6

MRI characteristics predicting seizure threshold in patients undergoing electroconvulsive therapy: *A prospective study*

Jeroen A. van Waarde
Lucas J.B. van Oudheusden
Bart A.R. Tonino
Nic J.A. van der Wee
Bastiaan Verwey
Rose C. van der Mast
Erik J. Giltay

Brain Stimulation 2013, in press; DOI 10.1016/j.brs.2012.12.003

Abstract

Background: In electroconvulsive therapy (ECT), the electrical current must pass the scalp, skull, cerebrospinal fluid (CSF) and brain tissues, to sufficiently exceed the seizure threshold (ST).

Objective: To investigate the relationship between these anatomical strata of the head and the level of the ST, in both right unilateral (RUL) and bifrontotemporal (BL) ECT.

Methods: Observational prospective study among 74 mainly depressed patients. STs were measured at the 1st (initial ST), 6th, 12th, 18th and 24th session. MRI scans were acquired before the 1st session. Scalp and skull thickness at electrode sites were measured on T_2-weighted images. Volumes of intracranial space (ICV), CSF, gray and white matter, and white matter hyperintensities were estimated using whole brain isovoxel T_1-weighted images. Separate multivariate regression analyses for RUL (n=55) and BL (n=19) treated groups were used to estimate the predictive values of the MRI variables.

Results: The patients had a mean age of 57.7±14.8 years, and 39% were men. After adjustment for age, gender and ICV, CSF volume strongly and independently predicted initial ST in both RUL (β=0.31; *P*=0.049) and BL ECT (β=0.64; *P*=0.007). Using multilevel regression analysis, CSF volume was associated with ST during the remaining RUL ECT course (β=0.20; *P*=0.02).

Conclusions: Taking into account the limitations in the titration method and MRI analysis, volume of CSF strongly and independently predicted initial ST. Therefore, the exclusive use of age-based ECT dosing methods may result in suboptimal electrical stimulus dosage in patients with CSF volumes that are not within the average range.

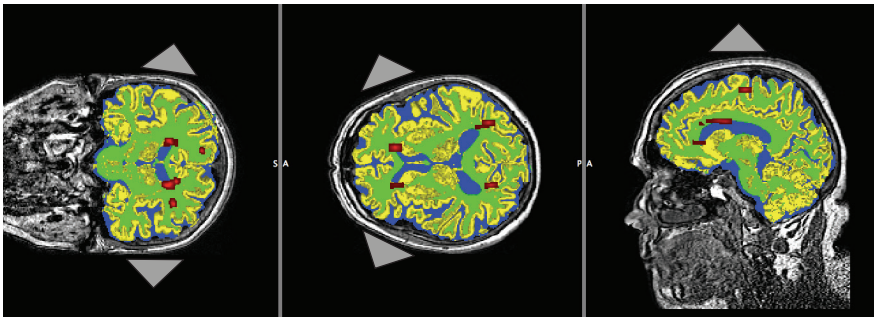
Introduction

Electroconvulsive therapy (ECT) is a fast, effective and safe treatment with remission rates up to 80% in cases of severe depression.[1-3] Generalized seizure activity is elicited at several consecutive ECT sessions.[4] Seizure activity will only be achieved when the patient's seizure threshold (ST) is exceeded by a flow of electrical current.[5] The initial ST (IST), as measured at the first ECT session, varies among patients over a forty-fold range,[6] with higher age and bifrontotemporal (BL) electrode placement as reported predictors of higher IST.[7-9] Also, ST has been shown to change during the course, at least in some patients.[10-12] For optimal ECT effectiveness, the electrical dosage must be substantially increased above the ST, especially in right unilateral (RUL) ECT.[13,14] Because of the presumed increase in ST, consecutive adjustment of electrical dosage during the ECT course has been advised.[12,15] In daily clinical practice, age-based dosing methods are frequently used to determine the proper initial electrical dose.[15,16] Alternatively, a stimulus titration method is advised to estimate an individualized electrical dose.[6,17]

The electrical stimulus must excite sufficient volumes of brain tissue to elicit seizure activity, and is determined by several parameters, e.g., pulse amplitude, shape, pulse width, train frequency, directionality, polarity and stimulus duration.[18] Higher electrical dosages (i.e., a higher number of pulses) activate larger brain regions.[5,19,20] Moreover, electrical currents will not move in a straight line between the electrodes, but traverse the tissues proportional to its resistances.[5,19] To reach brain tissue effectively, the electrical stimulus must successively pass through scalp, skull, meninges, and cerebrospinal fluid (CSF), with each compartment (Figure 1) having a typical resistance to the passage of the electrical stimulus.[5,19] The skull has a high electrical resistance and gray matter has less resistance, whereas CSF conducts current very well due to the high concentration of free ions in this aqueous solution,[5,19] Consequently, the stimulus dose determines whether the power of the electrical current is sufficient to pass through the different compartments to reach the essential brain tissue.

Electrode placement and head anatomy determine the electric field distribution in the brain.[18] The pathway of the electrical current depends on the electrode proximity to skull foramina, sutures and eye cavities, as well as on brain surface morphology with varying amounts of surrounding CSF.[21,22] In RUL application, the distance between the electrodes is much shorter than in BL, resulting in a more evenly distributed electrical stimulus across the anterior cortex and increased shunting of current.[5,21,23] Therefore, electrode placement plays an important role in determining the spatial distribution of the ECT-induced electric field and, consequently, the ST

Figure 1 Magnetic resonance imaging (MRI)* of scalp, skull, cerebrospinal fluid (CSF), gray matter, white matter and white matter hyperintensities related to right unilateral (RUL) and bifrontotemporal (BL) electrode placement in electroconvulsive therapy



*T_1-weighted MRI of the head in gray colors of a patient showing the highest volume of CSF. Voxels representing CSF are colored blue, gray matter voxels are yellow, white matter is green, and areas underneath the voxels that might be detected as white matter hyperintensities are colored red. Gray triangles represent electrode placement sites. RUL means 3 cm right of the sagittal midline on the vertex and 3 cm above the midline between the right meatus acusticus externa and lateral angle of the right orbita. BL means 3 cm above the midline between the meatus acusticus externa and lateral angle of the orbita, right and left frontotemporal, respectively.

level. RUL electrodes (positioned more closely together) cause more shunting in the scalp and produce more focal and weaker electric fields within the brain. Therefore, in RUL ECT, more electrical pulses are needed to elicit seizure activity than in BL ECT,[18,19] Additionally, after local seizure induction in areas directly beneath the electrodes, cortico-(thalamico-)cortical propagation is required to further spread the seizure.[24] This propagation may be hampered by interruption of these circuits, for instance, due to cerebral lesions such as white matter hyperintensities (WMH). In clinical studies, subcortico-frontal lesions predicted less effective ECT.[25-27] Therefore, information on the relevance of each barrier for the electrical stimulus to excite brain tissue effectively, as well as for the seizure to propagate sufficiently, seems important in order to optimize ECT in an individual patient.

However, prospective studies on the relationship between anatomical characteristics on magnetic resonance imaging (MRI) of the head on the one hand, and IST and ST change on the other, are sparse.[28] Therefore, this prospective study explores the influence of head anatomy on IST and ST during the ECT course.

Methods and materials

Participants and clinical data acquisition

In this observational prospective study, all consecutive patients indicated for ECT in Rijnstate Hospital (Arnhem, the Netherlands, a 36-bed psychiatric facility with a catchment area of 600,000 inhabitants), from December 1 2009 until November 15 2011, were asked to participate. Patients were excluded in case of age < 18 years, absence of written informed consent, and a contraindication for dose titration (e.g., life-threatening condition, severe cardiovascular comorbidity) or for MRI. Within two weeks before the first ECT session, an MRI of the head was made. Patient characteristics were extracted from the medical chart. At baseline, severity of depression was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) [29] and cognitive functioning using the Mini-Mental State Examination (MMSE) [30], both within one week before the start of ECT. Amount and severity of somatic comorbidity was rated using a modified Cumulative Illness Rating Scale (CIRS) [31]. The Medical Ethical committee approved the study protocol, and written informed consent was obtained from all participants.

Patient and clinical characteristics of the study population are described in detail elsewhere.[7] In short, higher age (β=0.24; *P*=0.03) and BL electrode placement (β=0.42; *P*<0.001) independently predicted higher IST.[7] During the ECT course, concomitant medications, including psychopharmacological agents, were continued in a similar dosage, and did not predict the level of IST.[7]

Electroconvulsive therapy and measurement of ST

ECT was administered using a constant-current (0.9 Ampère), brief-pulse (0.25 milliseconds [ms] in RUL and 0.5 ms in BL electrode placement) device (Thymatron IV; Somatics Incorporation, Lake Bluff, Illinois, USA), after induction of anesthesia with intravenous etomidate (1.5 mg/kg body mass), muscle paralysis with intravenous succinylcholine (0.5-1 mg/kg body mass), and with appropriate oxygenation until the resumption of spontaneous respiration. Electrode placement was initially RUL, except in patients at high risk for suicidality and/or somatic complications, or if previous ECT had successfully been administered bilaterally. STs were measured at the 1st, 6th, 12th, 18th and 24th ECT session, in which the latter measurements depended on the duration of the course. The same age-adjusted titration schedule was used at each titration session;[15] patients aged < 50 years started with 25.2 milliCoulombs (mC) and older patients with 50.4 mC. If the first stimulus dose failed to elicit a seizure of at least 20 s of motor activity measured with the cuff method and/or ≥ 25 s on the electroencephalogram, the stimulus charge was doubled according to the titration schedule (see Appendix 1 for the

independent stimulus parameters), and the patient was re-stimulated after 30 s. To become therapeutic, the consecutive electrical dosage was set at 6 times ST in RUL ECT and at 2.5 times ST in BL ECT. Patients were treated twice weekly. At the titration session, if the ST was reached and the levels of muscle relaxation and sedation were still appropriate, the patient was re-stimulated at a therapeutic dose also in this session.

MRI data acquisition

Imaging was performed on a 1.5 Tesla Philips Medical Instruments (Best, the Netherlands) MRI scanner, using a 16-channel SENSE receive head coil. The scanning protocol included a high resolution T_1-weighted (T_1W) turbo field echo MRI (sequence parameters: repetition time = 7.6 ms; echo time = 3.5 ms; flip angle = 15°; 145 sagittal slices; voxel size = 1.1 mm isotropic), a T_2-weighted (T_2W) turbo spin echo MRI (sequence parameters: repetition time = 4803 ms; echo time = 100 ms; flip angle = 90°; 24 transverse slices; in plane voxel resolution = 0.60x0.76 mm; slice thickness = 5 mm; slice gap = 1 mm), and a FLuid Attenuated Inverse Recovery (FLAIR) image (sequence parameters: repetition time = 8000 ms; echo time = 140 ms; flip angle = 90°; 26 coronal slices; in plane voxel resolution = 0.9x1.1 mm; slice thickness = 5 mm; slice gap = 1 mm).

Measurement of scalp and skull thickness

Since the flow of current through the skull is mostly normal to the surface and occurs in the vicinity of the electrodes due to the low conductivity of the skull,[5,18] skull thickness was measured at the electrode placement sites. Furthermore, it was considered that scalp thickness measured under the electrodes was representative for individual scalp thickness around the head. On T_2W images, two independent raters (BART, TWFP) measured the thicknesses in millimetres (mm) at the RUL (i.e., 3 cm right of the sagittal midline on the vertex according to d'Elia [32] and 3 cm above the midline between the right meatus acusticus externa and lateral angle of the right orbita) and at the BL electrode placement sites (i.e., 3 cm above the midline between the meatus acusticus externa and lateral angle of the orbita, right and left frontotemporal, respectively). Interclass coefficients (ICCs) between the raters ranged from 0.6-0.7. Means of the scalp and skull thickness, as measured by the two raters, were calculated for the three localisations (vertex, right and left frontotemporal).

Structural MRI analysis

All analyses were performed using the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL) tools (http://www.fmrib.ox.ac.uk/fsl/). Prior to analysis, all raw data were visually checked for the presence of (motion) artifacts.

Brain extraction.

For each subject, T_1W and FLAIR volumes were brain-extracted (BETv2.1, manually selected individual fractional intensity thresholds).

Mask.

For each subject, a FLAIR-based mask of WMH was created by manually delineating WMH on all coronal slices in FSL view.

Registration.

For each subject, linear transformation parameters from FLAIR native space to T_1W native space were estimated (FLIRTv5.5) and applied to the FLAIR-based mask of WMH, resulting in one T_1W-compatible probability mask that was then thresholded and binarized (automatically calculated individual thresholds to preserve total mask volume). All registrations were visually inspected.

Segmentation.

Each brain-extracted T_1W was segmented into partial volume maps of total CSF, total gray matter and total white matter (FASTv4.1). White matter that was erroneously classified as gray matter due to the presence of WMH (as WMH appear hypo-intense on T_1W) was identified using the T_1W-compatible WMH mask, subtracted from the total gray matter segmentation and added to the total white matter segmentation. All segmentations were visually inspected; no problems occurred during the analysis.

Volumes.

Volumes of total CSF, total gray and white matter, total WMH, and total intracranial volume (ICV) were calculated by multiplying the number of voxels within each partial volume map by the mean value of all voxels within each partial volume map, then multiplied by the voxel volume (1.1x1.1x1.1 mm) and, finally, divided by 1000 to obtain volumes in milliliters (mL).

Analysis of data

Data are presented as means ± standard deviations (SD) and ranges, medians and interquartile ranges (IQR), or numbers and percentages when appropriate. Normally distributed continuous variables (age and MADRS score) between the included/excluded groups were compared using t-tests, non-normally distributed continuous variables (CIRS score and MMSE score) using Mann-Whitney U tests, and categorical variables (gender and diagnosis) were compared using Chi-square tests. Descriptive statistics were used to describe the clinical and MRI characteristics. Mean composite scores for the three localizations of scalp and skull thickness

were calculated. Z-scores were obtained for all appropriate variables. Continuous clinical and MRI variables for RUL and BL electrode placement were compared using t-tests, non-normally distributed continuous variables using Mann-Whitney U tests, and categorical variables using Chi-square tests.

Because of the assumed differences between RUL and BL current distributions and used pulse widths,[5,33] preliminary analyses were performed, showing a significant interaction term (CSF*RUL/BL; $P<0.001$). Therefore, regression analyses were performed for RUL and BL groups separately. First, multivariate regression analyses, adjusted for age, gender and ICV, were done using the z-scores of the six compartments (composite mean scalp and skull thickness, and total volumes of CSF, gray matter, white matter and WMH, respectively) as separate independent variables, to find variables showing $P<0.10$ as possible predictor of the dependent variable IST. Preliminary analyses were conducted to ensure no violation of the assumptions of normality, linearity, multicollinearity and homoscedasticity. Hence, because of collinearity between both gray and white matter volumes and ICV (tolerance<0.1 and variance inflation factor [VIF] value>10), the latter was excluded in the next multivariate analyses. Then, multivariate regression analyses were done with IST as dependent variable and age, gender and all MRI variables showing $P<0.10$ as independent factors. Finally, multivariate regression analyses were repeated for the $ST_{6\text{-}12\text{-}18\text{-}24}$ measured during the ECT course (if available), and combined in a multilevel regression analysis (i.e., mixed linear analysis) entering only the previously identified independent predictors of IST, as well as age, gender and ICV. All tests were two-sided with $P<0.05$ denoting statistical significance; SPSS for Windows (version 18.0) was used for all analyses.

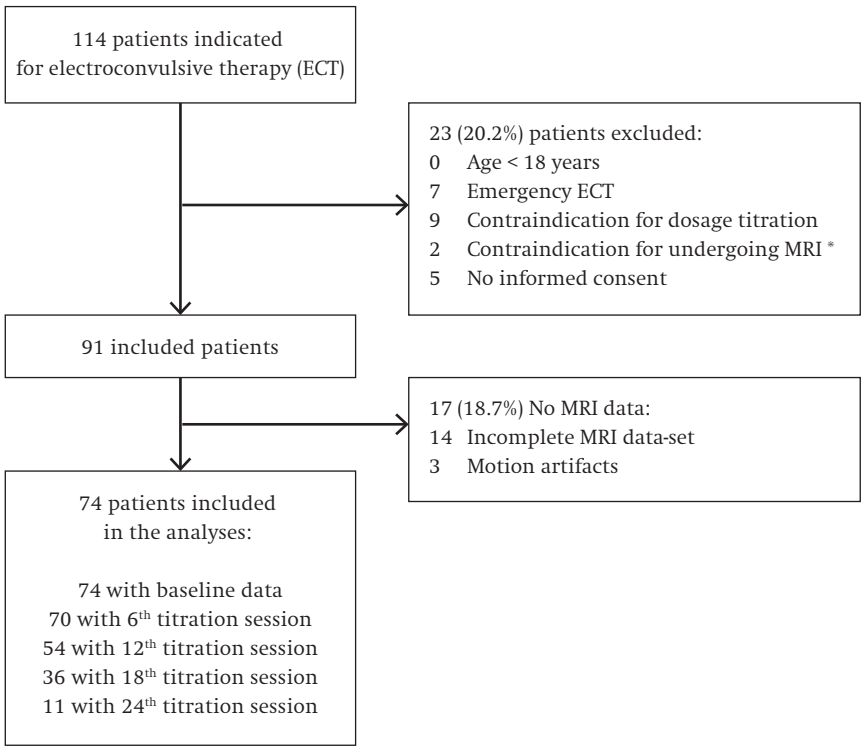
Results

Participants, clinical and anatomical MRI characteristics

Complete MRI datasets were obtained for 77 patients. Due to excessive motion artifacts on the T_1W images, another three subjects had to be excluded, yielding a final sample of 74 patients from the 114 patients indicated for ECT (Figure 2). The excluded patients did not differ from the study group regarding mean age ($P=0.82$), gender ($P=0.56$) and mean MADRS score ($P=0.55$), but excluded patients had a higher median CIRS score ($P=0.003$), a lower median MMSE score ($P=0.02$), and more often had psychotic depression ($P=0.03$) and catatonia ($P=0.003$).

Mean age of the study population was 57.7±14.8 (range: 22-93) years, with 39% men (n=29) (Table 1). The median CIRS score was 21 (IQR: 19-23). Of all patients, 99%

Figure 2 Flow diagram showing the patient selection process



*Magnetic Resonance Imaging

(n=73) suffered from a mood disorder and most patients used a constant dose of concomitant medication. During the index ECT course, an average of 18.1±7.2 (range: 6-38) ECT sessions was administered to 69 patients who completed the course. Anatomical characteristics of the patients are also summarized in Table 1. Patients treated with RUL (n=55) and BL (n=19) electrode placement did not differ from each other, except for their mean level of IST (45.4±17.8 mC in RUL and 87.5±52.0 mC in BL; $P<0.001$), as was expected.

Table 1 Clinical and anatomical characteristics on magnetic resonance imaging (MRI) of patients (n=74) with measured seizure thresholds (ST) during electroconvulsive therapy (ECT), and for right unilateral (RUL; n=55) and bifrontotemporal (BL; n=19) electrode placement

Patient and treatment characteristics	Mean ±SD*, range; n (%); or median; IQR** in all (n=74)	Mean ±SD, range; n (%); or median; IQR in RUL (n=55)	Mean ±SD, range; n (%); or median; IQR in BL (n=19)	P-value for comparison RUL and BL***
Male gender	29 (39.2)	22 (40)	7 (36.8)	1.0
Age, in years	57.7±14.8, 22-93	57.1±13.4, 22-80	59.7±18.5, 27-93	0.24
Diagnostic category, according to axis 1 of DSM-IV-TR****:				
Depressive disorder without psychotic features	45 (60.8)	35 (63.6)	10 (52.6)	0.43
Depressive disorder with psychotic features	16 (21.6)	11 (20)	5 (26.3)	0.54
Bipolar disorder, depressive episode	12 (16.2)	9 (16.4)	3 (15.8)	1.0
Other disorders (i.c. catatonia)	1 (1.4)	0 (0)	1 (5.3)	0.26
Use of seizure threshold influencing concomittant pharmacotherapy:				
Benzodiazepines	46 (62.2)	35 (63.6)	11 (57.9)	0.79
Anti-epileptics	6 (8.1)	4 (7.3)	2 (10.5)	0.64
Antidepressants	44 (59.5)	35 (63.6)	9 (47.4)	0.28
Antipsychotics	49 (66.2)	39 (70.9)	10 (52.6)	0.17
MADRS score$ at baseline	36.0±8.6, 17-54	35.4±8.9, 17-54	37.7±7.5, 23-49	0.18
MMSE score$$ at baseline	28 (26-29.8)	28 (26-29.3)	27 (25-30)	0.10
CIRS score$$$ at baseline	21 (19-23)	21 (19-23)	21 (18-24)	0.43
Electrode placement is bifrontotemporal at first titration session	19 (25.7)			
Total amount of ECT sessions during the course (n=69; 51; 18)	18.1±7.2, 6-38	18.6±7.6, 6-38	16.7±5.7, 10-28	0.44
Initial ST, in milliCoulombs (mC)	56.2±35.3, 25.2-201.6	45.4±17.8, 25.2-100.8	87.5±52.0, 25.2-201.6	<0.001

Thickness scalp, in mm^				
At d'Elia	4.9±1.9, 1.0-9.5	4.8±1.7, 2-9.5	5.2±2.4, 1-8.5	0.15
Right frontotemporal	7.9±2.7, 2.5-15.5	7.9±2.4, 2.5-14	7.5±3.5, 3-15.5	0.51
Left frontotemporal	8.5±3.3, 2.5-18.0	8.6±3.0, 2.5-16.0	8.4±3.9, 2.5-18.0	0.87
Mean composite scalp thickness	7.1±2.4, 2.5-13.3	7.2±2.2, 2.5-11.5	7.1±3.1, 2.7-13.3	0.99
Thickness skull, in mm				
At d'Elia	5.7±1.9, 2.5-10.0	5.9±1.9, 2.5-10.0	5.8±1.9, 2.5-8.5	0.65
Right frontotemporal	4.5±1.5, 1.5-8.0	4.3±1.5, 1.5-8.0	4.5±1.5, 2-7	0.27
Left frontotemporal	4.5±1.4, 1.5-7.5	4.5±1.5, 1.5-7.5	4.5±1.3, 2.5-7	0.24
Mean composite skull thickness	4.9±1.4, 2.2-7.3	4.9±1.5, 2.2-7	4.9±1.4, 2.3-7.3	0.31
Total volumes, in mL^^				
Intracranial volume	1456±140, 1182-1789	1454±143, 1208-1789	1464±139, 1182-1680	0.79
Cerebrospinal fluid	376±45, 302-528	372±42, 302-469	386±54, 315-528	0.25
Gray matter	537±60, 405-697	541±56, 434-697	526±70, 405-635	0.33
White matter	543±63, 420-697	540±66, 420-679	552±54, 436-640	0.49
White matter hyperintensities	3.1; 1.1-9.8	3.0; 1.1-6.5	4.3; 0.8-34.6	0.40

*standard deviation; **interquartile range; ***continuous variables tested with t-tests, categorical variables tested with Chi-square tests, and not-normally distributed continuous variables tested with Mann-Whitney U tests; ****Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; §Montgomery-Åsberg Depression Rating Scale; §§Mini-Mental State Examination; §§§Cumulative Illness Rating Scale (modified version); ^millimetres, measured by two independent raters; ^^milliliters.

Anatomical characteristics and ST

Table 2 shows the results of the regression analyses. Because total ICV may confound volumes of CSF and brain structures measured, the influence of ICV on the level of IST was analyzed first with univariate regression analysis and showed no association (in RUL β=-0.14, *P*=0.31; in BL β=0.08, *P*=0.73). In both RUL and BL groups, the volume of CSF was positively associated with IST (Table 2). Because of

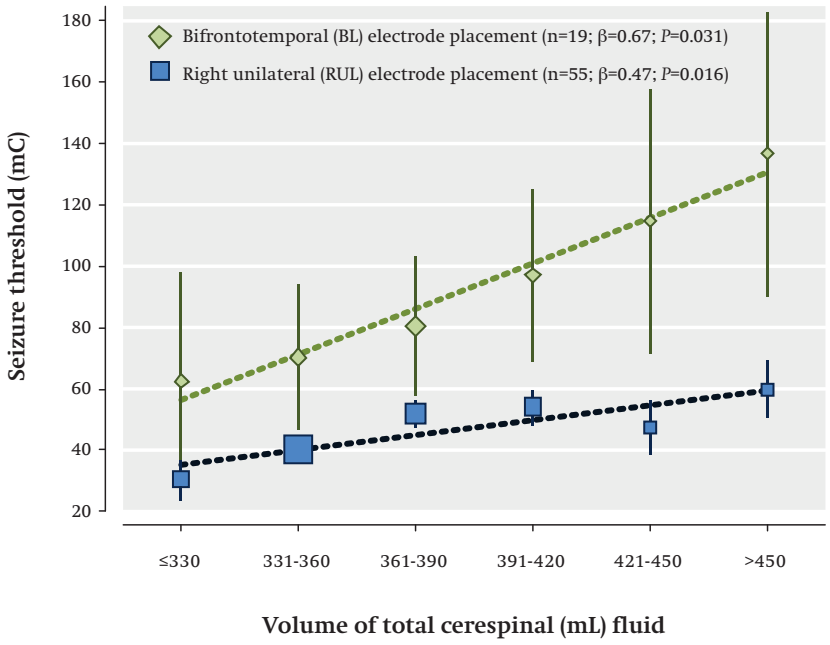
Table 2 Data on regression analyses to detect independent anatomical characteristics on magnetic resonance imaging predicting the variation of seizure threshold (ST) in 74 patients undergoing right unilateral (RUL) and bifrontotemporal (BL) electroconvulsive therapy (ECT).

Index-scores in RUL ECT	**Correlates of initial ST (n=55)***		**Multivariate correlates of initial ST** (n=55)**	
	β-coefficient	*P*-value	β-coefficient	*P*-value
Age	0.41	0.002	0.29	0.03
Gender	-0.03	0.82	-0.07	0.69
Thickness of the scalp	0.24	0.08	0.19	0.14
Thickness of the skull	0.21	0.11		
Volume of total cerebrospinal fluid	0.47	0.02	0.31	0.049
Volume of total gray matter	-0.56	0.15		
Volume of total white matter	-0.74	0.07	-0.30	0.10
Volume of total white matter hyperintensities	0.11	0.50		
Index-scores in BL ECT	**Correlates of initial ST (n=19)***		**Multivariate correlates of initial ST** (n=19)**	
	β-coefficient	*P*-value	β-coefficient	*P*-value
Age	0.64	0.003	0.33	0.24
Gender	-0.02	0.94	-0.14	0.49
Thickness of the scalp	0.02	0.94		
Thickness of the skull	-0.08	0.71		
Volume of total cerebrospinal fluid	0.67	0.03	0.64	0.007
Volume of total gray matter	-0.89	0.08	-0.05	0.84
Volume of total white matter	-0.66	0.26		
Volume of total white matter hyperintensities	-0.02	0.96		

*All six anatomical structures were adjusted for age, gender and intracranial volume (ICV). **Multivariate regression analysis only for variables showing *P*<0.10 at first regression analysis, adjusted for age and gender, and not for ICV due to multicollinearity.

multicollinearity with gray and white matter volumes, ICV was not entered into the multivariate analyses. After entering all variables showing $P<0.10$ in the first step of our regression analyses, only the volume of CSF was an independent predictor of the level of IST, in both RUL and BL treated patients (β=0.31; $P=0.049$ and β=0.64; $P=0.007$, respectively; see Table 2). In an additional confirmatory analysis, in which age, gender and ICV were entered into the model, the strong predictive value of CSF volume persisted in RUL and BL ECT (β=0.47, $P=0.02$ and β=0.67, $P=0.03$, respectively) (Figure 3).

Figure 3 Mean values of initial seizure threshold in milliCoulombs (mC; with error bars representing standard errors) according to categories of volumes of cerebrospinal fluid in milliliters (mL) in patients undergoing either bifrontotemporal (BL) or right unilateral (RUL) electroconvulsive therapy *



* The dotted lines represent the regression lines. The size of each square is proportional to the number of patients. Mean values are adjusted for age, gender and volume of intracranial space. Beta-coefficients and *P*-values by multivariable regression analyses. The *P*-value for interaction (i.e., CSF*RUL/BL) was statistically significant ($P<0.001$).

Subsequently, entering the CSF volume into the linear mixed model and using $ST_{6\text{-}12\text{-}18\text{-}24}$ as dependent variables, thereby adjusting for age, gender and ICV, a significant association was found with the consecutive ST levels during the RUL ECT course (β=0.20; *P*=0.02). In the BL treated group, the positive association appeared to be similar in strength, although not significant (β=0.23; *P*=0.24).

Discussion

In this observational prospective study, the total volume of CSF appeared to be the only independent and strong morphological predictor of IST in both RUL and BL ECT. This relationship persisted after adjustment for age, gender and ICV, and showed an even stronger association with BL than with RUL electrode placement. Although this relation has previously been hypothesized [28] and was estimated in computer models,[19] this prospective study is (to our knowledge) the first to demonstrate an important role for CSF volume on the level of IST.

The fact that CSF volume predicted the IST can be explained by its biophysical properties. CSF is a relatively cell-free, low-protein ultrafiltrate of blood, and contains an abundant amount of ions.[34] As a good electric conductor[19], CSF may serve as a spherical conducting shell (as a Faraday cage) that reduces the size of the ECT-induced electric field inside the brain. A weaker and more focal electrical field, in case of more surrounding CSF, has to be pulsed more times to trigger a seizure.[18,19] Therefore, in our patients with a relatively increased CSF volume, during titration with fixed current amplitude and pulse width, the number of electrical pulses probably had to be increased.
Different electrical shunting patterns were expected in RUL and BL electrode placement,[5,21] as was confirmed by the significant interaction term CSF*RUL/BL. In BL ECT, the relationship between CSF volume and IST was much stronger than in RUL ECT. Possibly, a larger distance between BL placed electrodes, and enhanced electrical shunting through more CSF, resulted in higher IST levels than in RUL placement. On the other hand, the larger 0.5 ms pulse width used in BL placement, which may show higher ST than with 0.25 ms used in RUL,[33] may have confounded the results.

Anatomical differences and disruptions of current pathways are suggested to explain variations of ST in patients.[23,28,35-37] In a recent computerized simulation study of ECT in spherical head models, a 15% decrease in volume of gray and white matter (corresponding to an increase of CSF volume of 116% and 113%, in the male and female model, respectively), led to a 55% decrease of stimulated gray matter

volume and about a 36% decrease of the stimulation strength and, thereby, to a higher ST.[19] Our clinical results seem to be in accordance with these computer model calculations, as higher volumes of CSF predicted higher IST. Furthermore, large effects of scalp and skull thickness on stimulation strength and excited brain volume were estimated in the computer models.[19] In detail, the RUL ECT model showed that lower scalp thickness resulted in stronger stimulation strength and larger stimulated brain volume with, consequently, lower ST. At the same time, higher skull thickness resulted in weaker stimulation strength, smaller excited brain volume and higher ST.[19] However, in our clinical study, these modeled influences on IST could not be confirmed, probably because in the computer model thicknesses were used derived from the literature, which probably did not exactly match ours at the electrode placement sites. Also, due to the sites that we selected for thickness measurement, the influence of the inferior portions of the head was not taken into account, which may explain the very weak univariate correlations between ST and scalp and skull thickness for BL electrode placement compared to RUL. Moreover, our MRI estimates of scalp and skull thicknesses were hampered by measurement differences between the raters, which could have weakened the influence of these variables in the regression models. Furthermore, we hypothesized that a higher IST is due to more white matter disruptions in neuronal circuitry; however, no predictive value of the total WMH volume on IST could be determined, possibly due to some important methodological limitations, which we discuss below.

It is remarkable that, in our study, the influence of CSF volume on IST was independent of age and gender, because older people often show increased CSF volume due to cortical atrophy,[38] especially men.[39] In our data, age is indeed correlated with CSF volume (r=0.26; P=0.03), and men show higher mean CSF volumes than women (P<0.001; data not shown), supporting the clinical experience of higher ST in older men.[2] It is noteworthy that age and gender did not limit the strong associations between CSF volume and IST. However, increased CSF volume, due to cortical atrophy, is not determined exclusively by age and gender. Cortical atrophy has also been associated with (amongst other parameters) hereditary factors, starvation, neurodegenerative and cerebrovascular diseases, alcohol abuse and the use of certain medications (e.g., lithium).[40] Moreover, compared to normal controls, larger CSF volumes have been demonstrated in patients suffering from major depression.[41] These risk factors for increased atrophy and increased CSF volume were present in our study patients.

During the ECT course, in 18-67% of our patients the ST levels increased with a median of 25-50 mC versus IST, mostly with BL treatment.[7] The CSF volume also

predicted the consecutive ST levels during the ECT course, although only reached significance in RUL ECT, most likely due to the limited sample size of the BL treated group. However, the estimated standardized associations were lower (βs were 0.2 [$ST_{6\text{-}12\text{-}18\text{-}24}$] instead of 0.3 and 0.6 [IST], in RUL and BL ECT, respectively). Since it is very unlikely that the CSF volume changed significantly during the ECT course, other ECT-related factors may have emerged as more dominant determinants of the consecutive ST levels.[7] For instance, consecutive ECT sessions may have decreased neuroexcitability through an increase of the inhibitory (e.g., gamma-aminobutyric acid) and/or a decrease of the excitatory (e.g., glutamate) neurotransmitter systems.[10,21]

Clinical implications

Our study provides new information for clinicians to estimate the proper ECT dose. Our results suggest that, in patients with higher CSF volumes on MRI scans, a higher electrical stimulus dose may be needed to elicit therapeutic seizures. Current age-based dosing methods do not take CSF volumes into account,[2] and age explained only 8-25% of the IST variance.[28] Therefore, with age-based methods, younger patients with increased CSF volumes may be treated with ineffectively low electrical doses, and older patients with less than average brain atrophy may be overdosed and, consequently, prone to more cognitive side-effects.

Study limitations

The most critical limitation in this study is probably our very crude and age-adjusted ST titration method. Substantial steps of 25-100 mC were used, which undoubtedly led to overestimation of ST in several patients.[7,33,42] Moreover, our pulse widths differed between the two electrode placements, which could have resulted in higher ST levels in the BL group, compared to the RUL treated patients.[33] Also, our dosage increments were accompanied by higher stimulus frequencies and durations (and change in pulse width at the final step in RUL ECT), which will have had considerable impact on the level of ST. Possibly, more discrete predictors of ST (e.g., anatomical factors) were not detected due to the crudeness of our measurements. Furthermore, age probably confounded the anatomical variables and choice of electrode placement, because of (severe) somatic comorbidity and/or pre-existing cognitive functioning. Despite these limitations, CSF volume was an important predictor of ST. Replication of this finding, using a more precise and age-neutral titration method, is definitely needed.

Another important limitation is the FSL program used to determine brain tissue volumes. The brain extraction tool limited outer-brain CSF estimates causing a systematic error with underestimation of the CSF volume.[43] Furthermore, the

segmentation process did not always adequately distinguish between CSF and brain tissue, and the registration processes had appointed some voxels to wrong structures, leading to erroneous calculations of the volumes. For example, Figure 1 shows that the CSF space between the superficial cortex and the skull was occasionally poorly segmented and that parts of the skull and CSF were assigned to white matter and gray matter. These errors most probably biased the effect estimates towards the null hypothesis implying that the predictive value of CSF volume on (I)ST may be even higher.

Several other potential limitations need to be addressed. Of the 114 potential participants, only 74 had complete head MRI datasets; moreover, compared with the study population, the excluded patients differed in clinical diagnosis, somatic comorbidity and cognitive functioning. Also, in the literature different titration methods are used, which limits comparison of our estimated ST levels with others. In our study, titration took place under anesthesia with etomidate, an anesthetic that has been associated with lower ST than propofol.[44] Therefore, our results can not be generalized to patients anesthetized with other anesthetics. Furthermore, usage of constant doses of concomitant medication during the ECT course could have influenced the ST. Although we did not show such association in our preliminary clinical study,[7] confounding of our results cannot be excluded. Finally, measurement of scalp and skull thickness by the two independent raters showed ICCs of only moderate strength (0.6-0.7), suggesting a measurement error which could have led to an underestimation of the true relationships in our regression analyses (type II error). Nevertheless, using the mean of these two raters reduced some of this measurement error (by a factor of 1.4) as compared to using one rating alone. Especially with RUL ECT, more shunting of current through the thicker layers of scalp tissue was expected to predict higher IST; however, in the multivariable model the effect was of moderate strength and only tended toward significance (β=0.24; P=0.08).

In conclusion, in this observational prospective study, taking into account the methodological limitations, CSF volume predicted the level of IST in ECT, besides the well-known predictors of age and electrode placement. Moreover, during the RUL ECT course, higher STs were predicted by higher CSF volume. Therefore, it is important to take into account that, when exclusively age-based dosing methods are used, less effective electrical stimuli may be administered in younger patients with increased CSF volumes and overdosing may occur in older patients with average CSF volumes. Additional studies relating CSF volume to IST and the clinical efficacy of ECT are needed before firm conclusions can be drawn.

Acknowledgments

The authors thank all the staff of the Department of Radiology in Rijnstate Hospital, especially Marc van Driel (head of the MRI section) and Mrs. Gonda Niehuis (quality manager) for their technical assistance, and Teun W.F. Pappot, MD, for his measurements as second rater of scalp and skull thickness on MRI; and all the staff of the Department of Psychiatry in Rijnstate Hospital, especially Oscar Büno Heslinga (ECT-nurse) for his excellent help in collecting the data.

References

(1) Mann JJ. The medical management of depression. N Engl J Med 2005;353:1819-34.
(2) Abrams R. Electroconvulsive Therapy. Fourth edition. New York, NY: Oxford University Press; 2002.
(3) UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. Lancet 2003;361:799-808.
(4) Ottosson JO. Seizure characteristics and therapeutic efficiency in electroconvulsive therapy: an analysis of the antidepressive efficiency of grand mal and lidocaine-modified seizures. J Nerv Ment Dis 1962;135:239-51.
(5) Sackeim HA, Long J, Luber B et al. Physical properties and quantification of the ECT stimulus: I. Basic principles. Convuls Ther 1994;10:93-123.
(6) Sackeim HA, Devanand DP, Prudic J. Stimulus intensity, seizure threshold, and seizure duration: impact on the efficacy and safety of electroconvulsive therapy. Psychiatr Clin North Am 1991;14: 803-43.
(7) Van Waarde JA, Van Oudheusden LJB, Verwey B, Giltay EJ, Van der Mast RC. Clinical predictors of seizure threshold in electroconvulsive therapy: a prospective study. Eur Arch Psychiatry Clin Neurosci 2013;263:167-175.
(8) Boylan LS, Haskett RF, Mulsant BH et al. Determinants of seizure threshold in ECT: benzodiazepine use, anesthetic dosage, and other factors. J ECT 2000;16:3-18.
(9) Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M. Seizure threshold in electroconvulsive therapy: I. Initial seizure threshold. Biol Psychiatry 1995;37:713-20.
(10) Sackeim HA. The anticonvulsant hypothesis of the mechanisms of action of ECT: current status. J ECT 1999;15:5-26.
(11) Fink M, Petrides G, Kellner C et al. Change in seizure threshold during electroconvulsive therapy. J ECT 2008;24:114-6.
(12) Krystal AD, Coffey CE, Weiner RD, Holsinger T. Changes in seizure threshold over the course of electroconvulsive therapy affect therapeutic response and are detected by ictal EEG ratings. J Neuropsych Clin Neurosci 1998;10:178-86.
(13) McCall WV, Reboussin DM, Weiner RD, Sackeim HA. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. Arch Gen Psychiatry 2000;57:438-44.
(14) Sackeim HA, Prudic J, Devanand DP et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. Arch Gen Psychiatry 2000;57:425-34.
(15) American Psychiatric Association. The Practice of Electroconvulsive Therapy. Second Edition. Washington DC: American Psychiatric Association; 2001.
(16) Van Waarde JA, Van den Broek WW, Verwey B, Van der Mast RC. Electroconvulsive therapy in the Netherlands: a questionnaire survey on contemporary practice. J ECT 2009;25:190-194.
(17) Swartz CM. Stimulus dosing in electroconvulsive therapy and the threshold multiple method. J ECT 2001;17:87-90.
(18) Peterchev AV, Rosa MA, Deng ZD, Prudic J, Lisanby SH. Electroconvulsive therapy stimulus parameters: rethinking dosage. J ECT 2010;26:159-74.
(19) Deng ZD, Lisanby SH, Peterchev AV. Effect of anatomical variability on neural stimulation strength and focality in electroconvulsive therapy (ECT) and magnetic seizure therapy (MST). Conf Proc IEEE Eng Med Biol Soc 2009;2009:682-8.
(20) Swartz CM. Electroconvulsive therapy stimulus dose expressed as volume of seizure foci. J ECT 2006;22:54-8.
(21) Swartz CM. Electroconvulsive and neuromodulation therapies. New York, NY: Cambridge University Press; 2009.
(22) Datta A, Bansal V, Diaz J, Patel J, Reato D, Bikson M. Gyri -precise head model of transcranial DC stimulation: Improved spatial focality using a ring electrode versus conventional rectangular pad. Brain Stimul 2009;2:201-7.

(23) Colenda CC, McCall WV. A statistical model predicting the seizure threshold for right unilateral ECT in 106 patients. Convuls Ther 1996;12:3-12.
(24) Enev M, McNally KA, Varghese G, Zubal IG, Ostroff RB, Blumenfeld H. Imaging onset and propagation of ECT-induced seizures. Epilepsia 2007;48:238-44.
(25) Simpson S, Baldwin RC, Jackson A, Burns AS. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. Psychol Med 1998;28:1015-26.
(26) Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B. Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. Biol Psychiatry 1995;37:151-60.
(27) Steffens DC, Conway CR, Dombeck CB, Wagner HR, Tupler LA, Weiner RD. Severity of subcortical gray matter hyperintensity predicts ECT response in geriatric depression. J ECT 2001;17:45-9.
(28) Van Waarde JA, Van der Mast RC. Seizure thresholds in elderly patients treated with electroconvulsive therapy for major depressive disorder. A review. Curr Psychiatry Rev 2010;6:184-90.
(29) Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382-9.
(30) Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
(31) Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968;16:622-6.
(32) d'Elia G. Unilateral electroconvulsive therapy. Acta Psychiatr Scand Suppl 1970;215:1-98.
(33) Sackeim HA, Prudic J, Nobler MS et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. Brain Stimul 2008;1:71-83.
(34) Nolte J. The Human Brain. An Introduction to its Functional Anatomy. 6th ed. Philadelphia, PA: Mosby Elsevier; 2009.
(35) Sackeim H, Decina P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. Arch Gen Psychiatry 1987;44:355-60.
(36) Shapira B, Lidsky D, Gorfine M, Lerer B. Electroconvulsive therapy and resistant depression: clinical implications of seizure threshold. J Clin Psychiatry 1996;57:32-8.
(37) McCall WV, Shelp FE, Weiner RD, Austin S, Norris J. Convulsive threshold differences in right unilateral and bilateral ECT. Biol Psychiatry 1993;34:606-11.
(38) Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS, Hesselink JR. Cerebral structure on MRI, Part I: Localization of age-related changes. Biol Psychiatry 1991;29:55-67.
(39) Gur RC, Mozley PD, Resnick SM et al. Gender differences in age effect on brain atrophy measured by magnetic resonance imaging. Proc Natl Acad Sci U S A 1991;88:2845-9.
(40) Soares JC, Mann JJ. The anatomy of mood disorders--review of structural neuroimaging studies. Biol Psychiatry 1997;41:86-106.
(41) Kempton MJ, Salvador Z, Munafo MR et al. Structural neuroimaging studies in major depressive disorder. Meta-analysis and comparison with bipolar disorder. Arch Gen Psychiatry 2011;68:675-90.
(42) Kotresh S, Girish K, Janakiramaiah N, Rao GU, Gangadhar BN. Effect of ECT stimulus parameters on seizure physiology and outcome. J ECT 2004;20:10-2.
(43) Keihaninejad S, Heckemann RA, Fagiolo G, Symms MR, Hajnal JV, Hammers A. A robust method to estimate the intracranial volume across MRI field strengths (1.5T and 3T). Neuroimage 2010;50:1427-37.
(44) Patel AS, Gorst-Unsworth C, Venn RM, Kelley K, Jacob Y. Anesthesia and electroconvulsive therapy: a retrospective study comparing etomidate and propofol. J ECT 2006;22:179-83.

Appendix 1

Independent electrical stimulus parameters in the titration schedule using a constant current of 0.9 Ampère ECT device.

Electrode placement	% of maximum output charge of ECT device	Charge, in milliCoulombs	Pulse width, in milliseconds	Frequency	Stimulus duration, in seconds
Right unilateral	5*	25.2	0.25	10	5.60
	10	50.4	0.25	20	5.60
	20	100.8	0.25	30	7.47
	40	201.6	0.25	60	7.47
	80	403.2	0.5	60	7.47
Bifrontotemporal	5*	25.2	0.5	10	2.80
	10	50.4	0.5	10	5.60
	20	100.8	0.5	20	5.60
	40	201.6	0.5	30	7.47
	80	403.2	0.5	60	7.47

* Patients aged < 50 years started with 5%, older patients with 10%