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Abstract

Electroconvulsive therapy (ECT) is the most effective treatment for a depressive episode but the mechanism of action and neural correlates of response are poorly understood. Different theories have suggested that anticonvulsant properties or neurotrophic effects are related to the unique mechanism of action of ECT. This review assessed longitudinal imaging investigations (both structural and functional) associated with ECT response published from 2002 to August 2013. We identified 26 investigations that used a variety of different imaging modalities and data analysis methods. Despite these methodological differences, we summarized the major findings of each investigation and identified common patterns that exist across multiple investigations. The ECT response is associated with decreased frontal perfusion, metabolism, and functional connectivity and increased volume and neuronal chemical metabolites. The general collective of longitudinal neuroimaging investigations support both the anticonvulsant and the neurotrophic effects of ECT. We propose a conceptual framework that integrates these seemingly contradictory hypotheses.

Keywords

electroconvulsive therapy, tomography, depressive episode, bipolar disorder, major depressive disorder

Introduction

Electroconvulsive therapy (ECT) is the most effective intervention for treatment-resistant depressive episodes when a rapid response is clinically indicated as in acute suicidality or severe anorexia. By the time patients with a depressive episode are referred to an ECT service, they have typically failed to respond to multiple antidepressant trials, psychotherapy, and various augmentation strategies. Up to 80% of these treatment-resistant patients respond to the ECT series, with many achieving full remission of their symptoms and resuming their previous level of functioning.[1] Despite its irrefutable success, ECT is also associated with significant risks, including exposure to general anesthesia, cardiovascular stress, and cognitive impairment. A barrier to the development of safer, more effective treatments is the lack of understanding regarding physical changes in the brain occurring with ECT and the therapeutic underpinnings of ECT response. The general collective of longitudinal neuroimaging investigations support both the anticonvulsant and the neurotrophic effects of ECT. We propose a conceptual framework that integrates these seemingly contradictory hypotheses. Greater understanding of the biological markers (ie, biomarkers) and mechanism of action of ECT response, unique among antidepressant treatments, will lead to improvements in other types of neural modulation and deepen knowledge of the pathophysiology of depressive episodes.

The anticonvulsant hypothesis posits that the increase in seizure threshold and decrease in seizure duration observed during an ECT series are linked to the therapeutic effect of ECT.[2,3] Many clinical and imaging studies have lent support to this hypothesis over the last 3 decades. Among these, several have shown increased seizure threshold, and indices of postictal suppression correlate with the antidepressant response.[3,4] Furthermore, therapeutic outcome after an ECT series has been associated with decreased posttreatment cerebral blood flow and increased postictal electroencephalographic slow-wave activity.[5-7] Finally, the hypometabolic state that occurs after ECT may be related to increased concentrations of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain.[3,8]

In contrast, the neurotrophic effect hypothesis posits that molecular and cellular investigations of animal models support short- and long-term neurotrophic effects of electroconvulsive seizures (ECSs).[9] After a single ECS, expression of neurotrophic

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(brain-derived neurotrophic factor, vascular endothelial growth factor, and fibroblast growth factor), neuropeptide molecules (vascular endothelial growth factor), transcription factors (c-fos, indicating neuronal activity), and arachidonic acid pathway (cyclooxygenase 2) is increased in the hippocampus.[10-12] After multiple ECSs, more neuropeptide factors (neuropeptide Y and thyrotropin releasing hormone) are released, and the transient increase in nerve growth factors persist for a longer period of time.[10,12] Most of the evidence of ECS neurotrophic effects comes from the dentate gyrus in the hippocampus,[13] the site of ongoing neurogenesis throughout the life cycle,[14] but neurotrophic effects and cell proliferation have also been observed in the prefrontal cortex,[15] amygdala,[16] and hypothalamus.[17]

In general, patients with severe depression will have a larger magnitude of response, thereby increasing the ability to detect biomarkers of therapeutic response in depression.[18] Furthermore, the high rates of response and rapid clinical improvement in ECT further support its use in identifying biomarkers. In spite of these advantages, reviews of longitudinal imaging studies in ECT prior to 2002 have reported conflicting results and been hampered by significant methodological confounds.[19-21] This review will assess longitudinal imaging investigations (both structural and functional) associated with ECT response published after 2002. We summarize the major findings of each investigation and common patterns with each imaging modality. In the discussion section, we interpret these findings in light of the anticonvulsant and neurotrophic theories of ECT's mechanism of action.

Methods

We performed a PubMed search with the following Medical Subject Headings terms: "tomography" AND "electroconvulsive therapy" AND "depression" between January 2002 and September 2013. We further limited the results to "English" and "Humans." We screened the abstracts to find investigations that met the following criteria: (1) publication date on or after 2002; (2) longitudinal design with pre- and post-ECT imaging assessments; (3) group statistics (excluded case reports and case series); and (4) human with a depressive episode (either unipolar or bipolar disorder). We also reviewed references from selected sources.

Results

We identified 26 longitudinal investigations published between 2002 and 2013 for a detailed review that met our inclusion criteria. The imaging modalities included single-photon computed emission tomography (SPECT, n = 6; Table 1), positron emission tomography (PET, n = 7; Table 2), electroencephalography (EEG, n = 2; Table 3), structural magnetic resonance imaging (n = 1; Table 4), proton magnetic resonance spectroscopy (^{1}H-MRS, n = 6; Table 4), and functional MRI (fMRI, n = 4; Table 5). The tables describe the clinical characteristics of the sample (diagnosis, sample size, age, gender, and ratio of ECT responders), ECT parameters (stimulus delivery, waveform, intensity, and number of treatments), the number of days from ECT series to the first post-ECT imaging assessment, the presence or absence of a healthy comparison (HC) group, and the main imaging findings. The sample size recorded in the tables includes the number of patients with a post-ECT scan entered in the final analysis. We used the term "responder" as defined in the investigation to mitigate issues related to the variability among the different studies (clinical opinion vs different percentage decreases in diverse depression rating scales at variable time points). Most investigations were obtained post-ECT imaging assessment within 7 to 14 days after the ECT series. Several investigations had longer follow-up periods (up to 1 year). In the following sections, the results are categorized by imaging modality, and the main findings of each investigation are summarized. Different imaging modalities and analysis methods precluded systematic meta-analysis; however, when possible, general patterns among similar analysis methods are identified.

Single-Photon Emission Computed Tomography

Six longitudinal SPECT studies assessed ECT-associated changes in regional cerebral blood flow (rCBF; Table 1).[22-27] Longitudinal changes in rCBF between the pre-ECT and 14 days post-ECT imaging assessment were divergent, demonstrating both increased and decreased rCBF associated with ECT response. These differences were largely dependent on analysis methods that included region of interest (ROI) with cerebellar uptake normalization and whole-brain voxel-wise analysis. In the normalized ROI method, rCBF ratios increased in posterior cerebral regions,[22] anterior cingulate, and frontal regions.[26,27] In contrast, whole-brain, voxel-wise analysis was more variable but generally showed decreased rCBF after ECT in the parietotemporal cortices.[25,26] In 1 study, greater reductions in depression severity were associated with greater decreases in rCBF in the left frontopolar gyrus, amygdala, nucleus accumbens, globus pallidus, and superior temporal gyrus.[27]

Kohn et al recognized the discrepant findings related to analysis methods.[26] Their whole-brain analysis found decreased cerebellar rCBF after ECT. They hypothesized that the decreased cerebellar rCBF would affect the ROI approach since the cerebellum was used as the reference region. To address this issue, they reanalyzed their whole-brain data (showing decreased rCBF) with ROI and cerebellar normalization. Utilizing an ROI approach on the same data set showed the opposite pattern (ie, increased rCBF ratios after a course of ECT). These results mirrored an earlier investigation showing increased mean rCBF ratios and reduced rCBF in whole-brain, voxel-wise analysis.[22] These examples illustrate the importance of analysis method when interpreting the directionality of change associated with ECT response.

Several investigations included long-term imaging assessments from 32 to 365 days either as the first[24] or as the second[14,18] post-ECT assessments. The investigations with multiple post-ECT imaging assessments demonstrated continued perfusion changes long after the ECT series. In particular, the left posterior

Table 1. Single-Photon Computed Tomography (SPECT) and Longitudinal Changes in ECT.

Author (Year)	n Diagnosis Mean Age (SD) Male/Female Ratio of Responders/Total Medication Status	Stimulus Delivery Stimulus Waveform Stimulus Intensity (When Reported) Number ECT Sessions (SD)	Time From ECT Series to Post-ECT Imaging Assessment HC Group: Yes/No	Image Analysis	Longitudinal Neuroimaging Results
^{99m}Tc-HMPAO to measure regional cerebral blood flow (rCBF)					
Awata et al[22] (2002)	9 MDD 63 years (4) 3 male/6 female 9/9 responders (at 14 days post-ECT) Medication was discontinued 3 days prior to the initial imaging assessment	Bitemporal Sine wave 8 treatments (1)	14 days (time 2) and 168 days (time 3) HC: yes	Region of interest with cerebellar uptake normalization and voxel-wise analysis (whole brain)	*ECT time 1 vs time 2 vs time 3*: Mean rCBF ratios increased at time 1 to time 2 and time 1 to time 3; in voxel-wise (whole brain) analysis, rCBF increased in posterior cerebral regions (time 1 to time 2 and time 1 to time 3); rCBF decreased in left posterior cortex (time 2 to time 3) *ECT time 1 vs HC*: Patients had decreased mean rCBF ratios; in voxel-wise analysis, patients had decreased rCBF in the subcallosal cingulate cortex, bilateral orbitofrontal, right insular, and right frontal cortices. *ECT time 2 and 3 vs HC*: Mean rCBF ratios normalized at time 2 and 3; in voxel-wise analysis, the rCBF deficits persisted in the patient group at time 2 and 3
Vangu et al[23] (2003)	13 MDD and bipolar 37 years (12) 4 male/11 female (2 patients excluded from final analysis) 7/13 responders Medication was discontinued (except for lithium)	Bitemporal Brief pulse 10 treatments (2)	5 days HC: no	Region of interest with cerebellar uptake normalization	*ECT time 1 vs time 2*: Increased rCBF ratio in the anterior cingulate and left frontal regions among all patients. Only analysis with responders was not significant
Navarro et al[24] (2004)	16 MDD (includes 5 MDD with psychotic features) 73 years (8) 5 male/11 female 16/16 responders Medication was discontinued 10 days prior to the first imaging assessment	Bitemporal Brief pulse 10 treatments (1)	365 HC: yes	Region of interest with cerebellar uptake normalization	*ECT time 1 vs time 2*: Increased rCBF ratio in bilateral, anterior frontal regions *ECT time 1 vs HC*: Patients had decreased rCBF ratios in bilateral anterior frontal regions *ECT time 2 vs HC*: Normalization of rCBF ratios between ECT responders and HC

(continued)

Table 1. (continued)

Author (Year)	n Diagnosis Mean Age (SD) Male/Female Ratio of Responders/Total Medication Status	Stimulus Delivery Stimulus Waveform Stimulus Intensity (When Reported) Number ECT Sessions (SD)	Time From ECT Series to Post-ECT Imaging Assessment HC Group: Yes/No	Image Analysis	Longitudinal Neuroimaging Results
Takano et al[25] (2006)	8 MDD 49 years (16) 5 male/3 female 8/8 responders Patients remained on medication	Bitemporal Brief pulse Seizure titration method 7 treatments (1)	5 days (time 2) and 32 days (time 3) HC: yes	Three-dimensional stereotactic surface projection	*ECT time 1 vs time 2 vs time 3*: Increased rCBF in the right medial frontal gyrus (time 1 to time 3, nonsignificant trend from time 2 to time 3) and the right parahippocamapal gyrus (nonsignificant trend from time 1 to time 2); decreased rCBF in the right cuneus (time 1 to time 2) *ECT time 1 vs HC*: Patients had decreased rCBF in frontal and limbic regions and increased rCBF in the occipital, parietal, and temporal cortices *ECT time 2 vs HC*: Patients continued to have decreased rCBF in frontal and limbic regions *ECT time 3 vs HC*: Patient continued to have decreased rCBF in frontal and limbic regions
Kohn et al[26] (2007)	8 MDD 68 years (8) 1 male/7 female 7/8 responders Medication was discontinued 14 days prior to the initial imaging assessment	Bitemporal Brief pulse 2.5× seizure threshold 10 treatments (2)	7 days	Voxel-wise analysis (whole brain)	*ECT time 1 vs time 2*: Decreased rCBF in the bilateral parietotemproal and cerebellar cortices *ECT time 1 vs HC*: Patients had decreased rCBF in bilateral frontal, temporal, insular, parietal, and cortical nuclei *ECT time 2 vs HC*: Patients had decreased rCBF as above and basal ganglia
99mTc-ECD to measure regional cerebral blood flow (rCBF)					
Segawa et al[27] (2006)	8 MDD; 2 bipolar II 48 years (9) 7 male/3 female 6/10 responders Patients remained on medication	Bitemporal Sine wave 10 treatments (1)	11 days HC: no	Voxel-wise analysis with linear regression to compare change in rCBF and change in HRSD	*ECT time 1 vs time 2*: Changes in rCBF and change in HRSD were negatively correlated in the left frontopolar gyrus, amygdala, nucleus accumbens, globus pallidus, and superior temporal gyrus (ie, larger decreases in rCBF were associated with larger reductions in HRSD)

Abbreviations: ECT, electroconvulsive therapy; HC, healthy comparison; HRSD, Hamilton Rating Scale for Depression; MDD, major depressive disorder; SD, standard deviation; ^{99m}Tc-HMPAO, technetium-99m-labeled hexamethylpropyleneamine oxime.

Table 2. Positron Emission Tomography (PET) and Longitudinal Changes in ECT.

Author (Year)	n Diagnosis Mean Age (SD) Male/Female Ratio of Responders/Total Medication Status	Stimulus Delivery Stimulus Waveform Stimulus Intensity (When Reported) Number ECT Sessions (SD)	Time From ECT Series to Post-ECT Imaging Assessment HC Group: Yes/No	Image Analysis	Longitudinal Neuroimaging Results
[^{18}F]-Fluorodeoxyglucose (FDG) to measure regional cerebral metabolic rate of glucose (rCMRGlu)					
Yuuki et al[28] (2005)	4 MDD with and without psychotic features; 3 bipolar I & II 58 years (9) 4 males/3 females 7/7 responders Patients remained on antidepressant medications; lithium and valproate were discontinued	Bitemporal Brief pulse Half-age stimulus intensity 6-20 treatments (range)	33 days HC: yes	Voxel-wise analysis (whole brain)	*ECT time 1 vs time 2*: decreased rCMRGlu in the bilateral medial frontal cortices and increased rCMRGlu in the left occipital and parietal lobes *ECT time 1 vs HC*: Patients had decreased rCMRGlu in frontal regions and the left caudate; patients had increased rCMRGlu in left parietal and right paracentral gyrus *ECT time 2 vs HC*: Patients continued to have decreased rCMRGlu in frontal regions and the left caudate; patients also continued to have increased rCMRGlu in the left parietal cortex. Patients did have normalization of aberrant rCMRGlu in the right DLPFC and right paracentral gyrus.
McCormick et al[29] (2007)	10 MDD with psychotic features 40 years (10) 6 male/4 female Median split divided sample into "better and poor" responders Patients remained on medications	RUL (n = 5), bitemporal (n = 5) Brief pulse Seizure threshold, RUL 6× threshold; bitemporal 2.5× threshold 10 treatments (6)	14-21 days (range) HC: no	Voxel-wise analysis (whole brain) and region of interest	*ECT time 1 vs time 2*: in voxel-wise (whole brain) analysis, decreased rCMRGlu in the right frontal operculum and insula, and increased rCMRGlu in left hippocampus; metabolic changes in left hippocampus and left ventral anterior cingulate also correlated with change in HDRS. In the region of interest analysis, the "better" ECT responders had increased rCMRGlu in the left subgenual anterior cingulate and left hippocampus relative to the "poor" ECT responders.
Suwa et al[30] (2012)	13 MDD; 3 bipolar II 33 years (8) 13 male/5 female 12/16 responders Patients remained on medications	Bitemporal Brief pulse Half-age stimulus intensity 10 treatments	12 days HC: yes	Voxel-wise analysis (whole brain)	*ECT time 1 vs time 2*: decreased rCMRGlu in frontal, parietal, and inferior temporal regions; increased rCMRGlu in the medial temporal gyrus and pons *ECT time 1 vs HC*: patients had decreased rCMRGlu in the left superior frontal gyrus and increased rCMRGlu in the bilateral temporal gyri *ECT time 2 vs HC*: patients had decreased rCMRGlu in left temporal and parietal cortices and bilateral frontal gyri; patients had increased rCMRGlu in the middle temporal and occipital regions

(continued)

Table 2. (continued)

Author (Year)	n Diagnosis Mean Age (SD) Male/Female Ratio of Responders/Total Medication Status	Stimulus Delivery Stimulus Waveform Stimulus Intensity (When Reported) Number ECT Sessions (SD)	Time From ECT Series to Post-ECT Imaging Assessment HC Group: Yes/No	Image Analysis	Longitudinal Neuroimaging Results
Reininghaus et al[31] (2013)	12 MDD 56 years (12) 7 male/5 female 3/12 responders Patients remained on medications	9 bitemporal, 3 RUL Brief pulse Dose adjusted for age 8 treatments (fixed)	1-7 days (range) HC: no	Region of interest with normalization to activity in the pons	*ECT time 1 vs time 2*: increased rCMRGlu in the left temporal lobe; correlations with symptom changes and cognitive changes were not significant
[^{11}C] FLB 457 measures extrastriatal D2 receptor binding					
Saijo et al[32] (2010)	7 MDD 43 years (11) 5 male/2 female 7/7 responders Patients were treated with SSRI's	Bitemporal Brief pulse Dose adjusted for age 6-7 treatments (range)	7 days HC: yes	Voxel-wise (whole brain)	*ECT time 1 vs time 2*: decreased D_2 receptor-binding potential in the right rostral anterior cingulate *ECT time 1 vs HC*: no differences *ECT time 2 vs HC*: no differences
[carbonyl-^{11}C]WAY100635 measures 5-HT_{1A} receptor binding					
Saijo et al[33] (2010)	9 MDD 45 years (9) 6 male/3 female 9/9 "improved" Patients were treated with SSRI's	Bitemporal Brief pulse Dose adjusted for age 6-7 treatments (range)	7 days HC: yes	Region of interest analysis	*ECT time 1 vs time 2*: no differences *ECT time 1 vs HC*: patients had less 5-HT_{1A} receptor binding in the midbrain raphe *ECT time 2 vs HC*: patients continued to have less 5-HT1A receptor binding in the midbrain raphe
Lanzenberger et al[34] (2013)	12 MDD 48 years (11) 4 male/8 female 10/12 responders 5-HT1A drugs were exclusionary; otherwise, psychotropic medication had to be at steady state	RUL with a transition to bitemporal if minimal improvement at the sixth treatment (n = 8) Brief pulse Seizure threshold, RUL 3× threshold 10 treatments (2)	<7 days of completing ECT series HC: no	Voxel-wise (whole brain)	*ECT time 2 (pre) vs time 3 (post)*: widespread decrease in 5-HT_{1A} receptor-binding potential in cortical and subcortical regions; peak differences in the anterior cingulate (including subgenual), the orbital frontal cortex, insula, hippocampus, and amygdala

Abbreviations: ECT, electroconvulsive therapy; HC, healthy comparison; MDD, major depressive disorder; SD, standard deviation; ^{99m}Tc-HMPAO, technetium-99m-labeled hexamethylpropyleneamine oxime.

Table 3. Electroencephalography (EEG) and Longitudinal Changes in ECT.

Author (Year)	n Diagnosis Mean Age (SD) Male/Female Ratio of Responders/Total Medication Status	Stimulus Delivery Stimulus Waveform Stimulus Intensity (When Reported) Number ECT Sessions (SD)	Time From ECT Series to Post-ECT Imaging Assessment HC Group: Yes/No	Image Analysis	Longitudinal Neuroimaging Results
Quantitative EEG					
McCormick et al[35] (2009)	17 MDD with psychotic features 46 years (10) 7 male/10 female 15/17 responders Patients remained on medications	9 RUL/8 bitemporal (at completion of ECT series) Brief pulse Seizure threshold, RUL 6× threshold; bitemporal 2.5× threshold 12 treatments (7)	14-21 days (range) HC: no	Whole-brain qEEG; whole brain and ROI low-resolution electromagnetic tomography (LORETA)	*ECT time 1 vs time 2*: qEEG revealed increased θ band activity (4-7.5 Hz); whole-brain analysis with LORETA confirmed that the subgenual cingulate was the primary site of θ activity; increased θ activity in the subgenual cingulate was associated with percentage change in psychotic symptoms
Motor cortex excitability					
Casarotto et al[36] (2013)	8 MDD 52 years (7) 2 male/6 female Responders not specified, but 5/8 with 50% reduction in HDRS Patients remained on medication	8 bitemporal Constant current pulses Seizure threshold, 2× threshold 6 treatments (1)	1 day HC: no	Transcranial magnetic stimulation-evoked potentials via an ROI analysis (6 neighboring EEG channels with the largest amplitude)	*ECT time 1 vs time 2*: The percentage reduction in HDRS was nonsignificantly correlated with the increased cortical activation

Abbreviations: HC, healthy comparison; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder; qEEG, quantitative EEG; ROI, region of interest; RUL, right unilateral.

cortex showed rCBF reductions at 168 days relative to 32 days after the ECT series.[22] This particular investigation had 3 patients who relapsed during the longitudinal follow-up, but differences in rCBF between participants with a sustained response and relapse were not assessed. The longest follow-up interval of 365 days demonstrated increased rCBF ratios in frontal regions among all of the ECT responders with a sustained response.[24]

The majority of SPECT investigations published since 2002 used a demographically matched HC group to establish normal rCBF patterns.[22,24-26] The pre-ECT/HC contrasts consistently demonstrated aberrant rCBF or rCBF ratios in the patient group. The longitudinal pattern again depended on the method of analysis. In ROI studies, rCBF ratios "normalized" with ECT (ie, no differences between post-ECT and HC imaging contrasts).[22,24] In contrast, the pattern of aberrant rCBF assessed with voxel-wise, whole-brain analysis persisted and failed to normalize at multiple post-ECT time points.[22,25,26]

Positron Emission Tomography

Four longitudinal PET studies assessed ECT-associated changes in [18F]-fluorodeoxyglucose (FDG) to measure the regional cerebral metabolic rate of glucose (Table 2).[28-31] Analysis was confined to the whole-brain, voxel-wise analyses completed with the majority of the studies to identify the common patterns among the different FDG studies.[28-30] The most consistent finding of the pre-/post-ECT imaging contrasts was reduced glucose metabolism in the bilateral frontal medial and inferior frontal regions[28,30] and right frontal operculum.[29] The left frontal basal region also had a nonsignificant trend of decreased glucose metabolism.[31] Three of these same studies also identified increased glucose metabolism in the hippocampus and medial temporal lobes.[29-31] Other areas associated with increased metabolism included the left occipital and parietal lobes[28] and pons.[30]

Two of the FDG investigations included an HC group to assess normalization of aberrant glucose metabolism.[28,30] In both investigations, the pre-ECT imaging assessment demonstrated decreased glucose metabolism relative to HC in the frontal cortex[28,30] and left caudate[28] and increased metabolism in the left parietal cortex, right paracentral gyrus,[28] and bilateral temporal gyri.[30] Twelve days after finishing the ECT series, the aberrant pre-ECT metabolism persisted and failed to normalize.[30] Thirty-three days after finishing the ECT series, the decreased metabolism in the dorsal lateral prefrontal cortex

Table 4. Structural MRI, Proton Spectroscopy (^{1}H-MRS), and Longitudinal Changes in ECT.

Author (Year)	n Diagnosis Mean Age (SD) Male/Female Ratio of Responders/Total Medication Status	Stimulus Delivery Stimulus Waveform Stimulus Intensity (When Reported) Number ECT Sessions (SD)	Time From ECT Series to Post-ECT Imaging Assessment HC Group: Yes/No	Image Analysis	Longitudinal Neuroimaging Results
Structural MRI					
Nordanskog et al[37,38] (2010, 2013)	6 MDD; 6 bipolar (2 with psychotic features) at time 2 40 years (16) 10 male/2 female 8/12 responders Patients remained on medication	10 RUL, 2 RUL/bitemporal Brief pulse Dose adjusted for age 10 treatments	<7 days (n = 12, time 2) and 168 days (n = 10, time 3), and 364 days (n = 7, time 4) HC: no	Region of interest (hippocampal volumes only)	*ECT time 1 vs time 2*: Bilateral hippocampal volume increase from time 1 to time 2
^{1}H-MRS					
Sanacora et al[39] (2003)	8 MDD 46 years (5) 5 male/3 female 2 remitters, 5 partial responders, 1 nonresponder Medication was discontinued 14 days prior to the first imaging assessment	7/8 bitemporal Brief pulse 9 treatments (2)	7 days (15 standard deviation) HC: no	Single voxel in occipital lobe (9.5 cm^3)	*ECT time 1 vs time 2*: Increased GABA concentrations in the occipital cortex
Michael et al[40] (2003)	13 MDD, 15 bipolar MDD: 60 years (15) Bipolar: 54 years (16) 7 male/18 female Mediation was discontinued 3 days prior to the first imaging assessment	27 RUL/1 Bitemporal Brief pulse Seizure threshold, 2.5× threshold 12 treatments (5)	1 to 2 days (range) HC: yes	Single-voxel STEAM in the left amygdala (3.38 cm^3) measured Glx, Cho, Cr, and NAA	*ECT time 1 vs time 2*: Among ECT responders, NAA and Glx increased *ECT time 1 vs HC*: MDD patients had reduced Glx *ECT time 2 vs HC*: Not assessed
Michael et al[41] (2003)	12 MDD with melancholic features 63 years (11) 4 male/8 females 8/12 responders Medication was discontinued 5 days prior to the first imaging assessment	12 RUL Brief pulse Seizure threshold, 2.5× threshold 10 treatments (3)	1 to 3 days (range) HC: yes	Single-voxel STEAM in the left DLFPC (3.38 cm^3) measured Glx, Cho, Cr, and NAA	*ECT time 1 vs time 2*: Glx increased from time 1 to time 2 in ECT responders *ECT time 1 vs HC*: Patients had decreased Glx relative to HC *ECT time 2 vs HC*: Glx normalized in ECT resonders (ie, no difference relative to HC)
Pfleider et al[42] (2003)	17 MDD 61 years (11) 5 male/12 female 12/17 responders Medication was discontinued 5 days prior to first imaging assessment	15 RUL/2 bitemporal Brief pulse Seizure threshold, RUL 2.5× threshold, bitemporal 2× threshold 13 treatments (5)	1 to 2 days (range) HC: yes?	Single-voxel STEAM in the left pregenual cingulum (3.38 cm^3) measured Glx, Cho, Cr, and NAA	*ECT time 1 vs time 2*: Glx increased from time 1 to time 2 in ECT responders *ECT time 1 vs HC*: Patients had decreased Glx relative to HC *ECT time 2 vs HC*: Glx normalized in ECT responders (ie, no difference relative to HC)
Merkl et al[43] (2011)	25 MDD ECT responders 52 years (13) 17/25 responders (at completion of ECT series; 8/25 "early" responders at time 2 imaging assessment) Patients remained on medication	23 RUL/2 bitemporal 24 ultrabrief/1 brief pulse Seizure threshold, randomization to 4×, 7×, and 10× threshold 9 treatments (fixed)	ECT series continued after ninth treatment (see text for details) HC: yes	Single-voxel point resolved spectro-scopy in the anterior cingulate (20 cm^3) and left DLPFC (8 cm^3) to measured Glu, Cho, Cr, and NAA	*ECT time 1 vs time 2*: ECT responders had decreased NAA in the DLFPC and increased NAA in the anterior cingulate *ECT time 1 vs HC*: No differences in metabolites in the DLPFC; patients had reduced NAA and Glu in the anterior cingulate *ECT time 2 vs HC*: Not assessed

Abbreviations: Cho, choline; Cr, creatine; DLFPC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; GABA, γ-aminobutyric acid; Glu, glutamate; Glx, glutamine; HC, healthy comparison; ^{1}H-MRS, proton magnetic resonance spectroscopy; MDD, major depressive disorder; MRI, magnetic resonance imaging; NAA, *N*-acetyl-aspartate; RUL, right unilateral; SD, standard deviation; STEAM: STimulated Echo Acquisition Mode.

Table 5. Functional MRI (fMRI) and Longitudinal Changes in ECT.

Author (Year)	n Diagnosis Mean Age (SD) Male/Female Ratio of Responders/Total Medication Status	Stimulus Delivery Stimulus Waveform Stimulus Intensity (When Reported) Number ECT Sessions (SD)	Time From ECT Series to Post-ECT Imaging Assessment HC Group: Yes/No	fMRI Task Image Analysis	Longitudinal Neuroimaging Results
Functional MRI (fMRI)					
Christ et al[44] (2008)	11 MDD and bipolar 53 years (11) 3/11 responders Medication was discontinued 3 days prior to the ECT series	7 RUL/4 bitemporal Brief pulse Seizure threshold, 2.5× threshold 12 treatments (6)	Time 2 imaging assessment after the 8 ECT treatment; time 3 completed after the ECT series (time not specified) HC: yes	fMRI tasks: auditory stimulation paradigm Image analysis: voxel-wise (whole brain) analysis; ROI to assess activation intensities	*ECT time 1 vs time 3*: In the voxel-wise analysis, decreased activation in frontal, temporal, parietal, occipital, and anterior cingulate cortices *ECT time 1 vs HC*: In the voxel-wise analysis, patients had more task-related activation throughout the brain; in the ROI analysis, patients had more activation in the temporal, occipital and subcortical areas *ECT time 3 vs HC*: Patients continued to have increased task-related activation
Beall et al[45] (2012)	6 MDD 39 years (5) 4 male/2 female 6/6 responders	6 bitemporal Brief pulse Dose adjusted for age 9 treatments (4)	7 to 21 days (range) HC: no	fMRI tasks: working memory and affective tasks (block designs); resting-state fMRI Image analysis: both ROI to ROI and activation (within an ROI) in the working memory and affective tasks; ROI to ROI in the resting-state fMRI	*ECT time 1 vs time 2*: Orbital frontal cortex activation change correlated with depression ratings change in the affective task; the results did not survive multiple comparisons correction in the working memory task and resting-state fMRI
Perrin et al[46] (2012)	9 MDD 46 years 6 male/3 female 9/9 responders Patients remained on medication	9 bitemporal Brief pulse Seizure threshold, 2× threshold 8 treatments	Not specified HC: no	fMRI task: resting-state fMRI (virtual ball passing task) Image analysis: changes in weighed global connectivity used to select seed region in left DLFPC for seed-voxel correlations	*ECT time 1 vs time 2*: Weighted global connectivity decreased in the left DLPFC; using this region as a seed, seed-voxel correlations revealed decreased connectivity in the anterior cingulate, medial frontal cortex, bilateral DLPFC's, left parietal region
Abbott et al[47] (2012)	12 MDD with (n = 3) and without (n = 9) psychotic features 66 years (10) 4 male/8 female 9/12 remitters Patients remained on medication	10 RUL/2 bitemporal Brief pulse Seizure threshold, RUL 6× threshold, bitemporal 2× threshold 11 treatments (3)	21 days (14) HC: yes	fMRI task: resting-state fMRI Image analysis: independent component analysis to select components of interest, functional network connectivity to measure correlations between component time courses	*ECT time 1 vs time 2*: ECT remitters had increased functional network connectivity between the posterior default mode/DMPFC and the posterior default mode/left DLPFC *ECT time 1 vs HC*: Patients had decreased functional network connectivity in both of the above component pairs *ECT time 2 vs HC*: Aberrant between network relationships normalized with treatment

Abbreviations: DMPFC, dorsomedial prefrontal cortex; DLFPC, dorsolateral prefrontal cortex; ECT, electroconvulsive therapy; GABA, γ-aminobutyric acid; HC, healthy comparison; MDD, major depressive disorder; MRI, magnetic resonance imaging; ROI, region of interest; RUL, right unilateral; SD, standard deviation.

and increased metabolism in the right paracentral gyrus had normalized (ie, no difference between post-ECT imaging assessment and HC).

Three investigations assessed changes in specific neurotransmitter receptors including dopamine (D_2)[32] and serotonin ($5\text{-}HT_{1A}$).[33,34] The D_2 receptor binding decreased in the right rostral anterior cingulate with ECT response. Despite the longitudinal changes associated with the ECT series, no differences were evident between D_2 receptor binding in the patient group relative to HC.[32] With $5\text{-}HT_{1A}$ receptor binding, the results were mixed. One investigation found no longitudinal changes but overall decreased $5\text{-}HT_{1A}$ binding in the midbrain raphe relative to the HC before and after ECT.[33] In contrast, Lanzenberger et al found widespread cortical and subcortical reductions in $5\text{-}HT_{1A}$ receptor-binding potentials from pre- to post-ECT.[34] Peak differences in $5\text{-}HT_{1A}$ receptor binding occurred in the anterior cingulate (including subgenual), orbital frontal cortex, insula, hippocampus, and amygdala.[34]

Electroencephalography

The EEG has measured longitudinal changes associated with ECT at rest[35] and during transcranial magnetic stimulation-evoked potentials (TEPs; Table 2).[36] Quantitative EEG (qEEG) measured standard frequency bands at rest before and after the ECT series.[35] The qEEG revealed increases only in the θ band activity (4-7.5 Hz). Whole-brain analysis with low-resolution electromagnetic tomography confirmed that the subgenual cingulate was the primary site of θ activity. The increased θ activity in the subgenual cingulate was associated with percentage change in psychotic symptoms. Pre-ECT low θ wave activity within the subgenual ACC also served as a predator of the antipsychotic response of ECT.

In the second study, TEPs were measured using 6-channel EEG in the prefrontal region of patients before and after ECT.[36] The immediate response area (a measure of cortical excitability generated from the biphasic wave of TEPs) increased after ECT for each patient. When assessed as a group, the correlation between the percentage reduction in the Hamilton Depression Rating Scale and the increased immediate response area had a nonsignificant trend.

Structural MRI

A longitudinal volumetric study assessed changes in volume with a focused ROI analysis of the bilateral hippocampi (Table 4).[37,38] The heterogeneous sample of 12 patients included unipolar/bipolar, nonpsychotic/psychotic, and responders/nonresponders and had significant attrition from 1-week post-ECT assessment ($n = 12$) to 1-year post-ECT assessment ($n = 7$). Reasons for patient attrition included refusal ($n = 2$), death ($n = 1$), and relapse ($n = 2$). Bilateral hippocampal volume was increased at the 1-week post-ECT imaging assessment but had decreased back to the pre-ECT volumes at the longer follow-up assessments at 180 and 365 days and was not correlated with antidepressant response or side effects.

Proton Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy investigations routinely measure several metabolites *N*-acetyl-aspartate (NAA) as an indirect measure of neuronal functionality, choline (Cho)-related compounds involved in membrane metabolism, creatine (Cr) as a marker of energy utilization, GABA, and glutamate or glutamate/glutamine (Glu or Glx) in a single cubic voxel (Table 4).[43] Six studies used ^{1}H-MRS to assess ECT effects on cerebral metabolite levels. In general, strengths of the longitudinal ^{1}H-MRS investigations included larger sample sizes (up to 28 patients with a depressive episode[40]) and use of an HC group. With the exception of 1 investigation,[43] a medication wash out preceded the pre-ECT imaging assessment. Two investigations obtained the final imaging assessment after a fixed number of treatments[43,48] and continued ECT for a variable number of treatments after the post-ECT imaging assessment. Clinical outcomes (final depression rating scale or determination of clinical response to ECT) occurred at the final imaging assessment[48] or at both the final imaging assessment and the end of the ECT series.[49]

Three investigations measured chemical metabolites in the anterior cingulate. The longitudinal investigations demonstrated both decreased[48] and increased[43] NAA in the dorsal anterior cingulate. In the latter investigation, the pre-ECT assessment identified decreased NAA relative to HC suggesting a trend toward normalization.[43] The third study focused on the pregenual cingulate and did not find any differences in NAA associated with the ECT series.[42] In these same studies, glutamate (Glu) and glutamate + glutamine (Glx) in the anterior cingulate were decreased prior to ECT relative to HC and increased or normalized during the ECT series.[42,48] Glutamate elevations also correlated with the decrease in depression rating scores.[48]

Two investigations measured chemical metabolites in the left dorsal lateral prefrontal cortex.[41,43] In the smaller investigation ($n = 12$), Glx was decreased prior to ECT relative to HC and increased over the longitudinal course of ECT[41] until differences with HC were no longer evident after the series. The larger investigation ($n = 25$) demonstrated increased NAA over the course of the ECT series while the comparison with HC did not reveal any differences before or after ECT.[43]

One investigation assessed changes in chemical metabolites in the left amygdala.[40] Both NAA and Glx increased during the ECT series. The pre-ECT Glx was reduced relative to HC suggesting normalization of Glx in the amygdala with ECT response (not assessed). Only the ECT responders had longitudinal changes in the amygdala, left dorsal lateral prefrontal cortex, and anterior cingulate.[40-42] Nonresponders received additional follow-up with ECT and pharmacotherapy. Many of these patients eventually responded and demonstrated the same changes in chemical metabolites as the earlier responding group.

The last investigation assessed changes in GABA with a single-voxel in the occipital cortex in a group of mixed responders (2 remitters, 5 partial responders, and 1 nonresponder).[39] The GABA concentrations increased after the ECT series, but changes in GABA concentrations did not correlate with clinical response.

Functional MRI

Affective,[45] working memory,[45] and auditory processing[44] tasks have been used in 2 studies to assess changes in fMRI activation patterns associated with ECT response (Table 5). During passive viewing of affective pictures task, diminished negative activation of the orbitofrontal cortex correlated with changes in depression ratings.[45] In a novel auditory processing task, ECT patients had more task-related activations throughout the brain relative to HC.[44] These activations decreased in frontal, temporal, parietal, occipital, and anterior cingulate cortices but failed to normalize with ECT (ie, differences persisted in the post-ECT/HC contrast).

Complimentary analysis methods have been used in resting-state fMRI investigations to assess changes in functional connectivity. Global weighted connectivity, a measure that quantifies the interconnectivity from each voxel to all of the other brain voxels, was used to demonstrate connectivity changes in the left dorsal lateral prefrontal cortex associated with the ECT series.[46] Seed-voxel correlations with this region demonstrated widespread reductions in functional connectivity in the anterior cingulate, parietal, medial frontal, and dorsal lateral prefrontal cortices. Another resting-state fMRI investigation used independent component analysis to identify brain regions with temporally coherent hemodynamic signals.[47] The focus of this investigation was to assess changes in network relationships between regions (or components) of interest affected in depressive episodes. The results showed increased correlations between the posterior default mode network (ie, posterior cingulate) and the left dorsal lateral prefrontal cortex and the dorsal medial prefrontal cortex. Compared to HC, these changes normalized with ECT response.

Discussion

The reviewed investigations assessed neural correlates of ECT response with longitudinal imaging assessments. Despite heterogeneity in imaging modalities, data analysis methods, and included sample, these investigations consistently demonstrated trait-related neural correlates associated with ECT. Several investigations took additional steps such as symptom correlations and assessments by clinical outcomes (ECT responders or remitters analyzed separately) to substantiate trait-related markers of ECT response. The overall results demonstrated that the identified neural imaging changes are indicative of the therapeutic underpinnings of ECT response and not epiphenomena from seizure activity (ie, general effect of the seizure on blood flow). Furthermore, the direction of the change (ie, increased or decreased perfusion, metabolism, chemical metabolite, etc) is likely to be dependent on the specific anatomic region. The patterns identified in these investigations support both the anticonvulsant and the neurotrophic models of ECT.

Decreased perfusion, decreased metabolism, or increased inhibitory chemical metabolites would provide support for the anticonvulsant hypothesis of ECT. This conceptual model received support from complimentary imaging modalities reviewed here. The SPECT studies assessed with whole-brain, voxel-wise analysis exhibited reduced rCBF in the parietotemporal cortices.[25,26] The FDG PET studies were more heterogeneous showing both increases and decreases in metabolism. One FDG PET investigation used an ROI analysis in the subgenual cingulate of patients with psychosis to show increased metabolism after ECT.[29] The remaining investigations with whole-brain, voxel-wise analyses demonstrated reduced metabolism in the frontal cortices.[28-30] In the spectroscopy studies, technical considerations prompted placement of the ^{1}H-MRS voxel to assess changes in GABA in the occipital lobe.[39] The increase in occipital cortex GABA concentrations associated with ECT added support to previous investigations showing increased GABA in serum[49] and cerebral spinal fluid following ECT treatment.[50] Seed-voxel correlations in resting-state fMRI demonstrated reduced connectivity in the left dorsal lateral prefrontal cortex.[46] The results were interpreted in the context of the hyperconnectivity hypothesis of major depression, which posits that depression is associated with increased connectivity in limbic and cognitive networks and successful treatment would be associated with reduced connectivity.[51] Although not tested, the reduction in connectivity may be related to ECT's anticonvulsant effect and promotion of inhibitory processes.

Increased perfusion, increased metabolism, and increased neuronal markers (NAA) in ^{1}H-MRS investigations support the neurotrophic model of the ECT response across imaging modalities. This model also received support from studies included in this review. The parahippocampal gyrus and the medial frontal gyrus demonstrated increased perfusion in association with ECT response.[25] Interestingly, the increased rCBF in the medial frontal gyrus was not apparent at an earlier imaging assessment that was completed 5 days after the ECT series and was only evident 30 days after completion of the series. With FDG PET, cerebral metabolism increased in the medial temporal lobe including the parahippocampus and hippocampus.[29-31] The ECT response was associated with increased volume[37] in the bilateral hippocampi and increased NAA in the amygdala, consistent with the neurotrophic effects.[40]

Longitudinal ECT changes in neural correlates associated with ECT response appear to support both the anticonvulsant and the neurotrophic models. Furthermore, each model appears to have an anatomic focus: anticonvulsant effects appear to be predominately frontally mediated and neurotrophic effects appear to be focused on the medial temporal lobes. The changes in perfusion and metabolism also appear to continue to change long after the ECT series is completed.[22,25]

A conceptual framework that integrates these seemingly discrepant findings and supports both anticonvulsant and neurotrophic models after taking into account the time frame of perfusion changes as well as clinical response has not yet been proposed. After an ECT response, relapse rates are as high as 40% despite optimal continuation therapies.[52,53] The majority of patients that relapse do so within 6 to 9 weeks of completing an ECT series. We propose a model of ECT therapeutic effect in which the reduced perfusion and metabolism to the frontal lobes are sufficient for the immediate ECT response but insufficient to protect ECT responders from relapse. Neurotrophic changes (increased NAA, hippocampal volume, and new patterns of functional connectivity) are necessary for a sustained response. The ECT nonresponder will have no changes in frontal perfusion or metabolism and no neurotrophic changes. The ECT responder who immediately relapses will have perfusion changes but no neurotrophic changes. The ECT responder who has a sustained response will have perfusion changes and neurotrophic changes. The diminished frontal activity during the immediate response period may be necessary for remodeling aberrant disease-related connectivity patterns.

Longitudinal ECT studies present many logistical and methodological challenges. Patients meeting the indications for ECT are often hospitalized and in need of urgent treatment. Scheduling imaging assessments in this context presents logistical difficulties reflected in several of the limitations of these investigations: small sample sizes, medication effects, and variability in ECT treatment parameters. The small sample sizes (mean sample of included studies, $n = 12$) limit the ability to detect differences with whole-brain analyses and correlations with symptom improvement. With respect to medication status, investigators either performed a medication wash out in the days preceding the imaging assessment or did not make any medication changes during the ECT assessment. Both approaches have limitations. Medication wash outs were often incomplete (a minority of patients could not tolerate the wash out but were included in the final analysis) and completed only days prior to the initial imaging assessment likely introducing an additional confound (ie, medication withdrawal or discontinuation syndrome in some cases). Patients remaining on medications limit the veracity of the conclusions that the observed changes are solely related to ECT. Consistent with clinical studies, synergy may exist between pharmacotherapy and ECT,[54] and the results must be interpreted in this context. Finally, ECT treatment considerations are often naturalistic and deferred to the ECT clinician resulting in mixed methods of stimulus delivery and even transitioning from one stimulus delivery to another in the context of nonresponse.

Conclusion

This review found consistent changes in neural correlates that bridged methodological differences. The pattern of change supports both the anticonvulsant and the neurotrophic models of ECT. We proposed a conceptual model that integrates the accumulating evidence supporting both theories and provides a testable framework for both immediate ECT response (decreased perfusion, metabolism, and functional connectivity) and ECT relapse (presence of neurotrophic effects). Relapse has been called the "most pressing issue in the field."[52] To date, disease chronicity (odds ratio = 1.84) and treatment resistance (odds ratio = 1.67) have been the only predictors of nonremission and relapse.[55] A neuroimaging assessment that could identify patients with increased risk of relapse following completion of the ECT series would significantly add to the clinical repertoire of treating psychiatrists.

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