Modulation of Intrinsic Brain Activity by Electroconvulsive Therapy in Major Depression

Supplemental Information

Supplementary Methods

Participant Inclusion and Exclusion Criteria

All patients were experiencing a major depressive episode (MDE) as defined by the DSM-IV-TR. Diagnoses of major depressive disorder (n = 24) and bipolar disorder (n = 6) were included because we were interested in examining the effects of ECT on recurrent MDE across these diagnostic categories (1); patients with psychotic symptoms were excluded from this study. All patients were characterized as treatment refractory, having tried and failed at least two other therapies prior to beginning ECT. Patients with comorbid psychiatric or neurological disorders, concurrent serious illness, or prior neuromodulation treatment within 6 months of beginning ECT (i.e., ECT, transcranial magnetic stimulation, or vagal nerve stimulation) were excluded. For controls, exclusion criteria were: any history of serious illness, neurological disorders, or psychiatric disorders (assessed using the Mini-International Neuropsychiatric Interview (2)). All patients ceased benzodiazepines, antidepressant and/or anti-anxiety drugs at least 48-72 hours prior to starting ECT. Depressive symptoms were assessed in patients using the Hamilton Depression Inventory (HAMD, 17 item) and the Montgomery Åsberg Depression Rating Scale. Patients also completed the Quick Inventory of Depressive Symptomatology. Because these measures were strongly intercorrelated, we report only HAMD measures in this manuscript.

ECT Protocol

Right-unilateral ECT was administered using standard protocols at UCLA Resnick Neuropsychiatric Hospital. For right-unilateral treatment, one electrode was placed on the right temple, while the other was placed just to the right of vertex (i.e., top) of the head (3). At the first

session, each patient's seizure threshold (ST) was determined (dose titration method), and subsequent treatments were delivered at 5-times ST. Per standard protocol, patients received a short-acting anesthetic and a muscle relaxant prior to each treatment. Patients underwent ECT sessions 3 times weekly for 2-4 weeks during an index series; average number of treatments between baseline and third MRI scan was 10.04 (SD = 2.93; Table S1).

MR Image Preprocessing and Normalization

Functional images were preprocessed, including slice-time correction, motion correction (6 degrees of freedom, aligned to middle volume), high-pass filter (0.01 Hz), spatial smoothing (6 x 6 x 6 mm^3) using FSL v5.0 (FMRIB). Additionally, spin-history artifacts resulting from interleaved slice acquisition (and often correlated with head motion, (4)) were removed from voxel timecourses using independent component analysis (ICA) and FSL's *regfilt*. Briefly, ICA was run on each fMRI session, independent components (ICs) representing spin-echo artifacts were identified by one observer and confirmed by a second observer (average inter-rater agreement was 85%) by examining IC spatial maps and timecourse spectra (refer to Friston *et al.* and Salimi-Khorshidi *et al.* for further details (4; 5)). The number of artifact ICs and total ICs did not differ between patients and controls at baseline (t = -0.23 p = 0.82 for total ICs and t = 0.78 p = 0.44 for artifact ICs), and did not differ between baseline and follow-up scans for patients (MD1 vs. MD3; t = -0.72 p = 0.48 for total ICs and t = 0.04 p = 0.97 for artifact ICs) or healthy volunteers (CO1 vs. CO3; t = -0.90 p = 0.37 for total ICs and t = -0.91 p = 0.36 for artifact ICs). Artifact ICs were removed from voxel timecourses by taking the residuals from a linear regression using noisy IC timecourses as regressors (with *regflilt*). Finally, preprocessed and denoised images were aligned to the MPRAGE from the first research session (i.e., MD1 or CO1) using FSL, and then normalized to MNI standard space using a nonlinear transformation and interpolated to 2 x 2 x 2 mm^3 resolution in SPM8 (Wellcome Trust Centre for Neuroimaging).

ICA of Resting-State fMRI Data

ICA was run using standard procedures in FSL MELODIC. Functional images (MD1, MD3, CO1, CO3) were concatenated to estimate RSNs with ICA, and the optimal number of ICs was estimated with probabilistic ICA (6). Thirty-one group ICs were identified with this approach. Upon visual inspection, spatial maps from 25 ICs overlapped gray matter and were identified as RSNs, and the remaining overlapped white matter and/or cerebrospinal fluid and were thus considered unlikely to correspond with neural function. Eight RSNs were targeted as networks of interest (Figure 1), which covered medial fronto-limbic and temporal areas previously implicated in depression and ECT response. These RSNs were selected and verified visually by study co-authors, and have been reliably demonstrated in healthy volunteers in previous research (7–10). Single-subject RSNs were derived using dual regression in FSL. A single healthy volunteer exhibited pronounced spin-echo artifacts in their Salience RSN map; this single-subject map was not considered in further analyses (4). Statistical analyses were restricted to voxels overlapping with group-averaged maps for any of the eight chosen RSNs ($p < 0.00001$) in order to reduce the number of statistical tests performed.

Because head motion can affect correlations between voxel timecourses, mean relative displacement (MRD) values were calculated during motion-correction procedures in FSL as described above, and were analyzed to confirm that head motion did not differ on average between scans (11). MRD was not different in patients and healthy volunteers during baseline scans (mean/SD = 0.10/0.05 mm for patients; mean/SD = 0.11/0.06 for controls; $t = -0.50$, $p = 0.62$). Additionally, MRD did not change between baseline and follow-up scans for patients ($t = -0.46$, $p = 0.68$) or healthy participants ($t = -0.06$, $p = .95$). Note that single-subject denoising to remove spin-echo artifacts (which are often caused by head motion) is also likely to ameliorate potential effects of head motion in subsequent statistical analyses, in addition to standard motion-correction procedures in FSL. Respiration and heart rate were not collected, and global

signal was not removed in these analyses (for discussion of both sides of this controversial issue, refer to (12; 13)).

Permutation Testing in Partial Conjunction Analyses

When analyzing ΔECT and ΔMD effects overlapping across multiple RSNs, we performed partial conjunction analyses followed by permutation testing to estimate the rate of false positives. First, we chose voxels exhibiting modest ΔECT effects in at least 3 RSNs ($p < 0.05$) and clusters containing at least 50 voxels. In permutation tests, we created 8 random fields matching the smoothness and spatial dimensions of the RSN maps (14), and created a distribution of cluster-size frequencies at our chosen parameter restrictions (i.e., voxelwise $p < 0.05$ in ≥ 3 RSNs) over 10,000 permutations of those 8 random fields/maps (i.e., one for each of 8 RSNs). We then used this distribution to calculate the probability of achieving a cluster size of at least 50 voxels. This permutation testing indicated that our chosen parameters were quite robust; the probability of achieving this partial conjunction at random was less than 0.01% (i.e., $p_{corr} < 0.0001$).

Graph Theory Analyses

Graph theory analyses were performed in MATLAB using the Brain Connectivity Toolbox and standard procedures (15). Pairwise correlations between each pair of ROIs were calculated (Pearson's *r* with Fischer's *z* transformation), resulting in a similarity matrix for each volunteer and time-point (i.e., MD1, MD3, CO1, CO3). Global network metrics were calculated on significant ROI-ROI connections only, as determined using a one-sample *t*-test for each group ($p < 0.005$, with further Bonferroni-correction for the number of pairwise tests per group); ROI-ROI correlations meeting this threshold for all four groups were considered significant.

Metrics analyzed included network strength, node strength, network global efficiency, node local efficiency, and network clustering. Strength was calculated as the sum of correlation

magnitudes for each node or ROI, and reflects the magnitude of RSFC between each node and the rest of the network. We also analyzed the mean strength across all nodes, which reflected the overall connectivity within the network. Efficiency is a measure of network integration. Local efficiency was calculated as the average shortest path length between a given node and all other nodes in the thresholded network; the average of this measure, or global efficiency, was also calculated across all nodes. The final measure we considered was the mean clustering coefficient, which is calculated as the proportion of a node's neighbors that are also neighbors with each other, averaged across all nodes in the network. This metric is thought to reflect the degree of separation or clustering in the network (and was not analyzed at the node-level). In all cases, weighted metrics were calculated where appropriate. A detailed description of the mathematical derivations and possible interpretations of these and other metrics can be found in existing methodological literature (15; 16). For visualization in figures, hierarchical clustering analysis was used to group ROIs based on their ROI-ROI connectivity profiles (Fischer's *z* transformation of Pearson's *r* values).

Table S1. Coordinates of significant effects

Statistical Model	RSN(s)	Region	MNI Center of Gravity			Volume (mm^3)
			X	Y	Z	
ΔECT	Thalamus / ventral basal ganglia	Dorsal anterior cingulate cortex	-5.3	12.3	30.0	2,128
	Anterior default-mode	Posterior cingulate cortex	6.2	-58.1	22.7	832
	Salience	Mediodorsal thalamus	-2.0	-18.1	7.0	744
		Right lateral cerebellum	17.1	-55.4	-19.2	552
	Posterior default-mode	Right hippocampus	21.4	-30.4	-10.8	488
	Anteromedial temporal lobe	Medial parietal cortex	2.8	-61.2	30.6	488
ΔECT	Overlapping at least 3 RSNs	Dorsal anterior cingulate cortex	-0.5	11.8	26.5	976
		Posterior cingulate cortex	-2.5	-41.3	9.6	744
		Right anterior temporal cortex	38.4	-8.7	-43.7	552
		Medial parietal cortex 1	2.5	-54.5	33.6	520
		Mediodorsal thalamus	-4.8	-17.5	6.9	520
		Medial parietal cortex 2	12.8	-61.2	47.6	408
ΔMD	Overlapping at least 3 RSNs	Right putamen	25.6	6.4	5.3	1,112
		Mediodorsal thalamus	16.1	-18.2	7.8	1,024
		Left lateral parietal cortex	-31.4	-75.7	38.0	664
		Right dorsomedial prefrontal cortex	-1.0	50.7	19.3	656
		Left hippocampus	-24.5	-38.1	-22.3	616
		Dorsal anterior cingulate cortex	0.1	23.8	31.4	584
		Subgenual anterior cingulate cortex	4.7	31.8	-17.4	568
		Right dorsolateral prefrontal cortex	19.2	40.9	38.9	536
		Right lateral parietal cortex	36.7	-52.2	36.0	504
		Right ventromedial prefrontal cortex	8.0	49.4	-10.8	416

MD, major depression; ECT, electroconvulsive therapy; MNI, Montreal Neurological Institute; RSN, resting-state network.

Supplemental References

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