening (min)</td>
<td>12.3 (3.0)</td>
<td>8.9 (1.4)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

ECT resulted in a significantly ($P=0.023$) longer seizure duration (median of 35 s, Table 2), according to EEG criteria, when compared with MST (median of 21 s). However, the motor seizure activity was comparable between the ECT group (median of 28 s) and the MST group (median of 21 s, $P=0.34$).

**Recovery times**

MST patients recovered significantly ($P<0.05$) faster than ECT patients as indicated by the shorter time interval from seizure induction to restoration of breathing (median of 1.5 vs 2.5 min, Table 2), and also to eye opening (3.0 (1.0) vs 6.7 (1.3) min, Table 2). In addition, a significantly ($P=0.004$) shorter time interval between propofol application and eye opening was observed in the MST group [8.9 (1.4) min] when compared with the ECT group [12.3 (3.0) min]. With respect to age, we found no significant correlation to any of the mentioned time intervals. Moreover, two-way analysis of variance (ANOVA) revealed that the effect of treatment modality (ECT vs MST) on...
recovery times was greater than would be expected by chance ($P<0.05$); however, the effect of age ($\leq 50$ vs $>50$ yr) was not.

### BIS on the left side

The BIS monitor itself was not affected by seizure induction in the MST group, and in 25 of the 29 treatments in the ECT group. However, in the remaining four treatments of the ECT group, a BIS error occurred due to the electrical current at seizure induction, which required a reset of the BIS monitor.

The BIS was comparable during baseline and before seizure induction (Table 3, Fig. 1) between both groups. After propofol application, the BIS decreased from 94.1 (4.1) to 56.2 (13.9) in the MST group, and from 95.5 (3.0) to 50.5 (11.5) in the ECT group (Fig. 1). In the MST group, the lowest BIS values were obtained shortly after propofol application and before the application of succinylcholine. Thereafter, the BIS increased with time but never reached baseline values even at 10 min after seizure induction [BIS $\approx 61.4$ (13.0), right $\approx 58.9$ (13.8)] thereafter (Fig. 3).

### Discussion

This is the first study showing that MST patients recover faster than ECT patients, despite a similar depth of anaesthesia at seizure induction. Earlier reports already described an earlier recovery after MST, but in these studies, the anaesthetic depth was either not comparable or not quantified. The recovery time after ECT or MST under general anaesthesia is determined mainly by anaesthetic depth and the mode of stimulation (ECT or MST). Hence, the latter effect can only be proved under conditions of a comparable anaesthetic depth. Moreover, we observed that this faster recovery is reflected by a significantly higher post-ictal BIS in MST patients. Several studies reported a low post-ictal BIS at awakening with a huge variation in BIS values ranging from 29 to 97. Hence, the post-ictal BIS was evaluated as not reflecting the clinical impression of anaesthetic depth anymore. In fact, we observed a mean BIS of 60 with an SD of 15 at first eye opening in the ECT group, which apparently reflects a different anaesthetic depth than a BIS of 60 as obtained pre-ictally. However, the clinical impression of post-ictal patients, which are comatose initially and slowly recover and become responsive as time goes by, is reflected by the slowly increasing BIS in both the ECT and the MST groups. Moreover, the higher post-ictal BIS in MST patients correctly signifies their faster recovery.

The BIS monitor has been validated based on EEG data sets that did not include post-ictal periods, as far as we know. Hence, the monitor cannot be expected to readily quantify depth of anaesthesia in patients during the post-ictal period. The discrimination as to whether the BIS is falsely low in post-ictal periods is not possible. The discrimination as to whether the BIS is falsely low in post-ictal periods is not possible. Hence, the latter effect can only be proved under conditions of a comparable anaesthetic depth. Moreover, we observed that this faster recovery is reflected by a significantly higher post-ictal BIS in MST patients. Several studies reported a low post-ictal BIS at awakening with a huge variation in BIS values ranging from 29 to 97. Hence, the post-ictal BIS was evaluated as not reflecting the clinical impression of anaesthetic depth anymore. In fact, we observed a mean BIS of 60 with an SD of 15 at first eye opening in the ECT group, which apparently reflects a different anaesthetic depth than a BIS of 60 as obtained pre-ictally. However, the clinical impression of post-ictal patients, which are comatose initially and slowly recover and become responsive as time goes by, is reflected by the slowly increasing BIS in both the ECT and the MST groups. Moreover, the higher post-ictal BIS in MST patients correctly signifies their faster recovery.

### BIS in a comparison between the left and right side

Significant differences in left and right BIS values were observed neither in the ECT group (Fig. 2) nor in the MST group (Fig. 3). However, in the ECT group, the BIS value on the right side was lower by $\sim 2$–$4$ index points at baseline ($\leq 94.1$ (4.1), right $\geq 92.7$ (5.4)), at seizure induction ($\leq 55.0$ (13.2), right $\geq 51.6$ (11.8)), and also 4 min ($\leq 51.9$ (19.9), right $\geq 47.9$ (16.7)) and 8 min ($\leq 61.4$ (13.0), right $\geq 58.9$ (13.8)) thereafter (Fig. 3).
suppression has been reported as a predictor of antidepressant response to ECT.\textsuperscript{39–41}

So far, only one study has been published investigating the BIS in MST: White and colleagues\textsuperscript{32} performed a study on 20 patients comparing BIS during MST and ECT and reported a faster recovery time in MST patients [4 (1) min] than in ECT patients [18 (5) min]. However, the BIS before seizure induction was \( \sim 20 \) index points higher in their MST group, that is, they

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**Fig 1** The time course of the BIS, as obtained on the left side, in a comparison between ECT and MST. \( n = 10 \) patients per group. Data = mean (SD).

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**Fig 2** The BIS in a comparison between the left and right side during the time course of ECT. \( n = 10 \) patients per group. Data = mean (SD).
had a significantly lighter depth of anaesthesia, than in their ECT group, which limits the comparability of both groups. Our study differs in methodology and results from theirs, since we especially aimed to achieve a comparable depth of anaesthesia in both groups before seizure induction. Moreover, we used propofol instead of etomidate and applied an advanced and more powerful MST paradigm (6 times compared with 1.3 times the seizure threshold, and 100 vs 50 Hz) which resulted in different seizure characteristics. For instance, they recorded a BIS of \( \approx 80 \) in both the ECT and the MST groups 4 min after seizure induction; however, it took the ECT patients 14 more min to recover. In contrast, the seizure duration was approximately half as long in our patients, and ECT patients did not reach BIS values as high as 80 even at 10 min after seizure induction.

Our study showed that bilateral BIS monitoring is feasible in both ECT and MST. However, the right unilateral stimulation during ECT applies high electric currents in the vicinity of the right frontal and temporal BIS electrode. This presumably caused an error of the BIS monitor in four of the 29 ECT treatments, which required a reset of the monitor after which it worked correctly again. Therefore, the manufacturer does not recommend to apply the BIS electrodes at the same side as the ECT stimulation electrode. We observed no significant left–right differences of the BIS in both the ECT and the MST groups. Hence unilateral, left-sided BIS monitoring seems sufficient for both ECT and MST. Our hypothesis of more pronounced side differences in the ECT group was rejected. Although the seizure was elicited during ECT by a right unilateral stimulation, the seizure affected both hemispheres equally, which might explain the absence of differences in left and right BIS values.

Our study has several limitations: both institutional and organizational reasons precluded a random allocation of patients to the ECT and MST groups, which might have introduced some bias. Patients of the MST group were younger than ECT patients (although this difference was statistically insignificant), which might have contributed to the faster emergence of the MST patients. However, we found neither a correlation between age and recovery times nor between age and BIS values. Moreover, two-way ANOVA revealed that the treatment modality (ECT vs MST) but not age (\( \leq 50 \text{ vs } >50 \text{ yr} \)) was the likely cause for the observed differences in recovery parameters and BIS values. In addition, the observers who assessed the recovery times were not blinded to the treatment modality, since the utilized ECT and MST devices were obviously very different. This might have introduced some additional bias, however it could not account for the observed difference in recovery times which was in a magnitude of minutes and not of seconds. MST patients received insignificantly less succinylcholine than ECT patients, which is in accordance with the study by White and colleagues, who similarly reduced the succinylcholine dose in MST patients to account for their faster recovery and to prevent them from a remaining muscle relaxation. The observed shorter time until restoration of breathing in the MST group might be related to their lower succinylcholine dosage. However, this could not account for the observed differences in the time to eye opening. Finally, the number of patients was relatively small, which is in line with prior MST studies.
Conclusions

We conclude that despite a comparable depth of anaesthesia, MST patients recover faster than ECT patients, which is correctly reflected by the higher post-ictal BIS in the MST group. Unilateral left-sided BIS monitoring is sufficient, since relevant side differences did not occur, not even during unilateral stimulation.

Authors’ contributions

M.S.: study design, data collection, analysis and interpretation, acquisition of funding, manuscript writing, and final approval. S.K.: patient recruitment, data collection, analysis and interpretation, acquisition of funding, manuscript writing, and final approval. R.K.E.: data analysis and interpretation, manuscript revision, and final approval. T.E.S.: data interpretation, manuscript revision, and final approval.

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Declaration of interest

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