Contemporary ECT, Part 2: Mechanism of Action and Future Research Directions


Simply telling patients “we don’t know how ECT works” neglects our abundant knowledge of what this treatment does. The authors review biological actions of ECT and discuss future directions for research.

Electroconvulsive therapy (ECT) continues to be a vital treatment for severe depression and a few other psychiatric diagnoses. Its more widespread use has been limited primarily by the unwarranted stigma attached to the procedure. In addition, critics often cite a lack of knowledge about its mechanism of action as a reason to eschew its use. Here we review some of the knowledge base of ECT’s biological actions and discuss future directions for ECT research.

Mechanism of action

Decades of research in both animal models of ECT (referred to as electroconvulsive shock, or ECS) and clinical trials in humans have contributed to a vast evidence base of neurobiological changes associated with induced seizures. Undoubtedly, the biological events ultimately leading to relief from depression with ECT involve a cascade of effects related to molecules, cells, and circuits. While various researchers have focused primarily on one of these neurobiological domains, there is no currently articulated theory of the mechanism of action of ECT in depression that incorporates events at all 3 levels. It is likely that many of the myriad observed changes are epiphenomena not essential to the therapeutic effects of ECT.

Many technologies have been applied to the study of the neurobiological effects of ECT or ECS, including single photon emission CT, positron emission tomography, functional MRI (fMRI), magnetic resonance spectroscopy (MRS), EEG, body fluid chemical analysis (blood, urine, cerebrospinal fluid) and, in animals, histological examination and molecular genetic assays. The main theories of mechanism of action of ECT in depression can be classified as follows: neurotransmitter, neuroendocrine, anticonvulsant, neurotrophic, and neural connectivity hypotheses.

ECT, Part 1:

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The neurotransmitter theory of action of ECT arises from long-standing interest in the monoamines (serotonin, dopamine, norepinephrine) and other neurotransmitters, such as GABA and glutamate, in biological theories of the etiology of depression. Animal studies have shown consistent effects of ECS on monoamine neurotransmitter functioning, such as enhancement of serotoninergic transmission; results have been inconclusive for humans.¹ MRS studies have reported increased cortical GABA concentrations after ECT in humans as well as increased glutamate/glutamine in the left dorsolateral prefrontal cortex and anterior cingulum.²,⁵

The neuroendocrine hypothesis of ECT is based on the findings of activation of the hypothalamic-pituitary axis during seizures, demonstrated by a surge in blood levels of adrenocorticotropic hormone, cortisol, and prolactin postictally.⁶ It is also based on the observation
that abnormal overdrive of the hypothalamic-pituitary-adrenal axis in depression, as measured by the dexamethasone suppression test, can predict response to, and relapse after, ECT. The anticonvulsant theory of ECT action arose from the observation that seizure threshold often rises and seizure duration shortens over a course of ECT, leading to the hypothesis that the inhibitory brain process associated with the progressive rise in seizure threshold is also responsible for depression relief. Support for this comes from EEG and cerebral blood flow studies that demonstrated suppression of neural activity (mostly in the frontal lobes) after a course of ECT, which correlates with antidepressant effect. The most recent conceptualizations of ECT mechanisms involve newer technologies for investigating cellular morphological changes, termed “neuroplasticity,” in animals, and “neural connectivity” in humans. The neuroplasticity (or neurotrophic) hypothesis of ECT mechanism holds that morphological changes, such as neurogenesis, gliogenesis, or alterations in dendritic or axonal arborization of existing neurons, are critical to the antidepressant effect of ECT. Extensive animal studies of ECS document consistent evidence of neurogenesis in the hippocampus (mossy fiber sprouting), prefrontal cortex, and other limbic structures.

**Brain imaging**

Remarkable brain structural detail can now be imaged with high–magnet-strength MRI. Such imaging has recently been applied to ECT patient populations at baseline (in the ill state, before ECT) and during and after a course of ECT. Findings indicate increased gray matter volume after ECT in the hippocampus, subgenual cortex, and amygdala. It may be that baseline brain morphology is abnormal in severely depressed patients, and that ECT-induced neuroplasticity results in a return to normal size and morphology of structures such as the hippocampus and amygdala. There have been several attempts to elucidate neurotrophic ECT mechanisms using MRS. Indirect support for neurogenesis in humans comes from MRS studies that show cell membrane turnover in areas felt to be critical to antidepressant mechanisms, which could reflect growth of new neurons. Other findings include increased N-acetylaspartate in the left amygdala and increased choline-containing compounds in the hippocampus with ECT. As these examples illustrate, MRS findings are diverse and do not allow a unifying conclusion. Undoubtedly, further refinement of MRS technology will enable assessment of other relevant brain molecules. It seems likely that neuroplastic and neurotrophic cellular events are the most critical of all in the causative chain of ECT antidepressant effect. Quantitative EEG and fMRI have only recently been applied to ECT populations. One study utilizing a new EEG analytic method—low-resolution electromagnetic tomography—found that increases after ECT in theta frequency (4 to 7 Hz) in the subgenual cingulate, an area of interest in the pathophysiology of depression, correlated robustly with reductions in psychotic depression. Perrin and colleagues found evidence that reduction of baseline frontal cortical hyperconnectivity correlated with resolution of depression with ECT. However, Abbott and colleagues demonstrated that improvement in depression correlated with increased frontal cortical connectivity. The researchers ascribed the differential findings to different fMRI techniques. In an fMRI study of 6 patients treated with ECT, Beall and colleagues found that orbitofrontal activation in response to an affect-laden task decreased with successful ECT, but the sample size was too small for definitive conclusions. Finally, Christ and colleagues studied 11 ECT patients with fMRI using an auditory task-related activation of multiple cortical areas. They found that patients had more task-related activation after ECT, but the implications of this finding are unclear. Methodologically sound, adequately powered fMRI studies in ECT populations are needed to advance our knowledge of neural network alterations in severe depression and subsequent recovery. While we await a definitive understanding of the biological changes underpinning the mechanism of action of ECT, there is no need to be defeatist. Simply telling patients “we don’t know how ECT works” neglects our abundant knowledge of what this powerful treatment does. As Andrade suggests, it is more helpful to patients to explain and categorize several of the biological effects of ECT; it is a “glass half full” approach, which is both truthful and positive.

**Future directions**

ECT research will continue to focus on refining aspects of technique and personalizing ECT type and schedule, as well as further elucidating its mechanisms of action. Technical refinements are aimed at preserving antidepressant efficacy while increasing cognitive tolerability. Techniques to more precisely target particular brain structures or areas for seizure initiation and/or to limit the spread of the seizure are under development.
electrical stimulus, 2 different sized electrodes, and novel electrode placement. Modifications of the stimulus package (ie, further reductions in pulse width and varying frequency, amplitude, or duration) are also being studied. Further research, including biomarker discovery for response/relapse prediction, should help inform practitioners about how to determine the optimal type and number of acute treatments for a given patient and how to individualize continuation/maintenance ECT schedules.

**Disclosures:**
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