Biological Psychiatry: Celebrating 50 Years

Better, Faster, Safer: Exploring Biomarkers of Response to Transform Electroconvulsive Therapy

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Electroconvulsive therapy (ECT) remains our most effective and rapidly acting treatment for severe depression and suicidal ideation. Studying the mechanisms by which ECT exerts its antidepressant action as well as its adverse cognitive side effects could greatly advance our ability to develop precisely targeted treatments that are even more effective, faster-acting, and safer versions of this often life-saving therapy. Although decades of research have demonstrated various changes in brain function induced by ECT (1), it is still an open question as to which changes are essential for antidepressant response, which changes are responsible for its adverse side effects, and which changes are nonspecific.

Developing robust biomarkers and a mechanistic understanding is key to advancing precision medicine–informed treatment options (2). Understanding the mechanisms of ECT response could advance patient care by selecting the individuals who are most likely to respond to conventional ECT and by developing novel therapies that target treatment-responsive circuitry more selectively and safely. However, understanding the actions of ECT is complex; e.g., the neuroplastic actions of ECT might be therapeutic or countertherapeutic depending on where they occur, what type of neuroplasticity is induced (structural vs. functional), and the impact they have on circuit function.

To address these questions, Leaver *et al.* (3) conducted the first study to use arterial spin–labeled perfusion functional magnetic resonance imaging measures of absolute cerebral blood flow (CBF) and gray matter volume during a clinical course of ECT in 57 psychotropic medication–free adults with depression. Measures of CBF and gray matter volume were collected before ECT, after two treatments, after an index course, and after 6 months. Leaver *et al.* (3) demonstrate that although ECT produces generalized seizures, regionally specific changes correlate with treatment outcome.

Responders and nonresponders demonstrated different baseline and treatment duration–dependent global CBF differences. The finding that lower baseline global CBF predicted response to ECT could be useful in selecting patients who are most likely to benefit. However, careful studies comparing ECT-relevant predictive biomarkers with other treatment modalities are necessary to disentangle prognostic versus predictive biomarkers in order to inform patient selection algorithms (4). Global CBF differences could also, as Leaver *et al.* (3) suggest, be a target for converting nonresponders into responders by using other means to lower CBF before ECT, such as via pharmacological or another neuromodulation intervention.

Beyond these global changes, increases in CBF and gray matter volume in the right hippocampus were noted for all patients, with increases being more pronounced for nonresponders. This finding is consistent with those reported by Oltedal *et al.* (5) that greater hippocampal volume increase was associated with worse antidepressant response. Oltedal *et al.* (5) posit that this may be because nonresponders received more treatments than responders, and that this structural change relates more to the cumulative effects of the treatment itself than to specific antidepressant mechanisms. Oltedal *et al.* (5) did not specifically comment on the possible impact of the number of cumulative treatments. In Leaver *et al.* (3), nonresponders received more treatments than responders (12.6 vs. 10.3, $p < .05$). Could a difference of two treatments really make a difference? The Leaver *et al.* (3) data demonstrate significant changes in CBF after only two treatments, so it is plausible that functional changes may be dependent on small differences in treatment number.

The study also demonstrated several regions of change specific to responders that provide insights into potential treatment target/response biomarkers. Increases in thalamic and somatomotor cortex CBF were demonstrated throughout the treatment period, while decreases in inferior frontal cortex, lateral parietal cortex, and precuneus CBF were noted earlier in the index treatment. The relative contribution of the regions in this network could be evaluated systematically by using focal neuromodulation to determine which regions are essential to antidepressant response and which regions may be nonspecific. Regions that are found to be causal would then become novel treatment targets for the next generation of focal therapies. These new interventions would be able to test the causal involvement of relevant target areas and maximize on-target effects while minimizing the off-target effects associated with amnesia. These response-related targets could be individually targeted with more focal forms of seizure therapy using magnetic seizure induction or lower amplitude electrical stimulation (6,7). We agree with the conclusion of Leaver *et al.* (3) that "the field needs testable, mechanistic models" that move beyond characterization and that allow us to develop novel therapies. This study is a step in that direction.

There are some limitations in this study that could be addressed in future research. Specifically, the naturalistic nature of the study led to variation in electrode placement. Twenty patients transitioned from right unilateral to bilateral electrode placement during the study, leading to different delivered doses to different brain regions. In addition, maintenance treatments were not controlled for, which could impact the 6-month follow-up scan results. As noted in the supplement accompanying Leaver *et al.* (3), heterogeneity of electrode placement and other parameters may hinder smaller, naturalistic studies. Larger

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studies are necessary to combine heterogenous data sets to understand how these variations in dosage impact the results. These limitations highlight the opportunities provided by data sharing and combining smaller data sets together to provide a more complete picture. International consortia, such as GEMRIC [Global ECT-MRI Research Collaboration (8)]—of which this group is a part—are necessary to produce larger sample sizes that can provide insights across heterogenous populations. Standardizing stimulus dosage and treatment protocol is an essential step to ensure reproducibility, given this variation in treatment technique.

In addition to larger sample sizes, future studies should include additional imaging and cognitive measures. Comparison with other forms of treatment will also be necessary to understand the specificity of these results to ECT. The use of arterial spin–labeled perfusion functional magnetic resonance imaging in this context is unique and should be further studied with complementary imaging modalities. For example, changes in functional connectivity have also been reported linking hippocampal plasticity with antidepressant response (1), so future studies could include multiple modalities to gain a more comprehensive mechanistic understanding of how these measures relate to one another. These studies could provide additional insight into the global versus specific involvement of areas, such as the thalamus and the sensorimotor cortex highlighted by Leaver *et al.* (3). Surrogate imaging biomarkers, built on a solid base of response biomarkers linked to clinical outcomes, could also be used to guide treatment duration and maintenance. In addition, measures of the delivered electric field in regions of interest where structural and functional plasticity are also measured could help illuminate the role of individual differences in delivered electric field and outcomes. The same may be said for simultaneous measures of the topography of the induced seizures, since ECT is the combination of delivered electric field and subsequent seizure induction.

A major consideration for future studies is to include measures of cognition to explore neural changes underlying any deficits. Although improved electrode placement and reduced pulse width have reduced cognitive side effects, concerns regarding amnesia drives, in part, the underutilization of ECT. Indeed, the US Food and Drug Administration, which recently down-classified ECT to class II for major depression in persons ≥13 years of age, has included monitoring of cognitive status as part of their special controls (9). van Oostrom *et al.* (J ECT 34:117–123) reported in a small sample that hippocampal volume increases were associated with worse cognitive function after ECT. While the relationship of ECT-induced changes in CBF and cognitive function were not reported by Leaver *et al.* (3), it is worth examining whether structural and functional plasticity in hippocampus post-ECT is mechanistically related to the adverse cognitive side effects of the treatment or correlated with, but not causally linked to, worse antidepressant response. Nonresponders receive more ECT treatments, exposing the hippocampus to more cumulative exposure both to the delivered electric field and to the resulting seizure, which has been hypothesized to be related to cognitive impairment post-ECT owing to saturation of long-term potentiation and increased long-term depression (10). Indeed, Chen *et al.* (10) point out that hippocampal changes may be linked to memory issues. By linking behavioral data with imaging data, researchers can use biomarkers of adverse events to develop safer forms of seizure therapy. Individualized and precise approaches to convulsive therapy, beyond maximizing on-target effects, could be used to minimize cognitive adverse events owing to off-target stimulation (7).

Taken together, research in this field is poised to enter a precision medicine phase, focused on delivering highly efficacious treatments tailored to the areas of interest of a specific patient's brain (2).

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