Brain Stimulation With ECT: Neuroscience Insights From an Old Treatment

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A patient of mine recently said to me that ECT saved his life (for which he is very grateful), but he speculated that 50 years from now, we will likely look back on ECT as a very crude procedure. I think he is probably correct on both counts.

Supporting the use of ECT often feels like swimming upstream, but if we are honest about what reliable treatments are available today for our most seriously ill patients, ECT must top the list. If ECT were newly introduced to the medical and scientific community in 2015, without the unfortunate baggage it has accumulated in the past 80 years, it would be hailed as a breakthrough—far superior in effectiveness to any of our psychotropic drugs. But the world likes innovation and new things, and an 80-year-old treatment, no matter how good, just seems out of place in the neuroscience knowledge explosion of today. Perhaps that would change if the mechanism of action of ECT were finally explained by applying the sophisticated tools of neuroscience to this oldest of brain stimulation techniques.

In a recent commentary in The American Journal of Psychiatry about the aims of the government’s BRAIN Initiative for psychiatry, Bargmann and Lieberman ask, “Can states of disturbed mental activity be stabilized with cognitive therapy, medications, or neuromodulatory or electroceutical interventions such as transcranial magnetic stimulation and deep brain stimulation?” Strikingly absent from the list of intervention targets is the one that induces the most profound effects on brain physiology—ECT. Does it not make sense to investigate the most effective treatment that induces the most pervasive brain changes as a way to understand both psychiatric illness and brain function? A wealth of knowledge supporting various hypotheses of the mechanism of action of ECT has already accumulated. Both human and animal research have documented ECT (or ECS, “electroconvulsive shock,” the animal model of ECT)-induced changes at the molecular, synaptic, and neuronal network levels, but a compelling, comprehensive explanation of how these effects result in resolution of depression or psychosis is still elusive. Some recent breakthroughs, using newly developed neuroscience investigational tools, suggest that if the research resources are available, we could soon make substantial advances in understanding the mechanism of action of ECT. Here I discuss some examples of exciting new findings.

Neuroimaging in ECT

Neuroimaging in its newest, most sophisticated iterations has only recently been applied to ECT. The amazing structural detail that can now be seen with high magnet-strength MRI has resulted in a re-thinking of the old dictum that ECT does not cause structural brain changes. The cry of “brain damage” from the anti-ECT contingent over the years was the reason that earlier MRI studies were needed to show that gross structural changes do not occur with ECT. But now we recognize that subtle brain alterations may be helpful (as in beneficial neuroplasticity) or possibly related to adverse effects.

Dukart and colleagues presented preliminary findings in 19 patients with unipolar disorder and 15 patients with bipolar disorder who underwent MRI before and after ECT. They demonstrated increased gray matter volume in the subgenual cortex and the hippocampal complex, and decreased gray matter volume in the prefrontal cortex. Tendolkar and colleagues reported increased hippocampal and amygdala volumes after ECT in 15 patients with treatment-resistant depression. Likewise, Nordanskog and colleagues showed that in 12 patients with depression, hippocampal volumes increased after ECT, but they reverted to normal within 6 months. These preliminary morphometric MRI findings are very exciting and lead to more questions than
answers; however, with additional adequately controlled and powered studies, the answers should be forthcoming. It should be possible to distinguish treatment effect (of the stimulus or the seizure) from the effect of a change in clinical state (brain change resulting from resolution of the depression). It should also be possible to disentangle which brain effects are associated with clinical benefit and those that may be responsible for adverse cognitive effects, and thereby further refine ECT technique.

Functional MRI (fMRI) has also recently been applied to ECT patient groups. Perrin and colleagues reported a decrease in functional connectivity of the left dorsolateral prefrontal cortex in 9 patients after successful ECT. Abbott and colleagues showed increased right hippocampal connectivity (as well as volume) in 19 depressed patients after they received predominantly right unilateral ECT. The study of regional brain connectivity is in its infancy, and these findings related to ECT are truly very preliminary—but provocative—and are likely to lead to important findings, when pursued. Task-based fMRI studies constitute another avenue of exploration that is eagerly awaited.

**Electroconvulsive shock (ECT)**

ECT has long been used as a model to explore the potent effects of seizures on the brain in relation to both psychiatric and neurological illnesses. Nordgren and colleagues demonstrated down-regulation of messenger RNA (mRNA) levels for key molecules needed to stabilize synaptic structures, but up-regulation of mRNA levels for neurotrophic factors, including brain-derived neurotrophic factor. They concluded that their data “provide correlations between ECS treatment and molecular events compatible with the hypothesis that both effects and side effects of ECT may be caused by structural synaptic rearrangements.” Dyrvig and colleagues studied gene expression of immediate early genes, synaptic proteins, and neuropeptides at 6 time points after acute ECS and found a complex pattern of increases and decreases with varying time courses, each characteristic for the specific gene. Most recently, O’Donovan and colleagues investigated the role of ECT in altering the hippocampal proteome and found that chronic ECS induced changes in abundance of hippocampal proteins with cytoskeletal and metabolic roles.

**ECT and memory research**

Another fascinating area of exploration is the use of ECT as a model to better understand the workings of human memory: that is, taking scientific advantage of a transient adverse effect of the treatment. In a recent study, depressed patients who were receiving ECT participated in an add-on study in which they were shown 2 slide show stories, one of which was reactivated a week later, just before ECT. A single ECT was shown to disrupt reactivated, but not non-reactivated, memories. Similar work had previously been done in rodents, using ECS. This line of investigation, also in its infancy, has the potential to inform us about the mechanism of human memory formation and retrieval, and thereby help devise more cognitively benign forms of brain stimulation.

**The future of ECT**

The above examples of exciting neuroscience breakthroughs using ECT and ECS as platforms of investigation could point the way to a bright research future, one in which the oldest and most potent form of noninvasive brain stimulation could help to unlock some of the mysteries of the etiology of psychiatric conditions and teach us much about how the brain works in mental illness versus mental health. ECT remains a vital treatment for our most severely ill patients and should be included as a platform for study in the BRAIN Initiative.
Right unilateral electrode placement in ECT.

Disclosures:
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References:


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