Progress in Neuro-Psychopharmacology & Biological Psychiatry 73 (2017) 31–35

Contents lists available at ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Cerebellar volume change in response to electroconvulsive therapy in patients with major depression

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ARTICLE INFO

Article history:
Received 21 July 2016
Received in revised form 12 September 2016
Accepted 21 September 2016
Available online 22 September 2016

Keywords:
Electro-convulsive therapy
ECT
Depression
Cerebellum
Cerebellar volume

ABSTRACT

Electroconvulsive therapy (ECT) is remarkably effective in severe major depressive disorder (MDD). Growing evidence has accumulated for brain structural and functional changes in response to ECT, primarily within corticolimbic regions that have been considered in current neurobiological models of MDD. Despite increasing evidence for important cerebellar contributions to affective, cognitive and attentional processes, investigations on cerebellar effects of ECT in depression are yet lacking. In this study, using cerebellum-optimized voxel-based analysis methods, we investigated cerebellar volume in 12 MDD patients who received right-sided unilateral ECT. 16 healthy controls (HC) were included. Structural MRI data was acquired before and after ECT and controls were scanned once. Baseline structural differences in MDD compared to HC were located within the "cognitive cerebellum" and remained unchanged with intervention. ECT led to gray matter volume increase of left cerebellar area VIIa crus I, a region ascribed to the "affective/limbic cerebellum". The effects of ECT on cerebellar structure correlated with overall symptom relief. These findings provide preliminary evidence that structural change of the cerebellum in response to ECT may be related to the treatment's antidepressant effects.

1. Introduction

Electroconvulsive therapy (ECT) is an effective and rapidly acting treatment modality in severe major depressive disorder (MDD), even if other treatment options have failed. The intriguing question of how repeated ECT-induced seizures interact with intrinsic brain processes has been subject to ongoing structural and functional brain imaging research, especially in MDD (Bouckaert et al., 2014; Depping et al., 2014; Gudayol-Ferre et al., 2015). Consistent evidence supports the notion that ECT enables structural neuroplasticity in limbic regions, i.e. within anterior cingulate and temporal cortex, hippocampus and amygdala (Tendolkar et al., 2013; Dukart et al., 2014; Ota et al., 2015; Sartorius et al., 2016; Wolf et al., 2016). While these cerebral effects of ECT have been substantiated by an increasing number of studies, cerebellar effects subsequent to ECT have not been investigated yet. There is however good reason to consider a potential modulation of the cerebellum by ECT: First, the cerebellum substantially contributes to affective, cognitive and attentional processes (Schmahmann et al., 2007). These contributions rely on functionally separate, topographically organized subsystems within the so-called "non-motor cerebellum" (Stoodley and Schmahmann, 2009; Stoodley and Schmahmann, 2010), i.e. within cerebellar regions that are predominantly involved in cognitive and affective processing. Second, in MDD, there is evidence for both disease- and treatment-related structural alterations of the "non-motor cerebellum" (Depping et al., 2016). Third, ictal cerebellar involvement during ECT-induced seizures has been repeatedly demonstrated (Blumenfeld et al., 2003; Enev et al., 2007; Takano et al., 2011). Ictal cerebellar involvement has even been promoted as one parameter that may be essential for ECT efficacy (Takano et al., 2011). Fourth, cerebellar neuroplasticity is well recognized in response to different stimuli, such as in motor learning (Dayan and Cohen, 2011) and in reorganization after injury (Seil, 2014).

In this study, we were interested in whether ECT – applied in severe MDD – would induce structural change of the cerebellum. To specifically detect cerebellar volume change, we applied cerebellum-optimized

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http://dx.doi.org/10.1016/j.pnpbp.2016.09.007
0278-5846/

voxel-based analysis methods, i.e. the Spatially Unbiased Infratentorial Toolbox (SUIT, http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm), to a structural imaging data set of 12 MDD patients (before and after ECT) that had previously undergone whole-brain multivariate statistical analyses for investigation of cortical structural effects of ECT (Wolf et al., 2016). 16 healthy control (HC) subjects were included for comparison purposes and were scanned once. SUIT provides a high-resolution, spatially unbiased atlas template of the human cerebellum (Diedrichsen, 2006). The cerebellar template preserves anatomical detail of cerebellar subregions by using automated nonlinear normalization methods, thus achieving a more accurate intersubject-alignment compared to whole-brain methods. SUIT has been successfully used to identify differences in cerebellar subdivisions in both psychiatric and neurological patient samples (Diedrichsen, 2006; Kuhn et al., 2011; Depping et al., 2016). Eventually, SUIT has been shown to be more sensitive to cerebellar structural differences in contrast to conventional whole-brain VBM (Diedrichsen, 2006; Kuhn et al., 2011).

We hypothesized that clinically successful ECT could be related to regional gray matter volume (GMV) change within the cerebellum. Specifically, we predicted ECT-induced modulation of cerebellar volume within the "non-motor cerebellum", i.e. within areas VI, VII and/or IX. Employing exploratory analyses, we sought to additionally reveal structure-symptom relationships. Based on our previous investigation of cerebellar morphology in ECT-naïve, medicated MDD patients (Depping et al., 2016), we hypothesized that successful ECT would be associated with structural modulation of non-motor cerebellar regions.

2. Materials and methods

2.1. Participants

12 ECT-naïve patients with pharmacoresistant (see below) MDD and 16 healthy controls (HC) were included in this study (Table 1). All participants were right-handed. Patients were recruited among inpatients at the Department of General Psychiatry, Heidelberg University. Diagnostic assessment was performed according to DSM-IV criteria. All patients fulfilled criteria for severe depressive episode according to DSM-IV. Depression severity was assessed by means of the 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton, 1967), and the cut-off for inclusion was HAMD score >18, indicating at least moderate depression (Zimmerman et al., 2013). Case notes were reviewed to corroborate a definitive diagnosis of MDD. Prior to enrollment, patients had responded insufficiently to treatment with at least two antidepressants from different classes (each administered in adequate dosage and duration), as well as to an augmentation trial with lithium (serum concentration 0.6–0.8 mmol/L, administered for at least 3–4 weeks). Lithium had been terminated for at least one week prior to enrollment. The choice of antidepressant medication at the time of enrollment was up to each patient's psychiatrist, but drug regimens remained unchanged throughout the entire study period. Medication details are provided as supplementary material (Table S2). All control participants were medication-free (except for birth control pills). Exclusion criteria in all participants were a lifetime history of severe neurological or medical illness, head injury, severe substance abuse or lifetime substance dependence according to DSM-IV. To detect cognitive impairment resulting from ECT (Verwijk et al., 2012), all MDD patients underwent standardized neuropsychological assessment before and after ECT. Specifically, the d2 test (Brickenkamp, 2000), the digit span (forward and backward conditions) derived from the Wechsler Memory Scale-Revised (Wechsler, 1997; Härting et al., 2000), and the Trail Making Test, parts A and B (Reitan, 1959), were applied to assess attention/concentration, verbal short-term memory, and executive functioning, respectively. Details of neuropsychological assessment are provided as supplementary material (Table S3). All ratings and MRI acquisitions in patients were performed within 5 days prior to the first ECT session and 6–8 days after the last ECT session. The study was approved by the local ethics committee (Heidelberg University) and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Table 1
Demographics and clinical variables for controls and patients with MDD. HAMD: Hamilton Depression Rating Scale, scores before (pre) and after (post) ECT; *: Chi-square test.

	Controls ($n = 16$)		MDD patients ($n = 12$)		
	Mean	sd	Mean	sd	p-Value
Age (years)	40.1	10.3	46.3	11.3	0.14
Education (years)	16.1	2.3	15.8	5.2	0.84
Gender (m/f)	8/8	n.a.	4/8	n.a.	0.459*
Duration of illness (years)			15.3	9.4	
Number of episodes			3.3	1.2	
Duration of current episode (weeks)			30.6	9.6	
Number of ECT sessions			10.6	2.6	
HAMD pre ECT			26.8	6.5	
HAMD post ECT			6.5	3.9	
HAMD reduction			20.3	7.3	

2.2. ECT

Right-sided unilateral (RUL) brief pulse, constant current, square wave ECT (Thymatron System IV, Somatics Inc., Lake Bluff, IL, USA) was administered three times per week. The stimulus intensity was set empirically, following standard clinical practice (UK ECT Review Group, 2003). The total number of ECT sessions in each patient was determined according to the individual clinical response to ECT, i.e. treatment was administered until symptom remission occurred or until no further clinical improvement was achieved. Anesthetic management included bodyweight-adapted etomidate followed by succinylcholine for muscle relaxation.

2.3. MRI acquisition

Structural MRI data were acquired on a 3 Tesla Siemens MAGNETOM Tim Trio MRI system equipped with a 12-channel phased-array head coil (Siemens, Erlangen, Germany). A T1-weighted three-dimensional magnetization prepared rapid gradient echo (MP-RAGE) pulse sequence was used, with isotropic spatial resolution of 1 mm^3 (image matrix = 256 × 256 × 192, repetition time = 1.57 s, echo time = 2.74 ms, flip angle = 15°).

2.4. MRI data analysis

We used the Statistical Parametric Mapping software package version 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm) running under Matlab version 7.14.0 (R2012a). For cerebellar data processing, the Spatially Unbiased Infratentorial Toolbox (SUIT, http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm) was used. First, individual T1 images were controlled for scanner artifacts and gross anatomical abnormalities, and each image's origin was manually set at the anterior commissure. Infratentorial structures (i.e. cerebellum and brainstem) were then isolated from the surrounding tissue. The isolation procedure included the segmentation of the brain into tissue-types using the unified segmentation approach (Ashburner and Friston, 2005; Schlerf et al., 2012; Piccinin et al., 2014; Stefanescu et al., 2015). To test for cerebellar GMV differences between groups, t-tests were computed where age and gender were included as nuisance variables. Local group differences were considered significant using a height-threshold of $p < 0.005$, corrected for spatial extent by applying a small volume correction (SVC) of $p < 0.05$ at the cluster-level after applying a sphere with a 6 mm radius to voxel maxima surviving the height-threshold. All anatomical localizations were determined using a probabilistic MRI atlas of the human cerebellum (Diedrichsen, 2006), as implemented in the