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Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: A longitudinal pilot study

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ABSTRACT

Electroconvulsive therapy (ECT) is the most potent biological therapy in depression. Animal studies suggest that ECT acts via neuroplasticity effects on limbic structures involved in the pathophysiology of depression but in vivo evidence at the human system level is scarce. Therefore, the aim of the present study was to investigate the effect of ECT on hippocampus and amygdala volume in 15 antidepressant-free patients with treatment refractory depression (seven males, range 42–63 years). ECT treatment was successful as indexed by a significant decrease in depressive symptoms ($t14 = 13.6$; $p < 0.001$). Analysis of normalized volumetric data before and after ECT treatment revealed a significant volume increase of both hippocampus and amygdala (minimum $p < 0.005$) with no evidence for a change in global brain volume. Though this change in volume cannot be clearly related to treatment effects, ECT is associated with broader neurotrophic effects other than mere adult neurogenesis in the hippocampus, which has been previously suggested as a core mechanism on the basis of animal data.

1. Introduction

Major Depressive Disorder (MDD) is a leading cause of disability worldwide. Despite 50 years of intensive research on its underlying pathophysiology, treatment options are still unsatisfactory, leading to severe cause and chronicity with large socio-economic consequences (Murray and Lopez, 1997). Currently, one third of all MDD patients suffer from a treatment-resistant form of depression. Notably, this group of patients consumes almost 50% of the total budget that arises for treatment costs (Murray and Lopez, 1997). Hence, it is of particular importance to investigate the neurobiological mechanisms of actions of those treatments that do have an effect in these cases. Electroconvulsive therapy (ECT) is the most potent biological therapy and therefore is often applied in treatment-resistant depression (Husain et al., 2004), leading to an improvement of about 50–70% even in this group of patients.

Knowledge on the neurobiological effects of ECT mainly stems from animal models. Common to these studies is the focus on neurotrophic effects of ECT on the hippocampus, a structure that is crucially involved in the pathophysiology of depression (for a review see MacQueen and Frodl, 2011). Chronic courses of MDD are associated with hippocampal atrophy (Campbell et al., 2004; MacQueen and Frodl, 2011), and research has focused on the question whether this can be reversed by ECT. Adult neurogenesis has been directly linked to the pathophysiology of depression and has been shown to be reversed by antidepressant treatment (for example Malberg et al., 2000). Electroconvulsive seizure (ECS), an animal model of ECT, has indeed shown to increase neuroplasticity in the hippocampus by inducing also neurogenesis next to gliogenesis (Wennström et al., 2003) and endothelial cell proliferation (Hellsten et al., 2004), which in turn even leads to more angiogenesis (Hellsten et al., 2005). Broader neurotrophic effects of ECT are further supported by earlier studies using hydrogen 1 magnetic resonance spectroscopic imaging before and after ECT (Ende et al., 2000; Obergriesser et al., 2003). Whereas no effect on N-acetylaspartate (NAA) signaling was found, choline-containing compounds (Ch) were associated with an increase in membrane turnover. Recently, Nordanskog and colleagues showed a bilateral increase in hippocampal volume in a small sample of medicated, unipolar and bipolar MDD patients after ECT treatment

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(Nordanskog et al., 2010). While of course this study confirms for the first time the significant effect of ECT on the integrity of the hippocampus of depressed patients, a replication of these findings is certainly needed since these results may have been confounded by the concurrent effects of medication and heterogeneity of the sample. Moreover, effects of ECT on the medial temporal lobe (MTL) have further been supported by an MRI study in elderly patients receiving ECT whereby only MTL atrophy but neither white matter hyperintensities nor global cortical atrophy was related to a poorer outcome of the ECT response (Oudega et al., 2011).

Structural imaging studies of MDD have further revealed that changes in hippocampal volume coappear with changes in amygdala volume and that interactive changes of amygdala and hippocampus may play an important role also in the pathophysiology of depression. The amygdala has strong modulatory impact on the hippocampus (McGaugh, 2000) and functional imaging studies have supported this at the human system level in healthy controls (Dolcos et al., 2004) and in depressed patients (van Eijndhoven et al., 2011). Typically the depressive state at least early in the course of depression is associated with an increase in amygdala volume (Frodl et al., 2002; van Eijndhoven et al., 2009) and this increased volume is related to an increased functional activity (Fales et al., 2008; Fu et al., 2004; Siegle et al., 2007), which in turn influences hippocampal activity (Hamilton et al., 2008). Amygdala volume and function normalizes with successful treatment with antidepressants (for example Sheline et al., 2001; Fu et al., 2004) and so may its hyperactive modulation on the hippocampus. Since responsitivity of the amygdala has even been suggested to be a treatment predictor in depression (Canli et al., 2005), it seems important to investigate the effect on ECT on amygdala volume as well. In the absence of any human in vivo structural imaging studies animal studies at least suggest an involvement of the amygdala in relation to gliagenesis during ECS (Wennström et al., 2004; Jansson et al., 2009).

The aim of our study was to conduct a prospective study in a homogenous sample of treatment resistant patients suffering from unipolar MDD without the concurrent use of antidepressive medication that may account for additional neurotrophic effects. Using structural magnetic resonance imaging (sMRI) before and after ECT treatment, we investigated whether the effect of ECT on the hippocampus found by Nordanskog and colleagues in a more heterogenous sample of patients and under medication can be replicated in the patients as defined above. Further we investigated whether ECT also has an effect on amygdala volume. Two potential outcomes could be envisioned with respect to potential effects of ECT on amygdala volume. On the one hand chronic depression has been associated with a normal or reduced amygdala volume (Kronenberg et al., 2009) so that ECT may have neurotrophic effects and lead to an increase in amygdala volume as well. In the light of studies showing an increase in function and volume related to the depressive state, a reduction of amygdala volume may also be possible on the other hand.

2. Methods

2.1. Subjects

Between 2009 and 2011, 22 patients with MDD were recruited from the Department of Psychiatry of Radboud University Medical Centre Nijmegen, the Netherlands. One patient was excluded because his scans showed severe white matter lesions and six patients did not participate in the follow-up measures. 15 remaining patients (seven men and eight women) with a mean age of 54 ± 6 years (standard deviation, range 37–63 years) were thus included for the study at hand. Diagnosis of MDD was established using the Structured Clinical Interview for DSM-IV (SCID). Patients were eligible to receive ECT treatment according to the Dutch guideline for depression (Spiker et al., 2006), which means that they had undergone a stepwise treatment without clinical response on serotonine-reuptake inhibitors, serotonine–noradrenaline-reuptake inhibitors, tricyclic antidepressants and lithium or antiepileptics before ECT (for overview see Table 1). All patients underwent a wash-out phase of minimum 1 week prior to ECT except for trancylcypromine that due to its irreversible binding qualities was reduced over several weeks before and stopped 3 weeks prior to ECT. None of the patients received an SSRI with long lasting half-life prior to start with the ECT treatment. Cognitive functioning was assessed within one week before ECT course (see Table 2). Depressive symptoms were rated using the Hamilton Depression Rating Score (HDRS, Hamilton, 1960) within one week before and after their ECT course. Patients were only included if they did not receive any antidepressive pharmacological treatment during the ECT course, but intermittent use of benzodiazepines 1–2 times/week was allowed.

Specific exclusion criteria for patients were ECT treatment within 1 year prior to the current course, bipolar depression, a co-morbid diagnosis of schizophrenia or substance dependence disorders. Further exclusion criteria were the current use of any psychotropic medication other than intermittent use of benzodiazepines, the presence of a current or past relevant somatic or neurological disorder, and MRI-related exclusion criteria like claustrophobia, a pacemaker and pregnancy. The study was approved by the local ethical committee and all subjects provided written informed consent prior to screening.

Table 1
Patient characteristics and summary of pharmacological treatment prior to ECT based on the Antidepressant Treatment History Form (ATHF) by Sackheim et al. (1990).

Subject	Gender	Age	Education[a]	SSRI[b]	SNRI[c]	TCA[d]	Lithium	MAO-Inhibitor[e]	Antiepileptics[f]
1	1	55	4	2	1	3	1	1	2
2	2	54	5	2	1	3	1	0	1
3	1	48	5	2	1	3	1	1	0
4	2	44	4	1	0	1	1	1	0
5	2	50	5	2	1	1	1	1	0
6	1	57	4	1	2	1	1	1	0
7	2	53	4	2	0	1	1	0	0
8	1	55	4	1	1	1	1	0	0
9	2	62	5	1	1	1	0	1	0
10	1	42	3	1	0	1	1	1	0
11	1	56	4	1	0	1	1	0	0
12	2	60	4	1	1	2	1	1	0
13	1	64	5	1	1	1	1	0	0
14	1	55	4	2	1	3	1	0	1
15	2	37	4	2	1	1	1	0	1

Gender 1 = male, 2 = female.

[a] Educational level is coded level 1 to 5 (5 = academic), according to the Dutch education system.
[b] Number of different serotonine-reuptake inhibitors used before ECT.
[c] Number of different serotonine–noradrenaline-reuptake inhibitors used.
[d] Number of different tricyclic antidepressants used.
[e] Number of treatments with Trancylpromine.
[f] Number of treatments with antiepileptics used before ECT.