SUPPLEMENTARY MATERIAL

Supplementary methods

PubMed, EMBASE, and the Cochrane Reviews were searched for publications with the following query: ("ECT" or "Electroconvulsive therapy" or "EST" or "Electroshock therapy" or "Electrotherapy") AND ("Schizophrenia" or "Schizo-" or "Schizoaffective" or "Psychosis" or "Psychotic") AND ("MRI" or "Magnetic resonance image" or "Magnetic resonance imaging" or "MRS" or "Magnetic resonance spectroscopy" or "Spectroscopy" or "PET" or "Positron emission tomography" or "BOLD" or "Blood oxygen level-dependent" or "Blood flow" or "SPECT" or "Single photon emission computed tomography" or "brain imag*" or "neuroimag*" or "DTI" or "Diffusion tensor" or "NIRS" or "Near infrared spectroscopy"). Two researchers (S.M. and M.K.) independently carried out literature search procedures.

We intended to include articles that 1) included patients with schizophrenia, 2) studied the effects of electroconvulsive therapy (ECT), 3) utilized at least one neuroimaging modality, and 4) were written in English. The exclusion criteria were as follows: 1) studies that did not involve patients with schizophrenia, 2) studies that did not implement ECT, 3) studies that did not use any brain imaging methods, 4) publications that were case reports or case series, 5) publications that were review articles, 6) studies involving nonhuman subjects, 6) articles published in languages other than English, 7) articles for which only the abstract was available, 8) publications that were errata, 9) duplicate publications, and 10) studies published before 1990, which were retrieved during the systematic review process.

Supplementary results

Effects of ECT on CBF

Of the three studies included in this review, each study utilized different modalities and the study/control groups varied (two studies compared patients with schizophrenia and patients with depression, and one study compared patients with schizophrenia with controls).

A PET study compared the effect of bifrontal ECT on patients with schizophrenia (n=5) and controls (n=6).[1] Following ECT, the CBF in the bilateral frontal lobes, right temporal lobe, and right putamen were decreased in the schizophrenia group.

A study using SPECT evaluated the effect of bifrontotemporal ECT on patients with catatonic schizophrenia (n=5) and catatonic depression (n=5).[2] Prior to ECT, the SPECT results did not differentiate between patients with schizophrenia and MDD with catatonia. One week after ECT completion, right parietal and bilateral temporal CBF was increased in patients with schizophrenia compared with patients with MDD. However, within-group comparisons including only the patients with schizophrenia did not show alterations compared to the baseline values.

The third study used NIRS to measure dynamic changes in blood flow prior to, during, and after each session of bifrontotemporal ECT in patients with schizophrenia (n=11) and MDD (n=10).[3] After ECT, the schizophrenia group showed an increased blood flow ratio of the left prefrontal cortex (PFC) to the right PFC, which was an asymmetry that was not observed in the MDD group. The authors noted a negative correlation of the asymmetry index of the left to right PFC with the duration of illness in the schizophrenia group.

Effects of ECT on brain metabolites

Three studies utilized MRS to measure changes in brain metabolites after ECT in patients with schizophrenia.

Gan et al.[4] used randomization to assign patients with schizophrenia (n=68) into either ECT or antipsychotic treatment only groups and compared them with controls (n=34). At baseline, the NAA/Cr ratio was lower in the left PFC and the left thalamus of the schizophrenia group than in the control group. After ECT, the NAA/Cr ratio in the left PFC and the left thalamus significantly increased, a change that was not observed in the antipsychotic treatment group. The left PFC and left thalamic NAA/Cr ratios also displayed significant associations with the demographic and clinical characteristics of the study group undergoing ECT treatment. Changes in the NAA/Cr ratio in the left PFC positively correlated with the age at onset (r=0.44), percent reduction in the Positive and Negative Syndrome Scale (PANSS) score (r=0.41), baseline PANSS total score (r=0.37), and ECT stimulus intensity (r=0.35), and negatively correlated with the duration of illness (r=-0.41). Changes in the NAA/Cr ratio in the left thalamus positively correlated with the age at onset (r=0.33) and negatively correlated with the duration of illness (r=-0.35). The authors suggested that an older age at onset and a shorter duration of illness will result in a greater increase in the NAA/Cr ratio in the left PFC and left thalamus after treatment with ECT.

Another study compared changes in metabolites in the prefrontal and thalamic regions of patients with schizophrenia after ECT (n=10) with patients undergoing antipsychotic treatment alone (n=10).[5] After treatment, patients who received ECT presented a significantly higher NAA/Cr ratio in the left prefrontal cortex than patients taking antipsychotic medications alone, and the choline/creatinine ratios in the left prefrontal and left thalamus were lower in the ECT group than in the antipsychotics alone group.

The third study measured medial prefrontal γ-aminobutyric acid (GABA) levels after ECT.[6] Patients with schizophrenia either received ECT (n=14) or antipsychotic treatment alone (n=17), and controls (n=19) were included. Medial prefrontal GABA levels did not significantly differ among the three groups, but when the group of patients with schizophrenia was analyzed as a whole, their GABA levels were lower than the control group. According to the post hoc analysis, GABA levels in the medial prefrontal cortex were increased in the ECT group, but not in the antipsychotics group.

Effects of ECT on brain structures

Six publications from three different groups were included in this review.

The first group examined the effect of ECT on patients with schizophrenia (n=9), patients with MDD (n=12), and matched controls (n=21).[7,8] Patient groups received right unilateral ECT. The whole-brain analysis yielded an increase in the GMV in the MTL network and the left DLPFC after ECT.[8] The increases in the volume of the left DLPFC and changes in the total PANSS score showed a significant correlation (r=-0.70).

The results using a different analysis approach, i.e., the selection of an ROI within the same dataset, found increased GMVs in the right amygdala, the anterior part of the right hippocampus, and the right insula in the group of patients with schizophrenia and MDD combined after ECT.[7] These changes did not correlate with symptom severity, but the baseline GMV in the amygdala displayed an inverse correlation with the post-ECT increases in GMV in this region (r=-0.75). Post hoc analyses revealed a significant within-group change in the right insula of patients with schizophrenia, while the results were not significant for patients with MDD. The post-ECT GMV values of the right amygdala/hippocampus region were greater in the MDD group and greater values were observed in the right insula in the schizophrenia group than the control values.

The second study group explored the effect of ECT on groups of patients with schizophrenia undergoing ECT (n=21), patients with schizophrenia treated with antipsychotics alone (n=21), and controls (n=22).[9-11] Using the whole-brain analysis method, the results showed significant differences between the three groups in the 1) left parahippocampal gyrus/hippocampus, 2) right parahippocampal gyrus/hippocampus, 3) right temporal pole and mid/superior temporal gyrus, and 4) right insula.[11] The post hoc analysis further revealed increased volumes of all four aforementioned regions in the ECT group compared to baseline, and the antipsychotics group actually presented decreased volumes compared to the pretreatment evaluation. Of the four regions, the increase in the volume of the right parahippocampal gyrus/hippocampus was associated with a reduction in score for the positive subscale of the PANSS (r=0.574).

Complementary analyses by the same group used ROI analyses to explore the effect of ECT on regions of the insula[9] and the hippocampus.[10] Regarding the insula, the GMV in the posterior insula was increased in patients with schizophrenia after ECT sessions compared to baseline.[9] These volumetric changes were also associated with changes in symptoms: increased GMV in the right posterior insula correlated with a reduced score for the PANSS positive scale (ρ=0.667), reduced total PANSS score (ρ=0.556), and reduced score for the PANSS general psychopathology scale (ρ=0.634). With the selection of the hippocampus as the ROI, bilateral hippocampal volumes in the ECT group were increased after treatment compared to the antipsychotics only group (the overall intracranial volumes were adjusted).[10] Furthermore, the authors categorized the ECT group into treatment responders (n=10) and nonresponders (n=11) using a 50% or more reduction in the total PANSS score as the response criteria. While increased hippocampal volumes were observed in both responders and nonresponders, volumes in the left hippocampus-amygdala transition area were larger in responders at baseline than in nonresponders.

The third study group used multiparametric markers of MRI to predict the effects of ECT measured by percent reductions in PANSS scores.[12] The authors integrated baseline GM features and white matter features (WM), which used T1-weighted and diffusion-weighted imaging modalities, respectively. The selection of GM and WM tract ROIs was performed by simulating the electrical fields used during ECT stimulation by modeling, and those regions with an electrical field strength greater than 35 V/m were included (23 GM ROIs and 37 WM tracts). Models were tested to predict differences in PANSS scores before and after ECT, and the model with the highest performance was shown to include both GM and WM baseline features. The important GM features were the left inferior frontal gyrus (IFG), right insula, left middle temporal gyrus (MTG), and right superior temporal gyrus (STG), and the important WM tracts were between the left calcarine-left superior temporal pole, right lingual-right inferior temporal gyrus (ITG), left middle occipital gyrus (MOG)-left ITG, right MTG-right ITG, and right IFG-right insula. The selected

model showed a performance with a root mean square error (RMSE) of 15.183 and a correlation efficient of 0.671 (RMSE=0 and r=1 represent the most accurate predictive model). Furthermore, this model was tested in a separate group of patients with schizophrenia undergoing ECT (n=15), which showed an RMSE value of 14.980 and a correlation coefficient of 0.777.

Effects of ECT on functional connectivity

Eight studies from four different study groups were included in this review.

Thomann et al.,[7] whose study included both patients with schizophrenia and patients along with controls, found that right unilateral ECT appeared to alter the functional connectivity between the right amygdala and the ipsilateral cortical brain regions. The authors performed an ROI analysis with amygdala, hippocampus, and insula as seeds to assess the connectivity with the other brain regions. Reduced rsFC was observed between the right amygdala and the right temporo-parietal junction (TPJ), right medial prefrontal cortex (mPFC), bilateral posterior insula, and right DLPFC in both patient groups after ECT. In contrast, an increase in rsFC was observed between the right amygdala and hypothalamus, which follows the ventral amygdalofugal pathway, and these increases inversely correlated with the baseline connectivity strength in the same region (r=-0.85). These changes were not associated with any symptom improvements in either group. Post hoc analyses only yielded significant increases in rsFC between the right amygdala and hypothalamus in the schizophrenia group after the course of ECT, which also did not correlate with symptom changes.

The same study group published another study using the whole-brain method.[13] In patients with schizophrenia, the rsFC of the 1) mPFC within the DMN, 2) executive network and the DMN, and 3) executive networks and the salience network was increased after ECT completion. Additionally, ECT reduced low-frequency oscillations in the striatal network in patients with schizophrenia.

Another study group examined changes in functional connectivity after ECT and compared the ECT schizophrenia group, antipsychotic-only schizophrenia group, and controls. First, Huang et al.[14] investigated the effect of ECT on the global functional connectivity density (gFCD) using resting-state functional magnetic resonance imaging (fMRI). The signal measured by gFCD construes rsFC for a particular voxel, with a higher signal density implying that the region serves as a functional hub. Significant differences were observed in the dorsal medial prefrontal cortex (dmPFC) and the ventral medial prefrontal cortex (vmPFC) among the ECT, antipsychotics only, and control groups. Within-group post hoc analyses showed increased gFCD in the dmPFC, vmPFC and left precuneus of the ECT group after the ECT course compared to the baseline.

Jiang et al.[9] investigated the effect of ECT on changes in functional connectivity involving the insula. Significant group differences were observed among the ECT, antipsychotics only, and control groups between the left posterior insula and left MOG and between the right posterior insula and left orbitofrontal cortex (OFC). Post hoc analyses further revealed decreases in the functional connectivity strength between the left posterior insula and left MOG, as well as between the right posterior insula and left OFC, in the ECT group after ECT compared to the baseline, whereas the antipsychotics only group did not show significant changes. Interestingly, before the treatments, the ECT group presented slightly higher measures of functional connectivity (FC) in the aforementioned regions than the antipsychotics only group, but the ECT group exhibited substantially lower FC than the antipsychotics group after treatment. Additionally, FC between the left posterior insula and left MOG was significantly correlated with reduced scores on the PANSS general symptom scale (ρ=0.587) and PANSS negative symptom scale (ρ=0.560), and FC between the right posterior insula and left OFC was associated with reductions in the scores of the PANSS negative symptom scale (ρ=0.460).

Jiang et al.[10] also explored FC between the hippocampus and other brain regions after ECT. Of the 21 patients who had undergone ECT treatment, 10 were classified as responders and 11 as nonresponders (a response was defined as a greater than 50% reduction in the total PANSS score). In responders, rsFC between the hippocampus and prefrontal cortex and between the hippocampus and DMN were increased after ECT compared to baseline. In nonresponders, post-ECT measures showed decreased rsFC between the hippocampus and primary sensory network compared to baseline.

In another complementary analysis performed by the same group, Wang et al.[15] studied the effect of ECT on rsFC of the thalamic subfields. The authors compared the ECT plus antipsychotics group (n=21) with the antipsychotics only group (n=21). FC between the right thalamus and right putamen was increased in the ECT group compared to FC in the antipsychotics only group after treatment. Additionally, in the ECT group, FC of the thalamus to the sensory cortex was increased after treatment, while the antipsychotics group showed a decrease. When treatment responses were considered, responders to ECT showed increased FC between the right posterior parietal thalamus (PPthaR) and right inferior temporal cortex and between the PPthaR and right cerebellum, while FC in the same regions decreased in ECT nonresponders. The results of the studies that classified patients as responders and nonresponders are summarized in Supplementary Table 3 (in the online-only Data Supplement).

The third study group utilized rsFC to predict ECT responses in patients with schizophrenia (n=47).[16] This same group used baseline GM and WM features to predict reductions in PANSS scores.[12] The authors first simulated the hypothetical electric field distribution of the human head when an ECT stimulus was administered. Following this simulation, 23 ROIs presented high levels of electrical strength (i.e., greater than 35 V/m). Using these ROIs and the baseline FC of patients, they attempt to determine the best fitted model that would predict reductions in PANSS scores after ECT. A model with the most predictive values included 10 ROIs that would best predict the ECT response. Of these 10 ROIs, the actual data from study subjects showed a significant decrease in FC between the right amygdala and left hippocampus. The authors concluded that their model incorporating baseline FC would subsequently assist clinicians in determining individualized therapy and predict the ECT response at the individual level (Supplementary Table 2 in the online-only Data Supplement).

A separate research group built a classification model using rsFC to differentiate between patients with schizophrenia (ECT+ antipsychotics, n=13; antipsychotics only, n=16) and controls (n=34) and tested the ability of these classifier scores to predict reduced PANSS scores after treatment with either ECT or antipsychotics alone.[17] The classifier score with six functional networks achieved a correct classification rate of 83.82% [specificity=91.18%, sensitivity=76.47%, area under the receiver operating characteristic curve (AUC)=0.90]. The six networks were the DMN, the MTL, the language network, the corticostriatal network, the frontal-parietal network, and the cerebellum. Changes in these classifier scores correlated with improvements in the PANSS scores for the total (r=0.71), negative (r=0.76), and general (r=0.66) scales. Additionally, baseline classifier scores had predictive value, with significant negative associations with the PANSS total (r=-0.75), positive (r=-0.70), negative (r=-0.78), and general subscores (r=-0.65). Low baseline classifier scores indicated a lower discriminatory power in differentiating between patients with schizophrenia and controls, and were shown to have predictive value for greater ECT responses. Notably, patients with schizophrenia undergoing antipsychotic treatment alone showed a similar pattern, with lower baseline classifier scores predicting larger treatment responses. Additionally, in the ECT group, FC in the posterior cingulate cortex (PCC), left STG, right angular gyrus, and right MTG increased, while FC in the right ACC, left MTG, and right precuneus decreased after ECT.

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