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International Journal of Public Health and Medical Research

ISSN: 3006-7707 (Print), ISSN: 3006-3752 (Online)
Volume 6, Number 7, Year 2026
DOI: https://doi.org/10.62051/ijphmr.v6n7.01



Brain Network and Synaptic Plasticity Changes Associated with Electroconvulsive Therapy for Depression: A Multilevel Review

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ABSTRACT

Electroconvulsive therapy (ECT) is an important treatment for severe, treatment-resistant, or high-risk depression, yet the relationship between its antidepressant effects, brain network changes, and cellular and molecular processes remains incompletely understood. Recent advances in multimodal magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), molecular biology, and animal electroconvulsive stimulation models have provided multilevel evidence for understanding the neurobiological mechanisms of ECT in depression. Current studies suggest that ECT is accompanied by changes in functional connectivity within large-scale brain networks, including the default mode network (DMN), the frontoparietal control network (FPCN), and prefrontal-limbic circuits. In parallel, processes involving neurotransmission, brain metabolism, neurotrophic factors, inflammatory responses, and synaptic plasticity may provide biological clues for interpreting these network-level changes. This review summarizes evidence related to brain network reorganization and synaptic plasticity-associated regulation in ECT for depression, and discusses how findings across levels may be integrated to inform future mechanistic research and treatment-response prediction.

KEYWORDS

ECT; Depression; MRI; Brain network reorganization; Synaptic plasticity

1. INTRODUCTION

Electroconvulsive therapy (ECT) is a long-established somatic treatment in psychiatry with well-documented clinical efficacy, used mainly for severe, treatment-resistant, or high-risk depression [1]. ECT has a relatively rapid onset of action and favorable clinical response rates, particularly in patients with an inadequate response to pharmacotherapy, rapid clinical deterioration, marked suicide risk, psychotic symptoms, or catatonic features [1, 2]. It therefore retains an important role in contemporary treatment systems for depression. Despite this clinical efficacy, the neurobiological mechanisms of ECT remain insufficiently clarified [3]. Earlier studies have related its antidepressant effects to monoaminergic neurotransmission, neuroendocrine regulation, and neurotrophic factors. However, neither depression nor the therapeutic response to ECT can be adequately explained by a single neurotransmitter system, brain region, or isolated biological pathway [4]. Existing molecular findings should therefore be integrated with evidence of synaptic plasticity and large-scale brain network changes to provide a more comprehensive framework for understanding the effects of ECT.

Recent advances in multimodal magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), molecular biology, and animal electroconvulsive stimulation research have expanded the evidence base for understanding the mechanisms of ECT. Neuroimaging studies have

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reported post-ECT changes in connectivity within and between large-scale brain networks, including the default mode network (DMN) and the frontoparietal control network (FPCN) [5], as well as altered hippocampal-DMN coupling [6] and amygdala-prefrontal connectivity [7]. Changes in hippocampal and amygdala volumes [8-10] and in structure-function coupling [11] have also been observed, suggesting that clinical improvement following ECT may be accompanied by alterations in large-scale brain network organization. At the same time, animal experiments and clinical molecular studies indicate that ECT or electroconvulsive stimulation may influence glutamate/gamma-aminobutyric acid (GABA) balance, monoaminergic activity, brain metabolic state, brain-derived neurotrophic factor (BDNF), inflammatory responses, and glial cell function [3]. Animal models of electroconvulsive stimulation provide complementary evidence for neuroplasticity-related processes, including changes in synaptic function and local circuit activity [3, 12]. Against this background, this review examines the neurobiological mechanisms of ECT in depression, and synthesizes evidence on ECT-related changes in large-scale brain networks and synaptic plasticity. It also considers potential links between macroscopic neuroimaging findings and molecular and cellular changes.

2. BRAIN NETWORK REORGANIZATION

Among the brain regions examined in structural imaging studies, the hippocampus and amygdala have shown the most consistently reported volumetric changes following ECT. Multiple longitudinal MRI studies and meta-analyses have reported increases in bilateral hippocampal and amygdala volumes in patients with depression after a course of ECT [8-10]. Gray matter changes have also been observed in other limbic-related regions, including the temporal regions and anterior cingulate cortex [9,10]. Several studies have found that increases in total hippocampal volume or specific hippocampal subfields are correlated with reductions in depression severity, suggesting that these structural changes may accompany clinical improvement following ECT [13]. Other studies, however, have not identified consistent associations between regional volume increases and treatment response after adjustment for factors such as the number of ECT sessions, baseline brain structure, concomitant medication, and electrode placement [9, 14]. Conventional structural MRI primarily captures macroscopic morphological changes and cannot directly determine their underlying cellular or molecular basis. Accordingly, volume increases following ECT should not be interpreted as direct evidence of neurogenesis, synaptogenesis, or uniformly enhanced neuroplasticity. Potential contributors may include morphological changes in neurons and glial cells, vascular and perfusion-related responses, alterations in extracellular space, and changes in tissue water content [3, 15]. Thus, hippocampal and amygdala volume changes represent important imaging correlates of ECT-related structural alterations, but their relevance to the antidepressant effects of ECT requires further clarification through integration with functional connectivity, metabolic, and molecular evidence.

At the functional connectivity level, the DMN has been a major focus of studies investigating the mechanisms of ECT [5, 6]. The network primarily comprises the medial prefrontal cortex, posterior cingulate cortex/precuneus, lateral parietal cortex, and medial temporal regions, and supports internally directed cognition, including self-referential processing and episodic memory [16, 17]. Its relevance to depression arises partly from the prominence of persistent self-focused thought and rumination, making the DMN a useful network-level context for examining treatment-related change [5, 16]. Longitudinal resting-state functional magnetic resonance imaging (rs-fMRI) data show that depression is characterized before ECT by lower static connectivity within the dorsomedial prefrontal subsystem and greater temporal variability between dorsomedial prefrontal and medial temporal DMN subsystems [5]. Following treatment, static connectivity increases within the dorsomedial prefrontal subsystem and between this subsystem and the core DMN, while temporal variability decreases within the medial temporal subsystem and between these two subsystems [5]. A separate longitudinal study reports reduced fractional anisotropy in the left parahippocampal cingulum, decreased hippocampal-posterior cingulate connectivity, and increased connectivity between the

posterior cingulate cortex and other DMN regions after ECT [6]. These findings are consistent with altered hippocampal-DMN coupling, although the relationship between white matter and functional changes remains uncertain. Within prefrontal-limbic circuitry, increased connectivity between the left amygdala and left dorsolateral prefrontal cortex is associated with reductions in overall depression severity, negative thoughts, and detachment, but not neurovegetative symptoms [7]. The involvement of dorsolateral prefrontal cortex is also consistent with the broader role of frontoparietal control architecture in cognitive regulation [18], although this network-level interpretation remains indirect. The available evidence therefore indicates that ECT is accompanied by changes within the DMN and across hippocampal-DMN and prefrontal-limbic systems, with some associations varying across symptom dimensions [5-7].

Beyond regional and network-specific findings, whole-brain analyses indicate that ECT-related effects may extend to the overall organization of functional brain networks. One longitudinal rs-fMRI study reports increased characteristic path length and reduced global efficiency after treatment, with changes in nodal degree, nodal efficiency, and interregional connectivity concentrated in the DMN, frontoparietal network, and limbic system [19]. A separate analysis identifies increased clustering and local efficiency in static networks together with reduced global flexibility in dynamic networks, particularly in hippocampal, frontal, and temporal regions [20]. Electroencephalography-based network analysis likewise detects treatment-related changes in global and nodal organization, although its spatial and physiological measures are not directly interchangeable with functional MRI-derived metrics [21]. Structure-function coupling also increases after ECT in regions associated with the DMN, particularly the bilateral superior frontal and cingulate gyri. This change is accompanied by altered functional connectivity without a significant longitudinal change in white matter structural connectivity [11]. Together, these studies suggest shifts in global integration, local segregation, and nodal organization, but the direction and interpretation of individual metrics remain method dependent [11, 19-21].

Network topology findings are difficult to compare across studies because graph metrics vary with the parcellation scheme, edge-density threshold, handling of negative correlations, head-motion correction, and preprocessing pipeline [19-21]. Treatment-related factors, including electrode placement, pulse width, stimulus dose, seizure number, anesthesia, concomitant medication, and the interval between ECT and imaging, also differ across cohorts [9, 14, 19, 20]. Reports that retain subject-level treatment parameters, include repeated control scans, and test results across prespecified parcellation and threshold schemes are better positioned to distinguish reproducible network changes from analysis-specific effects.

3. SYNAPTIC PLASTICITY-RELATED MECHANISMS OF ECT

Synaptic plasticity refers to activity-dependent changes in the strength, structure, and functional properties of synaptic connections, including neurotransmitter release, receptor activity, dendritic spine morphology, and synapse number [22]. Synaptic dysfunction has been implicated in major depressive disorder: postmortem studies have identified reduced expression of synapse-related genes and fewer synapses in the dorsolateral prefrontal cortex [23], while an in vivo 11C-UCB-J study associated lower presynaptic-marker binding in the dorsolateral prefrontal cortex, anterior cingulate cortex, and hippocampus with greater depressive symptom severity [24]. These findings provide a clinical rationale for investigating whether effective antidepressant treatments, including ECT, are accompanied by synaptic plasticity-related changes. In patients receiving ECT, such changes have been examined using molecular imaging, neurophysiological measures of cortical excitation and inhibition, MRS, and peripheral molecular markers, whereas animal electroconvulsive stimulation (ECS) models permit more direct assessment of activity-dependent gene expression, dendritic spine morphology, synapse number, and hippocampal neurogenesis.

Among the available clinical methods, positron emission tomography (PET) imaging of synaptic vesicle glycoprotein 2A (SV2A) provides an in vivo proxy for presynaptic terminal density. SV2A is widely expressed in presynaptic vesicles, and the radioligand 11C-UCB-J estimates SV2A availability rather than neurotransmitter release or synaptic efficacy. A longitudinal pilot study in late-life depression found that ECT-related gray matter enlargement did not correspond at the group level to changes in 11C-UCB-J binding [25]. This result cautions against interpreting structural MRI findings as direct evidence of synaptogenesis, although the small sample does not exclude subtle, region-specific, or response-dependent synaptic changes.

Neurophysiological studies provide a different view by examining cortical excitability and inhibition rather than synaptic density. Because short-interval intracortical inhibition and the cortical silent period partly reflect GABAergic inhibitory function, TMS studies have tested whether these measures change during ECT. An early study of right unilateral ECT reports increased short-interval intracortical inhibition and prolonged cortical silent periods, with no corresponding change in resting motor threshold or intracortical facilitation [26]. Later work does not detect significant longitudinal changes in cortical silent period or short-interval intracortical inhibition, although pretreatment cortical silent period differs between responders and nonresponders [27]. TMS combined with electroencephalography instead shows increased frontal cortical excitability after ECT [28]. Differences in electrode placement, pulse width, treatment exposure, cortical region, medication use, and measurement method may contribute to these divergent findings.

Because glutamatergic and GABAergic signaling contributes to excitatory-inhibitory balance and synaptic activity in prefrontal-limbic circuits, MRS studies have examined whether these neurochemical systems change following ECT [29]. Longitudinal measurements show an increase in the glutamate-glutamine complex (Glx) in the subgenual anterior cingulate cortex but a decrease in the left hippocampus, with both changes associated with reductions in depressive symptoms [30]. The same study identifies reduced N-acetylaspartate (NAA) in the dorsal anterior cingulate cortex and right hippocampus, while lower pretreatment NAA in the dorsal anterior cingulate cortex is associated with greater subsequent symptom improvement [30]. Evidence concerning GABA is less consistent: an early study reports increased occipital GABA after ECT [31], whereas later work finds no significant change in prefrontal or occipital GABA, glutamate, or glutamine and detects only a reduction in NAA [32]. Variation in voxel placement, magnetic field strength, spectral processing, concomitant medication, and the interval between treatment and scanning may contribute to these regional and between-study differences. MRS also measures the combined metabolite signal within a relatively large tissue volume and cannot distinguish metabolites located in neurons, glial cells, synaptic vesicles, or extracellular space. Changes in Glx or GABA should therefore be interpreted as region-specific alterations in the neurochemical environment rather than direct evidence of corresponding changes in excitatory or inhibitory synaptic transmission [33].

Animal ECS studies provide the most direct evidence that seizure induction is followed by molecular and structural changes related to synaptic plasticity. BDNF is an activity-regulated neurotrophin with established roles in synaptic modulation [34]. Acute ECS elicits cell-type-specific transcriptional responses across hippocampal neuronal populations, with particularly prominent changes in dentate granule cells [35], while early growth response 3 (Egr3) is required for ECS-induced hippocampal BDNF expression [36]. In a corticosterone-based neuroendocrine model of depression, ECS increases specific forms of BDNF expression and partly reverses stress-related alterations in dendritic spine morphology, linking neurotrophic signaling with structural synaptic changes [37]. Repeated ECS also increases the estimated number of hippocampal synapses, including spine, perforated, and nonperforated synapses, together with dentate gyrus neuronal number and volume [38].

These results support two related components of ECS-induced plasticity: rapid activation of activity-dependent transcriptional pathways and subsequent changes in dendritic and synaptic structure. Human MRS and TMS studies identify changes in regional neurochemical metabolism and cortical excitatory-inhibitory physiology, but their direction varies across brain regions and studies [26-28,

30-33]. Meta-analyses show that peripheral BDNF trajectories after ECT are variable and are not consistently associated with clinical improvement [39, 40]. Plasma VEGF may increase transiently after individual ECT sessions without a clear relationship to treatment response [41]. A broader synthesis of preclinical and clinical evidence likewise finds substantial heterogeneity in BDNF response [42], while preclinical work links VEGF signaling more broadly to antidepressant-related neurogenesis and behavior [43]. Studies of inflammatory markers report similarly heterogeneous cytokine trajectories and clinical associations [44-47]. Because peripheral proteins and cytokines do not directly index synaptic processes within the brain, these findings provide complementary but indirect evidence. Current evidence therefore supports activity-dependent gene regulation and structural synaptic remodeling as candidate mechanisms of ECS in animals, whereas the corresponding synaptic mechanism of clinical ECT remains supported mainly by indirect and partly inconsistent human evidence.

4. CROSS-LEVEL INTEGRATION OF MULTIMODAL EVIDENCE

Recent longitudinal studies have begun to examine ECT-related changes across biological levels by combining neuroimaging with metabolic, molecular, and cellular indicators. Structural MRI and MRS studies have assessed relationships between medial temporal or hippocampal volume changes and local N-acetylaspartate, glutamate–glutamine, and diffusion measures [30, 48]. Other studies have related hippocampal and white matter changes to peripheral BDNF and inflammatory markers, including interleukin-6, tumor necrosis factor-α, and interleukin-8 [45, 49, 50]. More recent PET-MRI and imaging transcriptomic studies have further examined whether gray matter or network changes correspond to SV2A binding, regional gene-expression profiles, and neurotransmitter-receptor distributions [11, 25, 51, 52]. These studies provide the main available evidence for evaluating how ECT-related molecular, metabolic, structural, and network changes may be associated across levels.

Longitudinal multimodal MRI and MRS data indicate that gray matter volume increases during an ECT course in the bilateral medial temporal lobes and right perigenual anterior cingulate cortex [30]. The increase in left hippocampal volume correlates with a reduction in the hippocampal N-acetylaspartate/creatine ratio, whereas an apparent association with the glutamate-glutamine complex/creatine ratio does not remain significant after correction for multiple comparisons [30]. Hippocampal metabolite changes are not significantly related to clinical improvement, while greater symptom reduction is associated with a larger increase in left medial temporal lobe volume [30]. A separate multimodal study finds that hippocampal and amygdala enlargement is accompanied by altered hippocampal diffusion measures but not by significant changes in the metabolites examined [48]. Regional volume changes may therefore covary with selected metabolic or microstructural measures, but the affected indicators and their directions are not consistent across studies.

Cross-level analyses involving peripheral biomarkers identify selective rather than uniform associations. In late-life depression, hippocampal volume increases after ECT but returns to approximately pretreatment levels at the 6-month follow-up; serum BDNF remains largely unchanged and does not covary significantly with either hippocampal volume or depression severity [49]. Another study links a greater reduction in interleukin-6 to a larger increase in total hippocampal volume, while the relationship involving tumor necrosis factor-alpha is weaker and region dependent [45]. White matter findings are similarly time sensitive: early changes in interleukin-8 correlate with tissue-specific fractional anisotropy in the right superior longitudinal fasciculus and right cingulum, and the associations across the full observation period are evident in responders but not nonresponders [50]. These studies connect peripheral immune changes with selected hippocampal or white matter measures, but the imaging subsamples are small and the observed relationships depend on the biomarker, brain region, and assessment time.

The most direct attempt to determine whether ECT-related gray matter enlargement corresponds to an in vivo synaptic marker uses 11C-UCB-J PET-MRI of SV2A [25, 53]. This longitudinal pilot study in older adults reports gray matter volume increases after ECT in the right temporal pole, medial temporal lobe, and parahippocampal gyrus [25]. At the group level, however, the magnitude of volume change does not correspond significantly to changes in 11C-UCB-J binding [25]. Exploratory analyses suggest that SV2A-related trajectories may differ between remitters and nonremitters, but the small sample precludes a stable response-specific conclusion. The study therefore does not support treating ECT-related gray matter enlargement as a direct proxy for increased synaptic density.

Imaging transcriptomic analyses address a different cross-level question by testing whether the spatial distribution of ECT-related imaging changes resembles gene-expression or neurotransmitter-receptor maps obtained from independent brain datasets [52]. In a typical analysis, a treatment-related imaging statistic is summarized across a common cortical or whole-brain parcellation and compared with regional gene-expression profiles from the Allen Human Brain Atlas or with independently derived receptor-density maps. Longitudinal multimodal data indicate increased structure-function coupling after ECT, particularly in the default mode and somatomotor networks and in bilateral superior frontal and cingulate regions [11]. Functional connectivity changes significantly after treatment, whereas structural connectivity does not show a significant longitudinal shift [11]. The spatial pattern of coupling changes corresponds to gene-expression profiles from the Allen Human Brain Atlas and to several neurotransmitter-density maps, including a positive spatial association with serotonin 1B (5-HT1B) receptor density [11]. Genes prioritized by this spatial analysis are enriched in glutamatergic synapse components and pathways related to phosphoinositide 3-kinase/protein kinase B (PI3K-Akt), mitogen-activated protein kinase (MAPK), cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate/protein kinase G (cGMP-PKG), neurotransmitter release, and long-term depression [11]. A separate analysis shows that pre-ECT abnormalities in left hippocampal-tail connectivity with prefrontal, temporal, and visual regions shift toward control levels after treatment [51]. Gene-expression patterns spatially associated with these connectivity abnormalities are enriched in synaptic signaling and transmission, ion transport, intercellular signaling, and neurogenesis [51]. These analyses do not measure treatment-induced gene expression or receptor changes in the patients themselves; they identify spatial correspondences between neuroimaging findings and molecular maps derived from independent samples.

Current cross-level evidence is therefore characterized by specific and method-dependent associations rather than a common multilevel biological signature of ECT. Medial temporal and hippocampal volume changes have been associated with NAA ratios and peripheral inflammatory markers, while white matter microstructural changes have been associated with interleukin-8 in selected tracts. By contrast, serum BDNF does not consistently covary with hippocampal volume, and gray matter enlargement does not correspond reliably to changes in SV2A-related synaptic density. Atlas-based analyses further identify molecular systems whose normal spatial distributions resemble ECT-related imaging effects, but they cannot establish that these molecular systems changed during treatment. Taken together, the available findings support region- and time-dependent relationships among selected molecular, metabolic, microstructural, and network measures, but do not yet establish a sequential pathway from a single molecular change to synaptic modification, brain network reorganization, and clinical improvement.

5. SUMMARY AND OUTLOOK

In summary, the neurobiological effects of ECT for depression may involve changes across multiple levels [3]. Current studies suggest that connectivity patterns in large-scale brain networks, including the DMN, FPCN, and prefrontal-limbic circuits, can change after ECT [5-7]. At the same time, micro-level processes involving neurotransmitters, brain metabolic state, neurotrophic factors, inflammatory responses, glial cell function, and synaptic plasticity may provide biological context for interpreting

treatment response [3, 12]. Compared with traditional single-transmitter hypotheses or local brain-region explanations, a cross-level framework spanning molecules, cells, circuits, and networks is better suited to integrating existing findings from neuroimaging, molecular biology, and animal experiments. However, the relationships among evidence across levels remain incompletely defined. In particular, whether molecular marker changes, synaptic plasticity-related adjustments, imaging-defined network reorganization, and clinical efficacy follow stable temporal sequences or causal relationships requires further investigation.

Future mechanistic studies of ECT should place greater emphasis on longitudinal, standardized, and cross-modal integration [3, 53]. Clinical symptoms, cognitive function, multimodal imaging, brain metabolism, and peripheral molecular markers should be collected at coordinated time points before, during, and after treatment so that relationships among changes at different levels can be examined dynamically. Multicenter studies with larger samples should harmonize imaging acquisition, ECT protocols, and treatment-response criteria to improve reproducibility and generalizability [8, 9]. Coordinated molecular sampling and prespecified assay procedures are also needed when biological measures are compared across sites [3]. Machine learning or other statistical modeling approaches may then help identify more stable predictors of therapeutic response and inform the optimization of treatment parameters and assessment of adverse-effect risk. At present, however, such models remain exploratory and cannot replace comprehensive clinical judgment. The main value of a cross-level explanatory framework based on multimodal evidence lies in deepening mechanistic understanding of ECT's antidepressant effects and providing a more reliable theoretical basis for research on response prediction and individualized treatment.

Analytically, future studies should distinguish explanation from prediction. Mechanistic analyses require prespecified temporal models that compare competing sequences of molecular, circuit, and symptom change; predictive models require out-of-sample validation and should be evaluated against clinical baseline models rather than against chance alone. Antidepressant response, remission, relapse, and cognitive change should be modeled as separate outcomes because a marker associated with acute symptom reduction may not predict durability or adverse effects. Recording electrode placement, pulse width, current amplitude, seizure quality, and cumulative electrical dose would permit imaging and molecular effects to be evaluated in relation to treatment exposure instead of session count alone. Repeated assessments after the acute course are equally important for determining whether a candidate mechanism tracks transient treatment effects or persists with clinical benefit.

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