Biological Psychiatry: Celebrating 50 Years

Archival Report

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

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ABSTRACT

BACKGROUND: Converging evidence suggests that electroconvulsive therapy (ECT) induces neuroplasticity in patients with severe depression, though how this relates to antidepressant response is less clear. Arterial spin-labeled functional magnetic resonance imaging tracks absolute changes in cerebral blood flow (CBF) linked with brain function and offers a potentially powerful tool when observing neurofunctional plasticity with functional magnetic resonance imaging.

METHODS: Using arterial spin-labeled functional magnetic resonance imaging, we measured global and regional CBF associated with clinically prescribed ECT and therapeutic response in patients (n = 57, 30 female) before ECT, after two treatments, after completing an ECT treatment "index" (~4 weeks), and after long-term follow-up (6 months). Age- and sex-matched control subjects were also scanned twice (n = 36, 19 female), ~4 weeks apart.

RESULTS: Patients with lower baseline global CBF were more likely to respond to ECT. Regional CBF increased in the right anterior hippocampus in all patients irrespective of clinical outcome, both after 2 treatments and after ECT index. However, hippocampal CBF increases postindex were more pronounced in nonresponders. ECT responders exhibited CBF increases in the dorsomedial thalamus and motor cortex near the vertex ECT electrode, as well as decreased CBF within lateral frontoparietal regions.

CONCLUSIONS: ECT induces functional neuroplasticity in the hippocampus, which could represent functional precursors of ECT-induced increases in hippocampal volume reported previously. However, excessive functional neuroplasticity within the hippocampus may not be conducive to positive clinical outcome. Instead, our results suggest that although hippocampal plasticity may contribute to antidepressant response in ECT, balanced plasticity in regions relevant to seizure physiology including thalamocortical networks may also play a critical role.

Keywords: Cerebral blood flow, Depression, Electroconvulsive therapy, fMRI, Hippocampus, Seizure

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Electroconvulsive therapy (ECT) is an effective intervention for severe major depression, with response rates (50%–80%) and response times (≤1 month) superior to other currently available treatments (1–3). With ECT, a controlled transient seizure is elicited every 2 to 3 days over 2 to 4 weeks with anesthesia and muscle relaxants and is sometimes followed by maintenance treatments after the ECT index phase (4). Although generalized seizures are elicited, a growing body of evidence suggests that ECT induces structural and functional neuroplasticity in specific brain structures and networks, though how these changes relate to therapeutic response remains less clear (5–11).

An increasing number of neuroimaging studies have addressed the neural effects of ECT, implicating several regions throughout the brain. ECT-related hippocampal volume enlargements are most replicated (10,11), complementing reports of decreased hippocampal volume in depression (12) and functional plasticity in hippocampal networks with ECT (13,14). Electroconvulsive shock, the animal model of ECT, is shown to promote neurotrophic effects including hippocampal neurogenesis (15,16), which may explain neuroplastic effects in humans. However, links between hippocampal plasticity and symptom improvement in ECT are less replicated and a subject of debate (17,18). Furthermore, ECT-related changes in several other brain regions have been identified, including the anterior cingulate cortex (7–9,19), thalamus (5,20–22), basal ganglia (14,23), and amygdala (11,24). A complete mechanistic understanding of ECT and its success as an antidepressant treatment thus remains elusive.

A critical issue in ECT research is parsing the nonspecific effects of ECT from those effects related to (and perhaps responsible for) antidepressant response to ECT. Although considered the gold standard treatment for intractable major depression, not all patients respond to ECT; for example, just over half (55%–65%) experience remission when using right-unilateral ECT with optimal parameters (25,26). Therefore,

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brain networks affected by ECT-induced seizures in all patients may differ from, or only partially overlap, networks supporting improved depressive symptoms. Previously reported ECT-related effects may thus not underlie clinical outcome, but instead reflect nonspecific physiological effects of ECT.

In the current study, we use arterial spin–labeled (ASL) perfusion functional magnetic resonance imaging (fMRI) to track absolute changes in cerebral blood flow (CBF) at rest (i.e., "functional neuroplasticity") associated with the lasting effects of ECT itself, as well as antidepressant response to ECT. Application of ASL-fMRI offers a novel, complementary contribution to existing functional neuroimaging literature with certain advantages. Most importantly, ASL-fMRI offers an absolute measure of brain function like positron emission tomography and single-photon emission computed tomography, but without the use of radioactive tracers and with greater spatial resolution. Because ASL-fMRI offers an absolute metric of blood flow (i.e., mL/min/100 g), it provides an important advantage over more widely used blood oxygen level–dependent (BOLD) fMRI, where relative metrics (i.e., arbitrary units) indirectly estimate brain function by determining 1) changes in BOLD signal between active and rest or baseline conditions or 2) correlations in BOLD time courses among brain regions to infer "functional connectivity." Thus, ASL-fMRI is particularly well-suited for multisession longitudinal studies, where CBF changes can be more directly interpreted as changes in brain function over time. To our knowledge, no previous ECT studies have measured CBF changes with ASL-fMRI, and thus ours constitutes a novel contribution to the field.

Here, we measured global and regional CBF with ASL-fMRI in patients with depression followed prospectively while receiving ECT, as well as control volunteers without depression who were not receiving treatment. We report CBF changes associated with ECT and therapeutic response occurring after the initial two ECT sessions and after the ECT "index" treatment series. We hypothesized that while some CBF changes would occur in all patients regardless of ECT outcome, separable brain regions would associate with positive antidepressant response. We also explored the extent to which acute and postindex functional neuroplasticity is maintained 6 months after treatment. Finally, because CBF measured with ASL-fMRI can be related to tissue content (27), we explored relationships, if any, between CBF and gray matter (GM) plasticity.

METHODS AND MATERIALS

Subjects

Patients (n = 57) and demographically similar volunteers without depression (n = 36) gave informed written consent to participate in this study, which was approved by the Institutional Review Board at the University of California, Los Angeles. All patients were diagnosed as experiencing a major depressive episode [DSM-IV-TR (28)] and were treatment refractory (i.e., did not respond to ≥2 prior antidepressant therapies). Patients with comorbid psychiatric or neurological disorders or concurrent serious illness were excluded. All patients ceased psychotropic medications (antidepressants and benzodiazepines) at least 48 to 72 hours prior to and for the duration of the index treatment and had not received neuromodulation treatment within 6 months prior. For healthy volunteers, exclusion criteria included any history of serious illness, neurological disorders, or psychiatric disorders [Mini-International Neuropsychiatric Interview (29)].

Depressive symptoms were assessed in patients using the Hamilton Depression Inventory (17 items) (30), Montgomery–Åsberg Depression Rating Scale (31), and Quick Inventory of Depressive Symptomatology (32). Scores on these inventories were highly intercorrelated; therefore, clinical response was characterized using a composite score calculated as the mean proportional change between baseline and post-ECT index scores (averaged across the three scales). ECT responders were identified as having ≥50% reduction in composite depression scores after ECT index (33). Prior publications including participants overlapping with the current cohort reported ECT-related structural (7,11,23,34), functional (14,35,36), and neurochemical (37,38) changes, and evaluation of cognitive measures (39).

Study Visits and ECT

Patients volunteered for this research study before initiating a clinically prescribed course of right-unilateral ECT (Supplemental Methods); 20 were transitioned to bilateral electrode placement per clinical determination (Table 1). Patients completed four MRI scans: 1) within 24 hours before first ECT session (baseline), 2) immediately before their third ECT appointment (~4 days after baseline), 3) after their clinically determined ECT index series (~4 weeks after baseline), and 4) approximately 6 months after ECT index. Volunteers without depression completed two MRIs approximately 4 weeks apart.

Image Acquisition and Preprocessing

ASL functional and T1-weighted anatomical images were acquired using a 3T Siemens Allegra scanner (Siemens, Erlangen, Germany) (Supplemental Methods). ASL images were first corrected for motion (FSL, Functional MRI of the Brain Software Library), and then CBF was quantified using the simple subtraction method in ASLtoolbox (27). CBF images were registered to T1-weighted anatomical scans and Montreal Neurological Institute templates including interpolation to $2 \times 2 \times 2$ mm^3 resolution using SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK) and smoothed (6-mm full width at half maximum Gaussian kernel, FSL). Images were then averaged to yield a single CBF image per session for subsequent analysis. Voxelwise GM volume (GMV) was calculated in SPM8 during standard Montreal Neurological Institute normalization processes. On visual inspection, 7 baseline (3 patients, 4 control subjects) and 13 follow-up (10 patients, 3 control subjects) ASL scans were identified to have poor quality (i.e., susceptibility artifacts, slice artifacts, and/or global CBF <20 mL/100 g/min) and were not analyzed further (Table 1). After preprocessing and normalization, ASL images were masked using SPM8's GM template (>20% probability GM classification) and to ensure a common field of view (ASL pseudo-BOLD value > 100 (27) for all images). Because the ASL-fMRI field of view did not include the entire cerebellum in all subjects, this mask did not include the cerebellum. Global CBF was calculated by averaging voxelwise CBF within this mask for

Table 1. Demographic and Clinical Information

	Patients With Depression				Control Volunteers	
Sample Size	57				36	
Age, Years, Mean (SD)	41.42 (12.98)				39.06 (12.29)	
Sex, Female/Male	30/27				19/17	
Clinical Information						
Diagnosis, unipolar/bipolar	47/10					
ECT lead placement, only RUL/Other	37/20					
ECT outcome (any scale), responder/nonresponder	25/21					
ECT outcome (composite), responder/nonresponder	19/27					
Age at first diagnosed depressive episode, mean (SD)	25.30 (11.46)					
	Baseline	Post-2 Tx	Postindex/4 Wk	Post-6 Mo	Baseline	Post-4 Wk
Study Visits						
HAM-17, mean (SD)	23.88 (5.94)	18.08 (6.93)[a]	13.26 (7.46)[a,b]	11.52 (8.22)[a]		
MADRS, mean (SD)	37.64 (8.49)	29.0 (10.97)[a]	19.05 (11.26)[a,b]	16.81 (12.76)[a]		
QIDS-SR, mean (SD)	19.75 (4.12)	15.84 (5.99)[a]	11.26 (5.77)[a,b]	10.48 (6.30)[a]		
Corrected sample size (after attrition and MRI QC)	57	51	43	27	32	33

Values are *n* unless otherwise indicated. Baseline depression scores were missing for a single volunteer owing to clerical error, and this volunteer was not included in any calculations or analyses requiring depression scores.

ECT, electroconvulsive therapy; HAM-17, Hamilton Depression Inventory (17 items); MADRS, Montgomery–Åsberg Depression Rating Scale; MRI, magnetic resonance imaging; QC, quality control; QIDS-SR, Quick Inventory of Depressive Symptomatology, self-report; RUL, right unilateral; Tx, treatments.

[a]Results of paired *t* tests for depression scores: significant difference between baseline and follow-up, $p < .0001$.

[b]Results of paired *t* tests for depression scores: significant difference from previous visit, $p < .005$.

each ASL-CBF image. GMV was similarly calculated by averaging voxelwise GMV within the mask for each GMV image.

Statistical Analyses

All statistical analyses were completed in R (https://www.r-project.org). See Supplemental Methods for additional details.

Global CBF was analyzed with linear mixed-effects models, targeting a main effect of time (a fixed categorical factor including all four time points) and ECT response (fixed factor) in patients with depression. Nuisance factors included age, ECT lead placement (percentage right-unilateral), total number of treatments (fixed factors), and subject (random factor). Pairwise comparisons were applied post hoc to assess significant change between time points in patients, as well as between patients and control volunteers (nuisance factors: age, global GMV).

Regional (voxelwise) CBF was analyzed with two omnibus linear mixed-effects models, which specifically targeted changes hypothesized to be most neurobiologically relevant to ECT and therapeutic response. These were 1) changes that occurred acutely (pretreatment vs. after two ECT treatments) and 2) changes that occurred after treatment (pretreatment vs. after ECT index). Here, time was the fixed factor of interest, and nuisance factors included age, change in depression score after ECT index, ECT lead placement, total number of treatments (fixed factors), and subject (random factor). These models examined effects of ECT on brain function irrespective of antidepressant response; thus, change in depression score postindex was a nuisance variable in this analysis. In these voxelwise analyses, a cluster-level correction of $p_{corr} < .05$ was applied using random field theory (40), with voxelwise threshold $p < .01$.

In clusters identified by voxelwise tests, post hoc region of interest (ROI) analyses assessed whether the results of the omnibus tests were influenced by tissue content (Supplemental Methods). These analyses used the same linear mixed-effects models described above but included mean GMV (calculated using SPM8 as described above) for each ROI as an additional fixed nuisance factor. Pairwise post hoc ROI tests compared CBF between relevant time points; each time point was compared with baseline and its immediate precursor using the same linear mixed-effects models, to yield five distinct tests per ROI. The Bonferroni method corrected for the number of tests performed at each ROI. Post hoc ROI tests also compared GMV across time points, also using the same statistical models and Bonferroni correction, but including mean CBF for each ROI as a nuisance factor.

Additional ROI analyses were applied to CBF data in healthy control volunteers, for each region defined by the previously described omnibus analyses. First, linear mixed-effects models measured possible CBF change in each region in healthy control volunteers (baseline vs. after 4 weeks), with age and GMV as fixed nuisance factors and subject as a random nuisance factor. Second, CBF was compared between healthy control volunteers and patients with depression, with age and GMV as fixed nuisance factors.

Finally, exploratory analyses attempted to identify regional (voxelwise) CBF changes associated with antidepressant response. Here, we separated depressed patients into responders and nonresponders to ECT as described in the Subjects section. In these analyses, we examined changes between baseline and postindex CBF, using the same voxelwise and post hoc ROI statistical tests described above.

RESULTS

Demographic and Clinical Variables

Depression scores improved significantly after ECT index ($p < .00001$ for all), with 22 of 42 of patients exhibiting at least

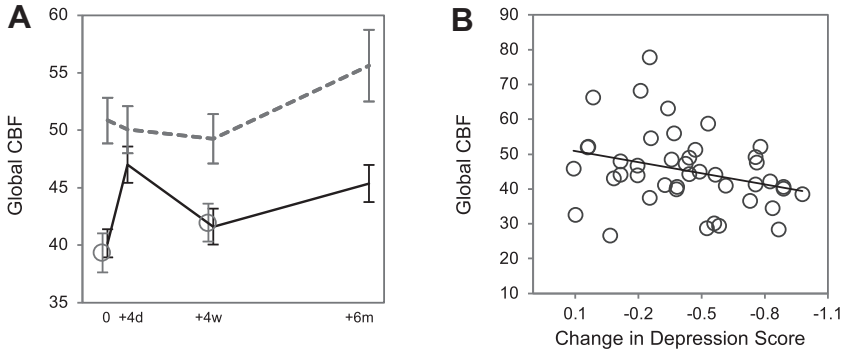

Figure 1. Global cerebral blood flow (CBF) and antidepressant response to electroconvulsive therapy (ECT). **(A).** Mean global CBF is plotted for responders (black solid line) and nonresponders (gray dashed lines) to ECT, measured before treatment (0), after 2 treatments or approximately 4 days later (+4d), after ECT index approximately 4 weeks after baseline (+4w), and 6 months after finishing ECT treatment (+6m). Global CBF is also plotted for healthy control volunteers (open gray circles), measured at baseline and approximately 4 weeks later (healthy control volunteers did not receive ECT). Error bars reflect standard error. **(B)** Baseline global CBF is plotted for each patient against change in depression scores after ECT treatment (where −1 = 100% reduction and/or improvement). Regression line highlights a modest negative correlation between these values, $p = .02$.

a 50% reduction in depression scores and 16 patients meeting criteria for remission on any symptom inventory (Table 1; see also Supplemental Table S1). Patients and healthy control volunteers did not differ in age or sex ($p > .05$ for both).

Global CBF

Global CBF did not change over time in patients or control volunteers, nor was there a significant response-by-time interaction in patients ($p > .05$) (Figure 1). However, there was an overall effect of response, such that CBF was elevated in patients who did not respond to ECT ($p = .02 \times 10^{-14}$).

In pairwise comparisons conducted post hoc separately for responders and nonresponders (Figure 1A), global CBF was elevated in nonresponders at baseline compared with both responders ($p = .004$) and healthy control volunteers ($p = .027$), while baseline global CBF was not different between responders and control volunteers ($p = .541$). Global CBF was also elevated in nonresponders after ECT index (vs. control volunteers, $p = .027$; vs. responders, $p = .06$) and at the 6-month follow-up visit at the trend level (vs. control volunteers, $p = .056$ vs. responders, $p = .177$). However, global CBF did not differ between responders and nonresponders after 2 treatments ($p = .181$), indicating an acute increase in global CBF occurred in responders at this time point ($p = .003$).

In analyses addressing the relationship between baseline global CBF and ECT response, change in depression scores after ECT index correlated with baseline global CBF (i.e., patients with lower baseline CBF were more likely to improve) (Figure 1B).

Regional CBF: Acute Changes After Two ECT Sessions

In all depressed patients, acute CBF increases were noted in the right anterior hippocampus, and CBF decreases were identified in the dorsal caudate after two ECT treatments (Figure 2). This cluster did not appear to overlap the amygdala (Figure 2A, bottom left panel), though previous studies demonstrated ECT effects in this region (11,24,41). These acute effects persisted in post hoc ROI analyses when controlling for GMV. Additional pairwise comparisons between other time points indicated that CBF remained significantly elevated in the right anterior hippocampus after ECT index and 6 months postindex compared with baseline measurements (Figure 2B). Notably, regional GMV in this anterior hippocampal region increased after ECT index as indicated previously for this dataset (11) and others (10,13,24,42); however GMV did not significantly increase acutely (after 2 sessions, see Figure 2C, left panel). Post hoc analyses also indicated that acute CBF decreases in bilateral dorsal caudate returned to baseline levels after ECT index, and this transient CBF decrease was accompanied by a transient increase in GMV. Coordinates for these and all other analyses are displayed in Table 2.

Regional CBF: Changes After ECT Index

After ECT index, CBF increased in the anterior portion of the right hippocampus (Figure 3A), extending slightly more posteriorly than the site of acute change described above. Post hoc ROI analyses indicated that CBF increases occurred both acutely and postindex when controlling for GM content (Figure 3B), with corresponding GM increases occurring after ECT index that were maintained for 6 months after index (Figure 3C).

CBF increases were also observed in bilateral ventral basal ganglia, overlapping the ventral striatum and pallidum (Figure 3A). Here, post hoc tests indicated that postindex CBF increases persisted when controlling for GMV (Figure 3B). GMV did not change significantly in these regions over time (Figure 3C).

Exploring Regional CBF With Respect to Antidepressant Outcome

In exploratory analyses targeting regional CBF separately in patients who responded to ECT, CBF increases were noted in the bilateral thalamus and left somatomotor cortex after ECT index, while decreases were observed in lateral parietal and inferior frontal cortices, as well as the precuneus (Figure 4A). These effects persisted in post hoc analyses controlling for regional GMV. CBF did not change significantly in these regions in ECT nonresponders or control volunteers. Notably, CBF in bilateral thalamus was lower in ECT responders prior to treatment when compared with both nonresponders and control volunteers.

By contrast, ECT nonresponders exhibited CBF increases after ECT index in a large cluster overlapping the right anterior hippocampus and ventral striatum, along with CBF decreases in the posterior cingulate cortex and inferior precuneus (Figure 4B). These effects were robust to tissue-content in post

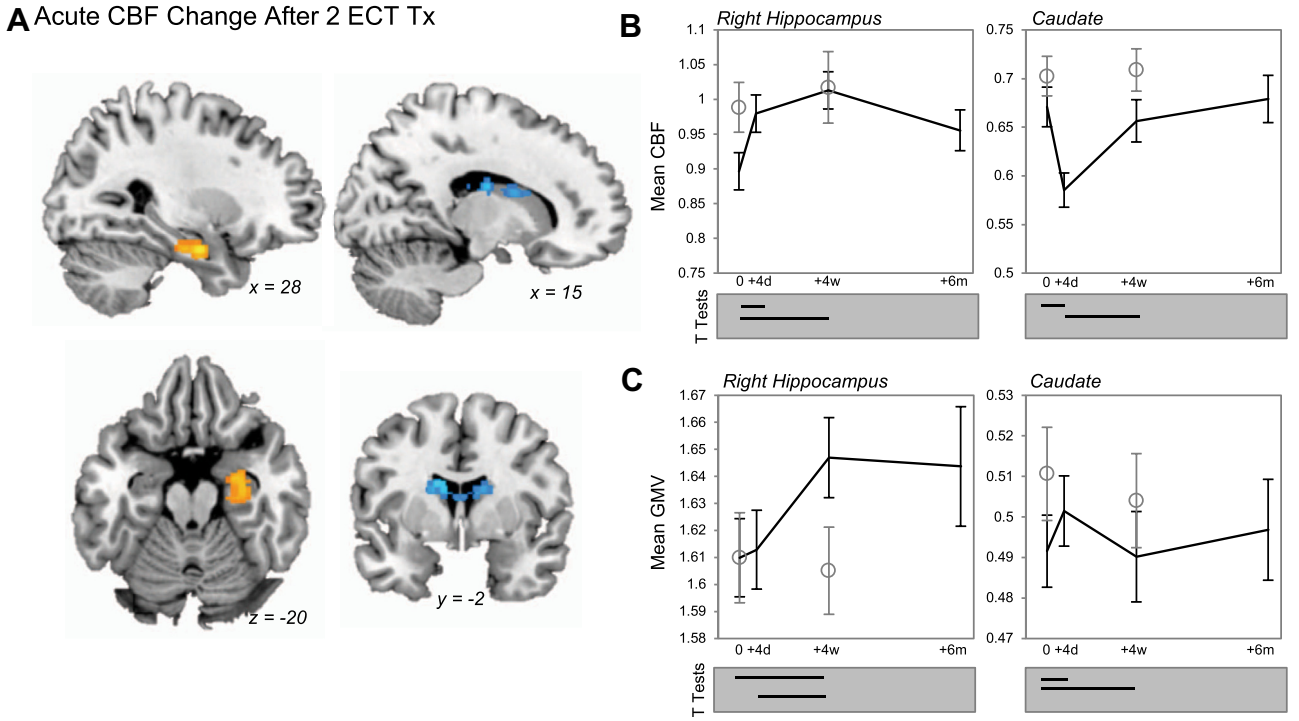

Figure 2. Acute regional cerebral blood flow (CBF) change after two treatments (Tx). **(A)** Basal brain function measured with CBF increased in right anterior hippocampus after two electroconvulsive therapy (ECT) treatments (orange) and decreased in bilateral dorsal basal ganglia (caudate, blue voxels). **(B, C)** Mean regional CBF (corrected for global CBF) and mean regional gray matter volume (GMV, corrected for global gray matter) are plotted for the significant results shown in panel **(A)** at top **(B)** and bottom **(C)** panels, respectively. Data for patients is plotted in black lines; open circles reflect data from healthy control volunteers. The results of post hoc pairwise comparisons among time points of interest in patients are indicated below each graph ($p_{corr} < .05$, Bonferroni correction).

hoc tests and did not change in responders or control volunteers over time.

DISCUSSION

Understanding the mechanisms of antidepressant response is paramount to developing more effective treatments for depression. In our study, we targeted ECT, arguably the most effective fast-acting treatment for severe depression, using ASL-fMRI, a powerful and novel quantitative functional neuroimaging technique. Our data demonstrate that ECT is associated with increased CBF in a subregion of the right anterior hippocampus in all patients regardless of antidepressant outcome. Notably, hippocampal CBF

Table 2. Regional CBF Change With ECT

Model Effect	Anatomical Location	MNI Coordinates (Center of Gravity) x	y	z	Volume (mm^3)	*p*, RFT Corrected
Baseline vs. +2 Tx	Right hippocampus	31.2	−13.1	−24.8	370	.0328
	Caudate	−2.7	−9.3	19.5	797	.000188
Baseline vs. Post-ECT (+4 Wk)	Right hippocampus	34.3	−15.1	−21.1	550	.00785
	Left putamen and accumbens	−19.3	3.3	−2.9	622	.00363
	Right putamen and accumbens	21.1	2.8	−2.9	477	.0177
Responders Only, Baseline vs. Post-ECT (+4 Wk)	Left thalamus	−10.9	−14.5	−3.0	1133	2.50×10^{-6}
	Left somatomotor cortex	−22.7	−10.2	60.4	879	3.68×10^{-5}
	Left occipital cortex	−13.7	−90.5	0.6	321	.0438
	Right angular gyrus	49.4	−50.2	24.0	2260	1.09×10^{-10}
	Right frontal operculum	43.6	13.0	3.1	457	.00622
	Precuneus	3.3	−50.2	66.7	344	.031
Nonresponders Only, Baseline vs. Post-ECT (+4 Wk)	Right hippocampus and accumbens	29.7	−5.1	−13.8	1931	1.79×10^{-7}
	Posterior cingulate cortex	−7.3	−58.3	33.3	843	.000767

CBF, cerebral blood flow; ECT, electroconvulsive therapy; MNI, Montreal Neurological Institute; RFT, random field theory; Tx, treatments.

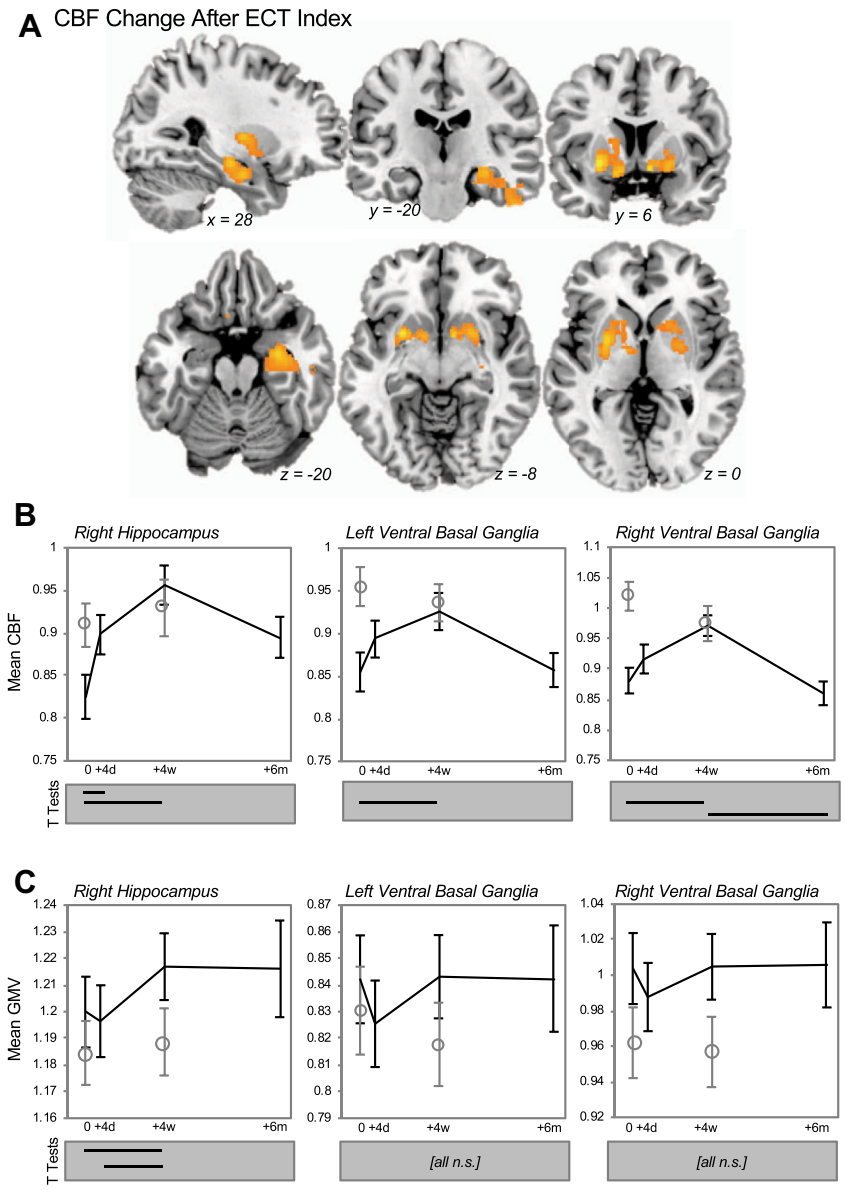

Figure 3. Regional cerebral blood flow (CBF) change after electroconvulsive therapy (ECT) treatment (index series). **(A)** Basal brain function measured with CBF increased in three regions after ECT treatment (orange), including the right anterior hippocampus and bilateral ventral basal ganglia. **(B, C)** Mean regional CBF (corrected for global CBF) and mean regional gray matter volume (GMV, corrected for global gray matter) are plotted for three regions surviving cluster-level thresholding at top **(B)** and bottom **(C)** panels, respectively. Black lines reflect means for patients, open circles plot means for healthy control volunteers, and standard error bars are plotted for both groups. The results of post hoc pairwise comparisons among time points of interest are indicated below each graph ($p_{corr} < .05$, Bonferroni correction). Note that analyses of CBF shown in panel (B) statistically control for cluster GMV and vice versa for panel **(C).** n.s., not significant.

increased acutely after only two treatments and appeared to precede associated GM increases reported previously (10,11,24,42). Furthermore, robust hippocampal and striatal plasticity in our study was associated with poor clinical response to ECT, while successful antidepressant response was linked to functional changes in other structures like the dorsomedial thalamus and cortical regions. Taken together, our results suggest that a balance between functional plasticity in brain regions located near the right-temporal ECT electrode (hippocampus, striatum) and plasticity in regions near the vertex electrode and associated with seizure generalization (dorsal thalamus and cortex) is key to successful clinical outcome in right-unilateral ECT (Figure 5). Our results also indicate that excessive hippocampal plasticity may not be a biomarker of positive ECT outcome.

Global vs. Regional Neurofunctional Plasticity in ECT

In ECT, alternating electrical current is briefly applied via electrodes placed on the head to elicit generalized seizures, where seizure activity occurs throughout the brain. A "successful" ECT session is typically defined as inducing a generalized seizure, evidenced by highly coordinated seizure activity at all or most recording sites during multichannel electroencephalogram and motor symptoms (43). However, there is an abundance of evidence from animal models (44,45),

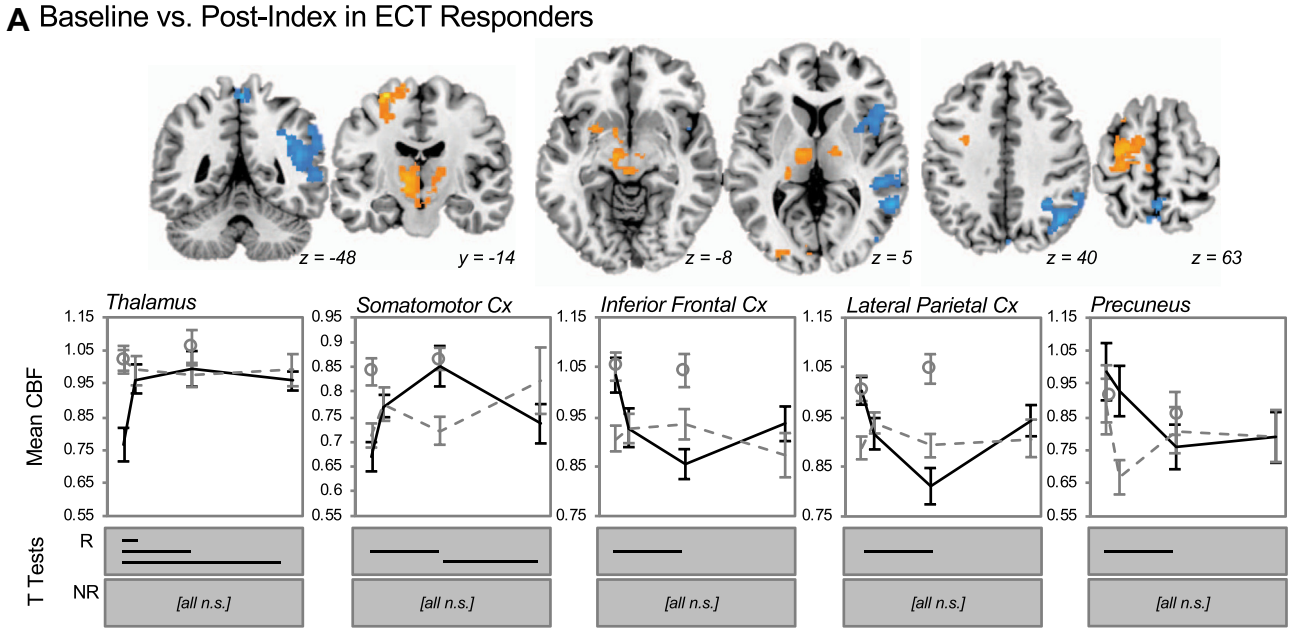

Figure 4. Exploratory analyses yielded different patterns of regional cerebral blood flow (CBF) change after electroconvulsive therapy (ECT) treatment (index series) in responders (R) and nonresponders (NR). **(A)** In ECT responders, basal brain function measured with CBF increased in the thalamus, brainstem, and left somatomotor cortex (Cx) after ECT treatment (orange) and decreased the regions of the right lateral frontal and parietal cortex (blue). Mean CBF values (corrected for global CBF) are plotted for each region below, with solid black lines indicating responders, gray dashed lines indicating nonresponders, and open circles reflecting data from healthy control volunteers. Error bars mark standard error. Statistically significant (Bonferroni correction, $p_{corr} < .05$,) changes over time are plotted for responders in solid black lines (top); nonresponders and healthy control volunteers did not change over time (not significant [n.s.]). **(B)** Regions of significant change in CBF after ECT index are shown for nonresponders, including increased CBF (orange) in right hippocampus and bilateral ventral basal ganglia and decreased CBF in posterior cingulate cortex (blue). At right, mean CBF (corrected for global values) are plotted for responders in black, nonresponders in gray dashed lines, and for healthy control volunteers in open circles. Again, error bars reflect standard error. Significant pairwise tests for these regions are indicated below each plot for nonresponders in gray dashed lines ($p_{corr} < .05$, Bonferroni correction); responders and healthy control volunteers did not change over time (n.s.).

patients with epilepsy (46), and ECT (5,22,47) demonstrating that neuronal activity measured during generalized seizures is not homogenous throughout the brain (20). Correspondingly, global CBF remained relatively static in our study, while robust regional CBF change occurred in circumscribed areas in all patients and according to antidepressant response (discussed further below).

Global CBF was, however, associated with ECT outcome. Pretreatment global CBF was lower in ECT responders than in both nonresponders and healthy control volunteers, and a modest linear correlation between pretreatment global CBF and symptom change was apparent. Global CBF also increased transiently after the initial two ECT treatments in ECT responders. This latter effect supports a previous

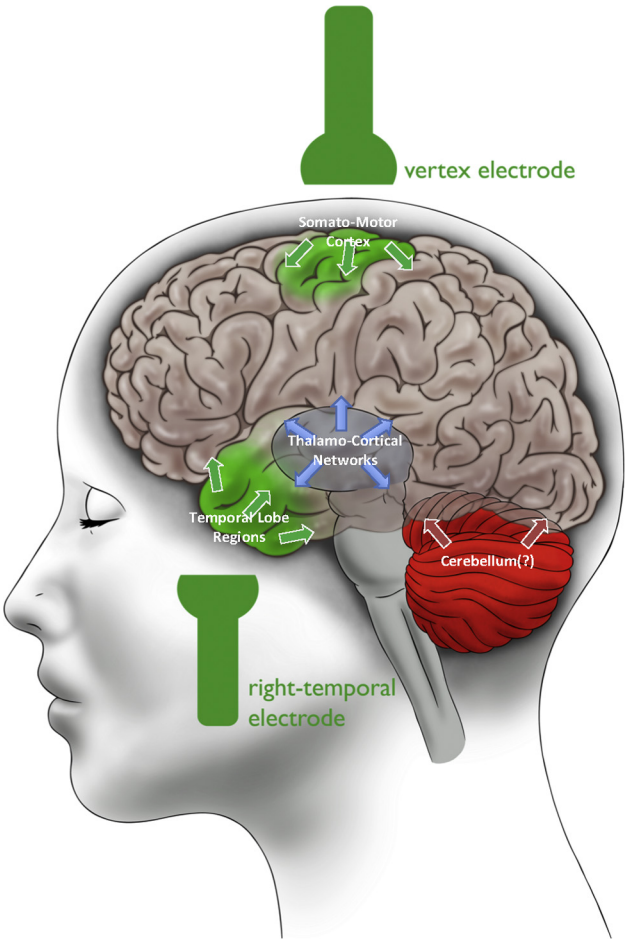

Figure 5. Results summary: balanced long-term neuroplastic effects in electroconvulsive therapy. We propose that a balance in functional neuroplasticity in brain regions associated with the three well-known stages of seizure progression—initiation (green), generalization (blue), and termination (red)—may be an indicator of positive antidepressant response to electroconvulsive therapy. This schematic summarizes the results of our study in electroconvulsive therapy responders, who exhibited cerebral blood flow changes in right hippocampus and somatomotor cortex (green) and thalamocortical regions (blue). The cerebellum (red) was not measured (as indicated by the question mark) but has been linked to seizure termination in previous studies and may also play a role in electroconvulsive therapy.

positron emission tomography study reporting increased global CBF during ECT-induced seizures, though relationships with antidepressant response were not reported (48). However, the nature of this potential link between lower levels of pretreatment global brain activity and successful antidepressant response is unclear. Lower global function at baseline could prevent neuronal hyperexcitability during treatment (which can be detrimental to cell health) or could allow more capacity for neurons to respond when exposed to ECT-related electric fields and/or seizure activity. Future animal studies will be better able to probe this putative relationship between baseline CBF and antidepressant response at a cellular level. Clinical studies could also explore whether inducing a state of lower global brain function prior to initiating ECT treatment would increase the probability of positive antidepressant outcome. This modest effect aside, overall our data support that the effects of ECT are not global, but instead occur in specific brain networks relevant to depression and seizure physiology.

Hippocampal Plasticity and ECT Outcome

The most consistent finding reported across the ECT literature is increased structural plasticity of the hippocampi and surrounding regions after treatment, including increases in a variety of neuroimaging markers of GM in humans (10,11,24,42,49), increased cellular plasticity including neurogenesis in animal models (15,16,50), and several reports of associated neurofunctional plasticity (13,14,19,38). Our data corroborate these findings using a novel technique; we report that brain activity measured with ASL-fMRI increased in right anterior hippocampus in all volunteers after right-unilateral ECT (effects were bilateral at more lenient thresholds). Notably, CBF increased after only two treatments, apparently preceding changes in GMV in this region. These neurofunctional changes could occur alongside microstructural changes not resolved by MRI (15,16,50), perhaps also related to inflammatory processes (and associated neurotrophic effects) (51). Furthermore, when analyzing data from ECT nonresponders separately from responders, hippocampal CBF change appeared more pronounced in nonresponders. Previous human neuroimaging studies have reported either modest (11) or no (10,24,42) correlations [including in meta-analyses (52,53) and a mega-analysis (54)] between improved depressive symptoms and GMV increases in hippocampus and/or surrounding cortical tissue. Thus, the nature of the link between hippocampal plasticity and antidepressant response to ECT remains tenuous, though our results suggest that more may not be beneficial when it comes to neurofunctional plasticity in the hippocampus and other ventral structures such as the striatum. Hippocampal plasticity may also be linked to possible ECT-related memory complaints (55), though this area is understudied (39,56).

Perhaps the most parsimonious explanation of ECT-related hippocampal plasticity is the long-term consequences of seizure activity owing to its proximity to the temporal electrode(s). The anteromedial temporal lobes are highly susceptible to seizures as indicated by the epilepsy literature (57). Single photon emission computed tomography studies have shown increased activity in anteromedial temporal regions at the beginning of the ECT session, which is often interpreted as reflecting seizure initiation (22). After seizure initiation, however, brain-activity changes occur elsewhere during ECT-induced seizures, typically including increased thalamic and brainstem activity coupled with decreased cortical activity (22,46,48,58) consistent with patterns of long-term changes we report in ECT responders (discussed below). Given the complexity of current models of both seizure neurophysiology and depressive neuropathophysiology, the hippocampus is unlikely to be the sole (or perhaps even the most) critical component of the mechanisms of antidepressant response to ECT.

Relevance of Dorsal Thalamocortical Regions to ECT Physiology

Patients who responded to ECT in our study had lower thalamic CBF before treatment compared with both nonresponders and healthy control volunteers. These thalamic CBF levels increased, or "normalized," acutely after two ECT treatments in ECT responders and remained stable through the 6-month follow-up MRI. The thalamus has been linked to the propagation of generalized seizures in animal models (59,60), and the thalamus and/or thalamocortical networks are thought to play an important role in the generalization of seizures during ECT (22,61), which may be critical to its clinical success (62). Acute increases in thalamic activity in responders were accompanied by decreased cortical activity in lateral frontal and parietal areas in our study, similar to patterns reported in single photon emission computed tomography studies tracking real-time changes in brain activity during generalized seizures induced during ECT (thalamic and brainstem increases, cortical decreases) (22,46,48,58). Clearly, generalized seizures occur in both responders and nonresponders to ECT; this is closely monitored during each treatment (43). However, our data suggest that perhaps the lasting neuroplastic effects of seizure generalization (i.e., long-term plasticity in thalamocortical networks occurring during ECT index) are more pronounced in ECT responders.

ECT responders also exhibited increased CBF in somatomotor cortices contralateral to the position of the vertex electrode, which is just right of midline in right unilateral ECT (63). Our group and others have reported links between ECT and motor and/or supplementary motor regions (35,64–66), which could be relevant to avolitional and amotivational symptoms often associated with depression [though complex goal-oriented and motor-planning behavior is typically linked to more rostrofrontal structures (67)]. Animal studies also show that lateral somatomotor cortex is susceptible to "kindling" (i.e., the initiation of seizure activity with electrical stimulation) (68,69). Given the proximity of our reported effect in lateral somatomotor cortex to the vertex electrode, it is also possible that CBF increases in this region reflect the lasting neuroplastic effects of motor-cortex seizure activity initiated under or near the vertex electrode and/or the effects of alternating current applied at the vertex electrode during treatment.

Conclusions and Limitations

Taken together, our results suggest that balanced neurofunctional plasticity across putative sites of seizure initiation near the right-temporal (hippocampus, ventral striatum) and vertex (somatomotor cortex) electrodes, as well as regions linked to seizure generalization (thalamus, cortex), may be critical to positive outcome. By contrast, "too much" plasticity in regions near the right-temporal electrode (hippocampus, ventral striatum) may not be conducive to positive outcome. Thus, although the distribution of electrical current applied at each electrode may be comparable during ECT (70,71) and all patients experience generalized seizures (43), the regional distribution of ECT-induced seizure activity and/or its lasting functional effects may differ according to antidepressant response (Figure 5).

Our results require further empirical validation in independent samples and using complementary model systems and techniques. We interpreted our results as reflecting the long-term effects of seizure activity; however, future longitudinal studies monitoring brain activity during ECT-induced seizures (e.g., high-field electroencephalogram, single photon emission computed tomography, high-resolution positron emission tomography MRI) will be able to directly assess these relationships and their consequences for antidepressant response. Such studies could also address relationships between pretreatment brain "states" and patterns of seizure activity elicited during ECT with respect to outcome. Several additional limitations could be addressed by future research (see also Supplemental Discussion). Our sample was intentionally heterogeneous to boost generalizability and translational value (72), yet multisite studies with larger sample sizes are needed to parse the potential contributions of diagnosis, comorbidities, ECT stimulation parameters, cognitive outcomes (39,55), antidepressant treatment history, and other factors on ECT-induced neuroplasticity. The cerebellum is linked to seizure termination in both humans (46) and animal models (73,74), and yet was excluded from our analyses because it was not fully captured by our field of view. New ASL sequences with improved spatiotemporal resolution will be helpful in measuring the effects of ECT on the cerebellum and smaller structures such as the amygdala. Finally, our interpretation is speculative (Figure 5); however, the field needs testable, mechanistic models beyond the continued characterization of ECT. We propose this interpretation with the goal of informing much-needed future research.

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