Meta-analytic evidence for volume increases in the medial temporal lobe after electroconvulsive therapy (ECT)

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To the editor:

Since its introduction to psychiatric practice more than 8 decades ago, electroconvulsive therapy (ECT) is widely recognized as a highly effective treatment for severe psychiatric disorders, but the exact mechanisms underlying treatment response have remained elusive. Neuroimaging research has put a spotlight on structural brain changes (1), initially inspired by the neurotrophic hypothesis that postulates neuroneogenesis as essential for antidepressant treatment response (2,3). Intriguingly, some longitudinal magnetic resonance imaging (MRI) studies indeed reported localized brain volume changes in patients after ECT. A straightforward interpretation of these findings, however, has been obscured given considerable heterogeneity of brain locations reported across studies. These inconsistent results might be attributable to several factors. Small sample sizes are a particular problem, as individuals undergoing ECT are amongst the most severely affected psychiatric patients (4) and, hence, hard to recruit. Intra- and inter-study inhomogeneity of clinical samples – e.g., due to diagnosis, age and chronicity -, and different statistical approaches for data analysis might further obscure the picture (5).

To investigate whether there is converging evidence for ECT-associated brain structural changes, we performed a quantitative coordinate-based meta-analysis using the activation likelihood estimation (ALE) approach. This approach allows to overcome the mentioned shortcomings, as it pools across large numbers of subjects from different cohorts and synthesizes results from different analysis approaches (6,7). Moreover, as ALE performs a voxel-wise analysis for significant convergence across the entire grey matter it does not require an a priori-hypothesis (7). These two characteristics – pooling over different analysis approaches and the use of unrestricted inference spaces – yield

the potential to provide an important additional perspective to recently published mega-analyses relying on region-of-interest (ROI) analyses from large ROIs, which would be insensitive to small, localized effects (8,9). Relevant studies were retrieved through PubMed and Google Scholar, review articles, and reference tracing. Inclusion criteria are reported in the legend to Table 1. In total, 12 studies published between 2014 and 2019 met inclusion criteria, 2 of those reporting no significant changes (Table 1), enroll a total of 308 patients (294 patients with major depression, 5 with bipolar disorder, 9 with schizophrenia). Our analysis pooled over all contrasts, regardless of their directionality (i.e., regional brain volume increases or decreases in the course of ECT). We, then, analyzed, which studies contributed to the ensuing cluster to gain more insight into the effects that drove the observed convergence. Due to the relatively small number of studies suitable for inclusion, we performed a jack-knife (leave-one-out) analysis on the 10 studies reporting significant findings to assess the robustness of our results. All results were thresholded at a cluster-level family wise error (cFWE) cluster-corrected threshold of $p(cFWE)<0.05$ (cluster-forming-threshold at a $p<.001$) as recommended (7). Maps of the leave-one-out analyses were binarized and then averaged to yielding the (per-voxel) probabilities of significant convergence when removing one of the studies from the analysis.

Our main analysis yielded two clusters. Only contrasts indicating regional brain volume increases contributed to these clusters. The larger cluster was located in the right medial temporal lobe (18, –6, –18) comprising mainly the amygdala, with a smaller portion extending into the right hippocampus and basal forebrain. A smaller left-hemispheric cluster (-14, -4, -20) was also located in the amygdala, while smaller parts extended into

the parahippocampal gyrus, hippocampus, and entorhinal cortex (Fig 1A). The right cluster was mainly driven by studies employing exclusively right unilateral (RUL) stimulations (these studies contributed 49% to this cluster), with smaller contributions from experiments with only bilateral (20%) and mixed (RUL and bilateral) stimulation (31%). Conversely, the majority of contributions to the left hemispheric cluster came from experiments with bilateral (40%) and mixed stimulations (38%), while experiments with right unilateral stimulations (22%) played a minor role. The leave-one-out analysis corroborated the bilateral spatial convergence in the amygdala and hippocampus. Results were more robust for the right cluster (100% convergence across the leave-one-out iterations for large parts of the cluster) than for the left one (80-90% convergence) (Figure 1B). Exploratory analyses did not suggest an influence of affective response, age, gender or number of treatments on brain structural changes, while too low power did not allow a similar analysis for cognitive impairment.

To our knowledge, this is the first observer-independent coordinate-based meta-analysis of MRI studies on brain structural changes during ECT. Our results provide robust evidence for a volume increase in the medial temporal lobes during ECT across different samples, sites and analysis pipelines. This is in line with the results of previous original studies and mega-analyses in the field (1,8-10), and further highlights the role of the amygdala that, common to the contrary perception (8), was found to be more affected in our study than the hippocampus. The amygdala is a central hub within an emotion-processing network, while the hippocampus plays a key role in memory formation (10). Consequently, the observed brain volume increases are located in brain regions that are plausibly related to the therapeutic effect of ECT (11) and the main side effects. The

amygdala closely relates to depressive (12) and psychotic (13) symptoms, while the hippocampus appears as linked to mnestic impairments (14). A straightforward interpretation of these findings as macroscopic correlates of neuroplastic effects, however, is challenged by ambiguous results regarding an association of regional brain volume changes and clinical response (9,15,16). Dysregulated ion intake during seizures with subsequent increase of neuronal volumes could also be a contributing factor (17). The strong contribution of electrode position might indicate a significant role also of the electrical field (18).

In sum, our findings corroborate brain volume increases in the course of ECT, in particular in two brain regions closely related to the therapeutic and the main side effects of ECT (amygdala and hippocampus). Electrode position seems to significantly influence the laterality of these findings. Once more studies are available for inclusion, future meta-analysis will have to focus on potential brain structural correlates of the main and side effects, as well as the influence of clinical and treatment parameters.

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Table 1. Overview over the included studies. We performed PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (https://scholar.google.de/) searches for structural magnetic resonance imaging (MRI) studies involving ECT. Additional studies were determined by reference tracking and from reviews. We applied the following inclusion criteria: (1) human studies, (2) whole-brain comparison of GMV pre- and post-ECT, (3) published until August 5th 2020 in original peer-reviewed journals, (4) peak coordinates of the activation foci available for all reported clusters in Montreal Neurological Institute (MNI) or Talaraich stereotactic space. If two studies used nearly identical patient populations, we excluded one.

Based on the PubMed and Google Scholar searches as well as the reference tracking, we screened a total of 11916 articles. We had to exclude 11904 articles. A total of 12 studies met the inclusion criteria. In two of those studies whole brain analysis yielded no significant result (17,20). The vast majority of studies included patients with MDD according to DSM-IV or ICD-10 criteria. However, there were two studies that included patients who were schizophrenic (24) or initially manic (1).

Abbreviations: TR: Repetition Time, TE: Echo Time, MPRAGE: Magnetization Prepared Rapid Acquisition Gradient Echo, TFE: Turbo Field Echo

Figure 1. Brain volume increases in the course of ECT. (A) Our meta-analysis found convergent evidence for brain volume increases in the medial temporal lobes of both hemispheres. The larger cluster was located in the right medial temporal lobe (18, -6, -18, z-value: 6.99) comprising mainly the amygdala and - to a lesser degree – the hippocampus. A smaller left-hemispheric cluster (-14, -4, -20, z-value: 4.84) was also located in these two medial temporal lobe structures. Results are displayed at a cluster level family wise error (cFWE) cluster-corrected threshold of $p(FEW)<0.05$ (cluster-forming-threshold at a $p<.001$). (B) Our leave-one-out analysis showed bilateral spatial convergence in the amygdala and hippocampus. Results were more robust for the right cluster (100% peak convergence across the leave-one-out iterations) than for the left one (80-90% peak convergence). Results are displayed at a cluster level family wise error (cFWE)-corrected threshold of $p<0.05$.