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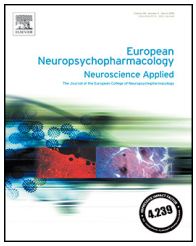

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Effect of electroconvulsive therapy on neural response to affective pictures: A randomized, sham-controlled fMRI study

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Abstract
Electroconvulsive therapy (ECT) is the most effective treatment for severe depression but its neurocognitive mechanisms are unclear. This randomized, sham-controlled functional magnetic resonance imaging (fMRI) study explored the effects of a single ECT on neural response to affective pictures. Twenty-seven patients with major depressive disorder were randomized to a single active ECT ($N = 15$) or sham ($N = 12$) session in a double-blind, parallel-group design. On the following day, patients underwent fMRI during which they viewed pleasant, unpleasant and neutral pictures and performed a free recall test after the scan. Mood symptoms were assessed before ECT/sham and at the time of fMRI. Subsequently, all patients continued active ECT as usual. Mood symptoms were reassessed after six active ECT sessions. A single ECT vs. sham

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session reduced neural response to unpleasant vs. pleasant pictures in the medial prefrontal cortex, a region showing greater response in the more depressed patients. This effect occurred in the absence of between-group differences in picture recall, mood symptoms or concomitant medication. In conclusion, modulation of medial prefrontal hyper-activity during encoding of negative affective information may be a common mechanism of distinct biological depression treatments.

Introduction

Major depressive disorder is the single largest contributor to the global burden of disease according to the World Health Organization (2017) and better treatment options are urgently needed. For patients with severe depression or who do not benefit from pharmacotherapy, electroconvulsive therapy (ECT) is the most effective and fast-acting treatment (The UK ECT Review Group, 2003). Neurobiological mechanisms include enhanced neuroinflammatory and haematogenous immune response, increased expression of neurotrophins including brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF), and upregulation of hippocampal neurogenesis (Bolwig and Madsen, 2007; van Buel et al., 2015). These actions are accompanied by structural increase in the hippocampus (Jorgensen et al., 2016), parahippocampal gyrus, anterior cingulate cortex (ACC) and temporal cortex, which are associated with symptom improvement (Pirnia et al., 2016). However, there is a conceptual gap in the scientific understanding of how such neurobiological actions of ECT translate into clinical improvement in mood and depressive symptoms.

Negative bias in cognitive and neural response to emotional information is a core feature of depression. Specifically, negative bias in the encoding and recall of emotional information is directly associated with the severity and persistence of depression (Bradley et al., 1995). Functional magnetic resonance imaging (fMRI) studies have shown that this bias is accompanied by hypo-activity in the medial prefrontal cortex (mPFC) during encoding of pleasant picture stimuli (Schaefer et al., 2006) and hyper-activity during encoding of unpleasant (vs. neutral and pleasant) pictures in a fronto-limbic circuitry, including the mPFC (Foland-Ross et al., 2014; Wagner et al., 2004), amygdala (Wagner et al., 2004) and hippocampus (Hamilton and Gotlib, 2008). The exaggerated hippocampal and amygdala activity to unpleasant pictures was accompanied by enhanced subsequent retrieval of these pictures and may thus be a neural correlate for negative encoding bias in depression (Hamilton and Gotlib, 2008). In addition, patients' mPFC hyper-activity to unpleasant pictures predicted greater depression severity at a long-term (18 months) follow-up (Foland-Ross et al., 2014).

Antidepressant drugs reverse negative bias in neurocognitive response to emotional information early in the course of treatment before statistically significant changes in mood symptoms emerge (Harmer et al., 2017). This modulation of neurocognitive bias is thought to provide a platform for cognitive restructuring and relearning that – in combination with social support – contributes to clinical improvement of mood symptoms (Harmer et al., 2017). At a neural level, antidepressant drug treatments reverse hyper-activity to negative affective stimuli in vmPFC (Brody et al., 1999) and the amygdalo-hippocampal complex (Scheidegger et al., 2016) and hypo-activity to positive affective picture stimuli in prefrontal, limbic and temporo-parietal regions (Schaefer et al., 2006). Notably, these effects on neural activity can be observed prior to changes in behavior or mood symptoms (Godlewska et al., 2012; Di Simplicio et al., 2012) and are putative early biomarkers of antidepressant efficacy. However, it is unclear whether reversal of negative bias is a common mechanism of distinct biological treatments of depression, including non-pharmacological interventions like ECT.

The aim of this randomized, sham-controlled study was to investigate whether ECT modulates neural response to unpleasant vs. pleasant affective pictures in a manner similar to antidepressant drugs. Since ECT is applied to bilateral fronto-temporal cortex, we expected the acute effects of ECT on neural response to affective pictures to be primarily observable in the PFC, in line with findings from other electrophysiological therapies (e.g. Cardoso et al., 2008; Ironside et al., 2016). We hypothesized that (i) a single session of ECT would reduce the response to unpleasant vs. pleasant pictures in the mPFC (*primary hypothesis*) and (ii) ECT-related changes would occur in the absence of any observable differences between groups in picture recall performance, mood symptoms or subjective state. For exploratory purposes, we also investigated the effects of ECT on neural response to unpleasant vs. pleasant pictures in the amygdalo-hippocampal complex.

Experimental procedures

Study design and participants

Patients were recruited from the Copenhagen University Hospitals Rigshospitalet and Bispebjerg, Psychiatric Centre Copenhagen, between November 2009 and July 2015. We decided to terminate the study after we had reached a total number of 29 (rather than the originally planned 32) patients in the study given the unexpectedly slow recruitment rate. Patients had an ICD-10 diagnosis of unipolar depression (UD) of moderate to severe degree as reflected by Hamilton Depression Rating Scale 17-items (HDRS-17; Hamilton, 1960) scores $\geq$ 18. Exclusion criteria were substance- or alcohol abuse, pregnancy, somatic illness contraindicating ECT, metal implants, bipolar disorder, schizoid disorder, schizophrenia or neurological disease.

Diagnostic evaluations, review of exclusion criteria for ECT and mood ratings were carried out by specialists in

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