Neuroscience and Psychiatry

Understanding the Mechanisms of Action of Electroconvulsive Therapy
Revisiting Neuroinflammatory and Neuroplasticity Hypotheses

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Electroconvulsive therapy (ECT) has been effectively used for almost a century, but its mechanisms of action remain poorly understood. Two primary hypotheses have been postulated: the structural neuroplasticity and the neuroinflammatory models. Structural neuroplasticity, which embraces different biological processes, including neurogenesis, synaptogenesis (eg, dendritic arborization), and supporting mechanisms like angiogenesis and gliogenesis, has been traditionally favored over ECT-induced neuroinflammation. Inflammation is generally considered a pathological process, one that is involved in the pathophysiology of depression,[1] so it may be counterintuitive to formulate it as a therapeutic mechanism. But inflammation is also a mechanism of repair and recovery, and parallel neuroinflammatory routes coexist; while systemic inflammatory processes modulating the hypothalamic-pituitary adrenal axis and neurotransmitter systems are associated with the pathophysiology of depression,[1] local and transient neuroinflammatory mechanisms, often cell-mediated involving glial activation, may account for repair mechanisms linked to the antidepressant therapeutic action of ECT.

Perez-Caballero et al[2] demonstrated that the early acute antidepressant response to deep brain stimulation (DBS) observed in patients could be replicated in rodent models by inserting electrodes to the medial prefrontal cortex of rats, which covers the prelimbic and infralimbic cortex homologous to the human subgenual anterior cingulate cortex (eg, BA25/24). This therapeutic behavioral response was associated with a local neuroinflammatory reaction driven by glial immunoreactivity, independent of whether the stimulation was on or off (ie, a local inflammatory response to a foreign body in a critical node of the circuit). Moreover, a retrospective analysis revealed that patients taking anti-inflammatory medications may have milder acute antidepressant benefit from DBS.[2] One may relate these neuroinflammatory and clinical changes to the therapeutic benefits of leukotomies in movement, major depressive, and obsessive-compulsive disorders, where a focal lesion is created in critical nodes of disease-relevant circuits to generate a focal scar (mediated by a focal neuroinflammatory response leading to gliosis), which generates an adaptive disconnection syndrome or therapeutic diaschisis, forcing structural and/or functional plasticity to reconfigure the circuit dynamics.

While there is strong evidence that, unlike DBS or leukotomies, ECT does not lead to focal or diffuse lesions, gliosis, or neuronal damage,[3] neuroimaging studies have consistently reported macroscopic and mesoscopic increases in volume.[4] These focal volumetric increases are not in the areas closest to the electrodes but in deeper regions with relevance to emotional processes, such as the hippocampus and the limbic temporal lobe.[5] Interestingly, these limbic regions have been traditionally considered the most susceptible to seizures. Could it be possible that ECT triggers a local neuroinflammatory response in those brain regions more susceptible to seizures? And could this local inflammatory response in limbic nodes lead to physiological changes responsible for the antidepressant (and amnesic) response to ECT? This hypothesis could relate the therapeutic response of ECT to the disconnection syndromes observed acutely in patients treated with DBS.

At the same time, it is feasible that the observed brain volumetric increases associated with ECT are directly explained by different mechanisms loosely included under the construct of neuroplasticity, such as synaptogenesis, gliogenesis, or angiogenesis, which ultimately may also modulate the abnormal neurophysiological dynamics. Noninvasive human neuroscience techniques, such as structural magnetic resonance imaging (MRI), have limited resolution to fully understand the molecular and cellular basis of these brain volumetric increases. Therefore, neuroimaging studies can relate ECT-mediated structural changes to a neuroplastic signal but cannot rule out other interpretations. For example, neurogenesis induction, which is one of the structural neuroplastic mechanisms that has been suggested to promote ECT-induced structural changes, could not explain volume increases in nonneurogenic regions (eg, outside the dentate gyrus of the hippocampus).

When trying to explain the molecular basis of these volumetric increases, the use of hydrogen magnetic resonance spectroscopy in combination with structural MRI may help us to elucidate the biochemical underpinnings of these structural brain changes. Specifically, magnetic resonance spectroscopy allows us to noninvasively capture in vivo *N*-acetyl aspartate (NAA) concentrations (among others with less conclusive findings, such as glutamine). As NAA is a neuronal marker considered to be associated with healthy neural function, reductions in NAA concentration may be indicative of a transient neuronal disruption (including due to inflammation), while NAA increases would support the structural neuroplastic hypothesis. Considering only the findings observed in 3T magnets, which offer better signal-to-noise ratio, 6 of 7 studies found NAA concentration reductions in the hippocampus, anterior cingulate cortex, and dorsolateral prefrontal cortex.[6] Importantly, none of these studies observed a difference in NAA ratio between patients and controls in the same regions showing changes after ECT; therefore, these findings do not support the idea that NAA reductions are a consequence of an ECT-induced normalization of NAA levels. They may be better interpreted as an ECT-induced neural disruption, which would agree with the neuroinflammatory hypothesis.

Similarly, studies using diffusion-weighted MRI have identified focal changes in the white matter associated with ECT. Such changes include increases in mean diffusivity associated with higher water concentration due to increased permeability of the blood-brain barrier or decreases in axial diffusivity associated with axonal remodeling, both mechanisms suggestive of focal neuroinflammatory responses. However, decreases in mean and radial diffusivity

and increases in axial diffusivity, brain changes related to structural neuroplasticity, have also been reported.[7]

One could consider that the local and transient neuroinflammatory processes may be engaging neurotrophic and neuroplastic effects needed for therapeutic recovery. In an environment where a certain degree of systemic inflammation is exhibited at baseline (such as in depression), electroconvulsive stimulation may mediate adaptive focal neuroinflammatory processes through microglial activity regulation.[8] In depression, microglia appear to be activated with a proinflammatory phenotype.[9] ECT may modulate microglial activity from the proinflammatory M1 state into the neuroprotective M2 state[10] or even to a brain-derived neurotrophic factor–mediated trophic microglial phenotype.[9] In addition, it should be noted that structural neuroplasticity encompasses distinct mechanisms, including gliogenesis or angiogenesis, which are also part of the neuroinflammatory response. Could patients with treatment-resistant depression need an acute, transient, and circuit-specific neuroinflammatory reaction to engage structural neuroplastic mechanisms? A likely hypothesis is that ECT may not be associated with either inflammation or neuroplasticity as mutually exclusive mechanisms but instead with a complex cascade of biological processes that starts with a focal and adaptive neuroinflammatory response, leading to structural plasticity and eventually to a reconfiguration of physiological dynamics.

Why is this important? Irrespective of whether the mechanism of action of ECT is due to structural neuroplasticity, neuroinflammation, or both, ECT is one of the most effective treatments in psychiatry. We certainly know that there is not a single therapeutic path out of depression or other neuropsychiatric disorders. Understanding the mechanisms of action of our most effective treatment (ie, ECT) is a critical strategy to inform future treatment development, eg, developing tools that engage the response biomarkers characteristic of the remarkable efficacy of ECT (targets) and avoid its cognitive adverse effects (antitargets). In an era where international collaborative research (such as the Global ECT-MRI Research Collaboration) is emerging as a strategy to effectively address complex questions with aggregated power, aiming to provide confirmatory answers to generate better pathophysiological models and support translational developments, we hope future mechanistic ECT research will disambiguate, and possibly reconcile, the structural neuroplastic and neuroinflammatory theories of ECT action.

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Published Online: April 19, 2023. doi:10.1001/jamapsychiatry.2023.0728

Conflict of Interest Disclosures: Dr Cano is supported by a Sara Borrell postdoctoral contract (CD20/00189) from Instituto de Salud Carlos III. Dr Camprodon has received grants from the National Institute of Mental Health (R01 MH112737-01); is a member of the scientific advisory board of Hyka and Flow Neuroscience; was a member of the scientific advisory board of Feelmore Labs; and is a consultant for Mifu Technologies. No other disclosures were reported.

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