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Neuromodulation in response to electroconvulsive therapy in schizophrenia and major depression

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ABSTRACT

Background: Electroconvulsive therapy (ECT) is one of the most effective treatments in severe and treatment-resistant major depressive disorder (MDD). ECT has been also shown to be effective in schizophrenia (SZ), particularly when rapid symptom reduction is needed or in cases of resistance to drug-treatment. However, its precise mechanisms of action remain largely unknown.
Objective/Hypothesis: This study examined whether ECT exerts disorder-specific or unspecific modulation of brain structure and function in SZ and MDD.
Methods: We investigated neuromodulatory effects of right-sided unilateral ECT in pharmacoresistant patients with SZ or MDD. Magnetic resonance imaging was conducted before and after ECT to investigate treatment-related effects on brain structure and function. Imaging data were analyzed by means of Voxel Based Morphometry and Resting State Functional Connectivity (RSFC) methods.
Results: Right unilateral ECT induced transdiagnostic regional increases of limbic gray matter and modulations of neural coupling at rest. Structural effects were accompanied by a decrease in RSFC within temporoparietal, prefrontal and cortical midline structures, and an increase in hypothalamic RSFC. The extent of structural and functional change was partially inversely associated with the baseline measures.
Conclusion: The present findings provide first evidence for transdiagnostic changes of brain structure together with modulation of brain function after ECT. The data indicate diagnosis-unspecific mechanisms of action with respect to regional gray matter volume and resting-state functional connectivity.

1. Introduction

Electroconvulsive therapy (ECT) is one of the most potent treatments available in psychiatry. Clinical benefits of ECT in severe and treatment-resistant major depressive disorder (MDD) are well-known [1]. In schizophrenia (SZ), ECT is frequently considered as a treatment option, particularly in drug-resistant cases with persistent psychotic symptoms or when rapid symptom relief is required, e.g. in patients presenting with enduring catatonic features [2]. More than seven decades after the inception of ECT, its precise mechanisms of action still remain unclear [3]. Recent studies have linked an increased expression of neurotrophic factors, especially within the hippocampal dentate gyrus as the site of lifelong neurogenesis [4], to electroconvulsive stimulation (ECS) [5–7]. Yet neurotrophic effects of ECS are not exclusively related to the hippocampal formation; they have also been observed in frontal cortices and in the amygdala [8,9].

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So far, in humans the extant knowledge on ECT-related effects on brain structure and function is exclusively derived from neuroimaging studies conducted in patients with MDD. Region-of-interest (ROI) based studies focusing on the medial temporal lobe demonstrated significant volumetric increases of the hippocampus and the amygdala following a series of ECT [10,11]. ECT induced gray matter volume (GMV) increases of hippocampus and amygdala, amongst other regions, in MDD have been recently confirmed by whole brain approaches [12–14]. More recently functional MRI (fMRI) has been employed to study effects of ECT on brain activity in MDD. ECT-related changes in functional neuroanatomy have been mostly addressed under resting-state conditions [15–17], an approach that seems particularly suitable for studying brain function in patients presenting with severe symptom expression. Briefly, fMRI studies in MDD demonstrated a modulation of dorsolateral-prefrontal, anterior cingulate and amygdala dysbalance, i.e. key regions implied in MDD pathophysiology [18]. It is unknown whether ECT-related neural effects observed in MDD are similar in SZ. It is possible that ECT modulates neural substrates that are not diagnosis-specific. Alternatively, ECT may act differentially on distinct neural pathways in MDD and SZ, respectively, yet these questions have not been addressed so far. Further, potential relationships between ECT-induced structural and functional brain change remain elusive. In order to facilitate an interpretation of the extant data, and to evaluate the potential advantage of multimodal imaging approaches in the context of ECT research, clarification on whether ECT related structural changes are either independent from or directly linked to changes in brain activity is essential.

The present MRI study investigated the effect of ECT on brain structure and function in patients with treatment-resistant SZ and MDD. We addressed the question whether both disorders would exhibit common or unique brain changes in response to ECT. Specifically, we investigated effects of ECT on brain structure and sought to establish relationships between regions exhibiting ECT-induced volume change and functionally connected regions. We predicted ECT-induced changes in GMV to be most prominent within the hippocampus and the amygdala. In patients with SZ we expected changes of hippocampal and dorsolateral prefrontal function, consistent with proposed models of functional decoupling in SZ [19,20]. Given the strong interconnectivity between limbic structures and cortical regions subserving affective processing and emotion regulation (i.e. cortical components of the „affective network“ [AN]) [21] in MDD we expected an association of structural changes of hippocampus and amygdala with modulated functional connectivity subgenual and pregenual divisions of the ACC [22].

2. Methods

2.1. Participants

We included a total of 42 adult Caucasian participants comprising 21 ECT-naïve inpatients (9 SZ, 12 MDD) recruited from the Department of Psychiatry at Heidelberg University. Diagnoses were established according to DSM-IV criteria. Disease severity was rated on the Positive and Negative Syndrome Scale (PANSS) [23] in SZ and on the 17-Item Hamilton Depression Rating Scale (HAMD) [24] in MDD within 5 days prior to the first ECT session, and 6–8 days after the last stimulation. Twenty-one healthy controls were recruited from the general population. Clinical evaluation included a detailed physical and neurological examination. None of the participants had a lifetime history of severe neurological or medical illness, head injury, severe substance abuse or lifetime substance dependence. All individuals were right-handed [25]. During the study, patients received medication according to their psychiatrists' choice. Medication was unchanged for a minimum of two weeks before the first MRI scan. Drug regimes were kept constant throughout the whole stimulation period including the final MRI acquisition. A summary of the participants' demographics and clinical characteristics is presented in Table 1. The study was approved by the local ethics committee (University of Heidelberg, Germany) and was carried out in accordance with the latest version of the Declaration of Helsinki. All participants gave written informed consent following a complete description of the study.

2.2. ECT procedure

Right-sided unilateral brief pulse, constant current, square wave ECT (Thymatron System IV, Somatics Inc., Lake Bluff, IL, USA) was administered 3 times a week. During the first ECT session, seizure threshold was individually determined by the administration of repeated stimuli of increasing intensity until a generalized seizure occurred. Subsequently, stimulus intensity was set at 2.5-times seizure threshold. Further adjustments to stimulus intensity were made as necessary for inadequate seizure duration, defined as < 25s of electroencephalogram seizure activity. The total number of ECT sessions was individually chosen according to each patient's clinical response until remission or until no further improvement occurred. Anesthetic management included etomidate followed by succinylcholine. Blood pressure, heart rate and oxygen saturation were continuously monitored. Throughout the procedure, patients were oxygenated with a disposable bag and mask.

2.3. MRI acquisition

MRI data were acquired on a 3 Tesla Siemens MAGNETOM Tim Trio MRI system (Siemens, Erlangen, Germany). First, T1-weighted three-dimensional magnetization prepared rapid gradient echo (MP-RAGE) pulse sequence with isotropic spatial resolution of 1 mm^3 (image matrix = 256 × 256 x 192, repetition time = 1.57 s, echo time = 2.74 ms, flip angle = 15°) was acquired. Secondly, 180 T2*-weighted blood oxygenation sensitive (BOLD) whole brain images were acquired (eyes closed) by means of a two-dimensional gradient-echo echo-planar imaging (GE-EPI) pulse sequence with anisotropic spatial resolution of 3.5 × 3.5 × 4.5 mm^3 (image matrix = 64 × 64, number of slices = 30, repetition time = 2 s, echo time = 30 ms, flip angle = 76°). In patients, the initial MRI scan was acquired within 5 days prior to the first ECT session, the final MRI scan was obtained 6–8 days after the last stimulation.

2.4. Image processing

MRI data were analyzed using Statistical Parametric Mapping 12 Software (SPM12, http://www.fil.ion.ucl.ac.uk/spm12), VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm8) and resting state data analysis toolkit (REST, http://www.restfmri.net/forum/REST_V1.8) [26]. Affected brain structures and cyto-architectonical probabilities were identified by means of the Anatomy toolbox version 2.2 and for hypothalamic regions using the recommendations by Baroncini et al. [27] and Makris and colleagues [28].

2.5. VBM image processing

Patients structural MR-images were processed according to a longitudinal processing pipeline, whereas MR-images of corresponding healthy participants were treated cross-sectional. Before segmentation into tissue classes, images were visually inspected to remove images with artifacts, manually aligned to orientation as defined by the used brain templates, and origin was set on the

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