Mechanisms of Antidepressant Response to Electroconvulsive Therapy Studied With Perfusion Magnetic Resonance Imaging

Supplement

Supplemental Methods

ECT

In this naturalistic MRI study, patient volunteers underwent a clinically prescribed course of ECT (5000Q MECTA Corp) at the UCLA Resnick Neuropsychiatric Hospital. Treatment was administered by ECT attending physicians using standard protocols in an inpatient or outpatient setting. In brief, patients began with right-unilateral lead placement (ultra brief pulse; 5-6x seizure threshold) (1), but transitioned to bitemporal lead placement (2x seizure threshold) if indicated clinically (**Table 1**). ECT was administered three times weekly for an average of 10.9 total treatments (SD=3.8) using short-acting anesthesia and a muscle relaxant.

Image Acquisition

Using a 3T Siemens Allegra scanner, continuous ASL images were acquired: 60 volumes (30 label, 30 control), 4x4x7.5 mm^3 resolution, 18 axial slices, repetition time 4000 ms, echo time 16 ms, label time 2100 ms, post label delay 1000 ms, and 95% duty cycle. During ASL sequences, subjects were resting with eyes closed. A T1-weighted anatomical scan (MPRAGE) was also collected at each session (2–4).

Statistical Analyses

All statistical analyses were completed in R (https://www.r-project.org). Linear mixed-effects models were implemented using the lme4 package (5). The oro.nifti package was used for voxelwise analyses (6).

Estimating p-values for the contribution of individual model factors (e.g., time in our model) in linear mixed-effects models (LMMs) is a matter of debate amongst statisticians (5, 7, 8). In our study, we followed the recommendations of the lme4 R package developers (5) and used likelihood ratio tests to compare two nested LMMs, where the factor of interest (i.e., time) is removed from the “null” model. The values resulting from likelihood ratio tests are asymptotically normal; therefore, chi-squared distributions are used to derive p-values for the contribution of the factor of interest (in our case, time) to the model fit (5). Although we report p-values in the main text and Figures, we also include the difference in Akaike Information Criterion (AIC) for target and null models in **Figure S1** for reference.

With regard to model terms, we constructed a single target statistical model a priori for the sake of simplicity. Model optimization (e.g., by testing different algorithms, nuisance factors, etc.) would be problematic for voxelwise analyses, which involve many thousands of univariate tests – and thus the potential for many

different optimal model fits. Future multi-site and/or database studies such as the recently established Global ECT MRI Research Collaboration (GEMRIC) (9) will be better able to address these issues, but their empirical treatment is outside the scope of the current manuscript.

We chose nuisance model terms likely to have the strongest effects on CBF and neurobiology of antidepressant response to ECT. Age was chosen because it is strongly associated with CBF (10, 11). ECT lead placement and number of treatments both affect ECT "dose" including the amount and distribution of applied current and associated seizure activity, and thus could also affect the lasting neurobiological consequences of ECT. Additionally, both lead placement and number of treatments were associated with clinical decisions made during the course of treatment in relation to symptom change in our sample (Supplemental Table), and thus should be controlled when examining the neurobiology of clinical response. Biological sex is clearly relevant to depression, but its links to CBF, as well as ECT- and depression-related neurobiology, are unclear and understudied; therefore, biological sex was not included in our analyses. Future studies with larger sample sizes will be better able to address the role of sex and other relevant factors.

Parsing the contribution of tissue content (i.e., partial volume effects) to CBF quantified with ASL-fMRI is not necessarily straightforward. CBF quantification itself makes assumptions regarding tissue content because perfusion profiles differ for gray and white matter, and tissue content can vary from voxel to voxel even within a gray-matter mask (as used in the current study). To address this issue, we used standard CBF quantification methods assuming a single tissue distribution (12), and addressed the potential contribution of GMV in post-hoc statistical analyses.

In recent years, neuroimaging researchers have begun to re-examine approaches to statistical analyses, specifically with regard to voxelwise tests. One concern is balancing the potential for both Type I and Type II error given the large number of tests performed and the sometimes subtle effects studied. Both the criticism of standard methods and the development of new methods requires extensive tests of various MRI modalities, preprocessing parameters, and statistical models (13–15). The thresholds we have chosen for our study are within standard limits (16, 17), though alternatives should be considered in the future. Relatedly, there has been discussion in the field regarding the utility of p-values vs. other statistical metrics addressing significance of model parameters. Thus, for completeness, we also include statistical maps of the difference in Akaike information criterion (AIC) values for the target and null models (i.e., with and without time as a model term, respectively) in the **Figure S1**. Note that all AIC difference values in regions identified as statistically significant (i.e., p(corr) < 0.05 in Figures 2 and 3) are greater than 2 (18).

Supplemental Discussion

There are several additional potential limitations that warrant discussion, though their thorough empirical treatment is outside the scope of the current study. Study limitations are also discussed in the final section of (and throughout) the main text, as well as the Supplemental Methods above. Additional issues are addressed below.

ECT lead placement was not balanced in this naturalistic study – all patients received right-unilateral (RUL) treatment and the majority received only RUL ECT. Perhaps correspondingly, our hippocampal findings were right-lateralized, though effects were bilateral when more permissive thresholds were considered (e.g., when dropping cluster-correction). Notably, depressed patients exhibit reduced hippocampal volume bilaterally (19), which could explain the relative increased efficacy of bilateral vs. RUL ECT. Indeed, a recent large-scale analysis of multi-site ECT data indicated that ECT lead placement (bilateral versus RUL) affected the extent of volume change in the left, but not the right hippocampus (20). Multi-site studies like these will be better powered to address whether the laterality of functional neuroplasticity in the hippocampus related to ECT lead placement, pathophysiology underlying depression, or a combination of both.

All depressed volunteers were tapered off antidepressant medications prior to our study and beginning ECT. However, long-term use of various antidepressant medications and therapies is a potential confounder in all studies of treatment-resistant patients, including the current study. Variable treatment histories may introduce additional variability that prevented us from identifying smaller effects of ECT and antidepressant response to ECT. Maintenance treatment was not controlled in the 6-month period after ECT, which also likely increased variability at this fourth timepoint. This issue may prevent our study and others from assessing the “pure” effects of ECT and antidepressant response to ECT. However, given that ECT is typically used in treatment-refractory patients, one may also argue that it is best studied in these most severe cases. A future study including treatment-refractory patients undergoing “treatment as usual” may be an interesting way of examining the effects of long-term medication use on the longitudinal studies like this one.

There are several brain regions that have been previously linked to depression and ECT that were not identified in the current study. One of these is the cerebellum, which was omitted from analysis due to restrictions of the ASL-fMRI field of view. Another is the amygdala, which has been repeatedly implicated in depression and ECT (21–23). Our results do not necessarily imply that these structures are not relevant to depression or ECT; rather, technical limitations like limited spatial resolution and/or the modality chosen are more likely explanations. For example, neuro-functional changes in the amygdala after ECT may be

stimulus-evoked (23) and may not effect “resting” baseline function. Future studies using faster imaging sequences and/or cross-modal analyses will give a more comprehensive view of ECT.

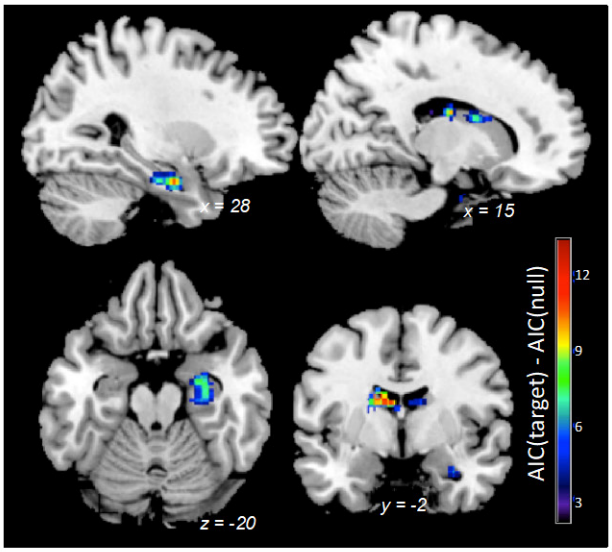
Much of our Discussion in the main text emphasizes the role of seizure physiology, specifically hypothesizing that the regional distribution of the long-term effects of ECT-related seizure activity differs according to antidepressant response. However, other relevant neurobiological processes warrant discussion. The current study primarily addresses neurofunctional change measured via CBF, yet these are very likely to occur alongside molecular, microstructural, and anatomical changes not measured by this study. Inflammation is a good example. Inflammation is thought to play a role in depression (24–26), and is also modulated by ECT (27). Inflammatory processes are also associated with increased blood flow, though the relationship between systemic or neural inflammation and CBF measured with ASL is unclear. Certainly, inflammation is associated with neurotrophic factors (27) that could play a role in ECT-related neuroplasticity. Multimodal analyses synthesizing ECT’s effects on serum inflammatory markers, MRI data, and other factors would be informative.

Table S1. Demographic and clinical information for Responders and Nonresponders

	Responders	Nonresponders
Sample Size	n = 17	n = 26
Age, mean (SD)	43.53 (13.17)	39.50 (13.97)
Sex, females/males	7/10	16/10
Clinical Information		
Diagnosis, unipolar/bipolar	13/4	21/5
Age at 1st diagnosed depressive episode, mean (SD)	27.24 (12.31)	23.12 (12.14)
ECT lead placement, only-RUL/other	15/2	11/15[a]
Number of ECT Index Treatments	10.35 (2.62)	12.62 (3.57)[a]
Baseline Study Visit		
HAM-17, mean (SD)	27.06 (5.60)	22.27 (4.98)[a]
MADRS, mean (SD)	43.71 (7.40)	33.69 (5.73)[a]
QIDS-SR, mean (SD)	21.71 (3.51)	18.73 (3.99)[a]
Corrected Sample Size (after attrition and MRI QC)	17	26
Post-2tx Study Visit		
HAM-17, mean (SD)	19.88 (6.20)[b,c]	16.5 (7.55)[a,b,c]
MADRS, mean (SD)	32.76 (7.78)[b,c]	25.20 (11.83)[b,c]
QIDS-SR, mean (SD)	16.35 (4.65)[b,c]	14.60 (6.67)[b,c]
Corrected Sample Size (after attrition and MRI QC)	17	23
Post-Index Study Visit		
HAM-17, mean (SD)	7.12 (3.53)[b,c]	17.50 (6.23)[a,b,c]
MADRS, mean (SD)	8.59 (5.30)[b,c]	26.35 (8.04)[a,b]
QIDS-SR, mean (SD)	6.76 (4.02)[b,c]	14.23 (4.81)[a,b,c]
Corrected Sample Size (after attrition and MRI QC)	17	26
Post-6mo Study Visit		
HAM-17, mean (SD)	12.80 (8.23)[b,c]	10.71 (6.91)[b,c]
MADRS, mean (SD)	18.20 (13.41)[b,c]	16.00 (11.70)[b,c]
QIDS-SR, mean (SD)	11.13 (5.57)[b,c]	9.65 (6.11)[b,c]
Corrected Sample Size (after attrition and MRI QC)	13	14

Results of chi-squared and t-tests are indicated as follows: a Significant difference between Responders and Nonresponders, $p < 0.05$, b significant difference between baseline and follow-up (within group), $p < 0.005$, c Significant difference from previous visit (within group), $p < 0.02$. All other comparisons were not significant.

A. Acute CBF Change After 2 ECT Tx, AIC(target) – AIC(null)



B. CBF Change After ECT Index, AIC(target) – AIC(null)

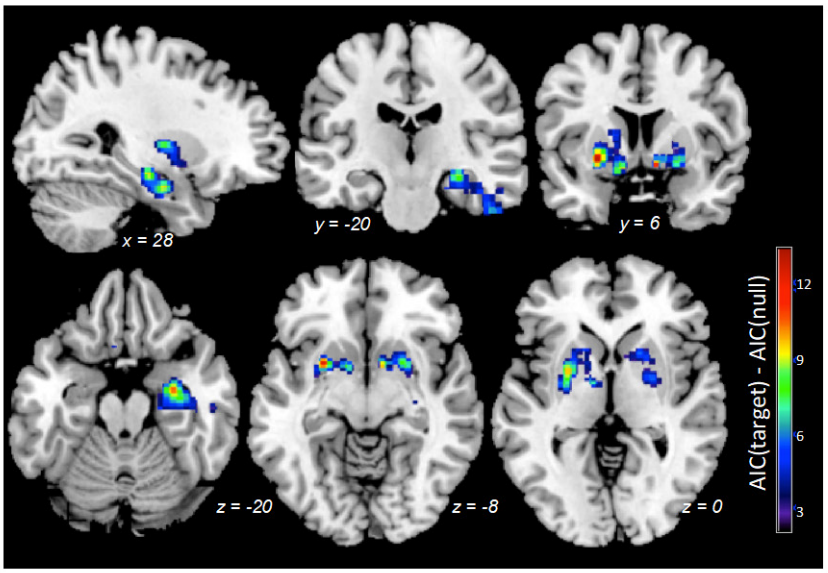


Figure S1. Difference in Akaike Information Criterion (AIC) values are displayed for voxelwise analyses of CBF change (A) between baseline and after 2 ECT sessions and (B) baseline and after ECT index. Maps are thresholded using the same criteria as described in the main text (p(corr) < 0.05), but here each voxel's color indicates the corresponding AIC difference value (key at bottom right in each panel). Difference in AIC between target at null models were above 2 in all voxels shown, with ranges 2.72-13.45 for acute change (panel A) and 2.88-13.71 for post-index change (panel B).

Supplemental References

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