Electroconvulsive Therapy (ECT) induced neurochemical modulation as measured by ^{1}HMRS in Major Depression

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Introduction:

Proton magnetic resonance spectroscopy (^{1}HMRS) offers a non-invasive technique for measuring neurochemical disturbances in cortico-limbic regulatory circuits in depression. Electroconvulsive therapy (ECT) is a rapidly acting treatment for patients with severe depression. Converging evidence suggests altered neurochemistry in major depression [1, 6] where ECT induced neuroplasticity and changes neurochemistry measured with ^{1}HMRS [2, 3] may account for treatment effects. Here, we examined cross-sectional and longitudinal ECT treatment effects on glutamate/glutamine (Glx), N-acetyl aspartate (NAA), creatinine+phospocreatinie (CrPCr), and *myo*-inositol (mI) in the hippocampus, and the dorsal and subgenual cingulate in patients with major depressive disorder (MDD) and cross-sectional effects of diagnosis by comparing metabolite levels between patients assessed prior to ECT and age and gender matched healthy controls.

Methods:

Subjects included patients with a DSM-V diagnosis of MDD (*N=43, 20M/23F*, ages *20-64* years) and demographically similar control subjects (*N=32, 14M/18F*, ages *20-74* years). Patients were assessed at 3 time points: T1: <24 hours before the first ECT treatment, T2: <24 hours after the second ECT treatment, and T3: within one week of completing the ECT treatment index series at transition to maintenance therapy. Healthy controls completed two testing sessions (C1 and C2 including 32 and 30 subjects respectively) approximating the time interval between the patient T1 and T3 assessments. Single-voxel point resolved spectroscopy (PRESS) sequences were acquired on a Siemens 3T Allegra system (TR/TE: *2200/30* ms; spectral width 2000 Hz; 1024 samples) with and without water suppression (*128/1* averages). A volumetric navigator was used to correct for motion and B0 inhomogeneities in real time [4]. Voxels of interest (*30 x 12 x 12* mm) were positioned in the midsagittal dorsal and subgenual cingulate cortex and in left and right hippocampal gray matter using T1-weighted MPRAGE images resliced in 3D. Following denoising [5] of the MRS signals for each voxel, water-referenced metabolite concentrations were computed using LCModel. Tissue segmented T1 images were used to correct metabolite concentrations for voxel CSF content. Longitudinal effects were examined with General Linear Mixed Models (GLMMs). Cross-sectional effects of diagnosis were examined by comparing metabolite values between patients and controls scanned at baseline. Sex and age were included as covariates in all analyses.

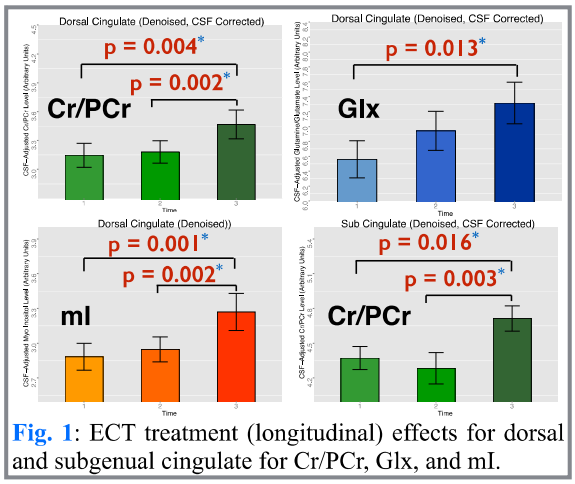

Fig. 1: ECT treatment (longitudinal) effects for dorsal and subgenual cingulate for Cr/PCr, Glx, and mI.

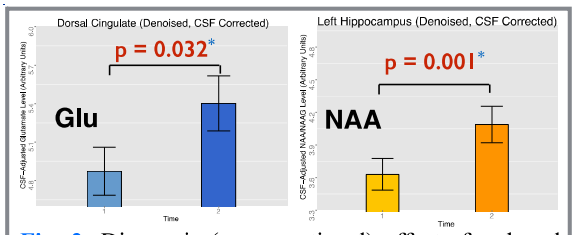

Fig. 2: Diagnosis (cross-sectional) effects for dorsal cingulate (Glu) and hippocampus (NAA).

Results

In the dorsal cingulate, significant effects of ECT (Figure 1) were found for Glx (*F=3.458, p=0.032*), CrPCr (*F=6.24, p=0.005*), and mI (*F=7.44, p=0.002*). Additionally pairwise contrasts showed significant increases for Glx between T1 and T3 (*p=0.013*), for CrPCr between T1 and T3 (*p=0.004*), and T2 and T3 (*p=0.002*), and for mI between T1 and T3 (*p=0.001*) and T2 and T3 (*p=0.002*). In the left hippocampus, significant ECT effects were found for Glx (*F=5.55, p=0.005*). Pairwise contrasts showed decreases in Glx between T1 and T2 (*p=0.003*), with a trend between T1 and T3 (*p=0.066*). In the right hippocampus, main ECT effects were found for NAA (*F=3.795, p=0.032*). Pairwise decreases in NAA were observed between T1 and T3 (*p=0.016*), and between T2 and T3 (*p=0.029*). In the subgenual cingulate, significant ECT effects were found for CrPCr (*F=5.975, p=0.007*), and increases in CrPCr occurred between T1 and T3 (*p=0.016*), and T2 and T3 (*p=0.003*). Effects of diagnosis (Figure 2) showed significantly reduced Glu (*F=5.905, p=0.032*) and NAA (*F=5.395, p=0.023*) in patients in the dorsal cingulate, and significantly reduced NAA (*F=11.24, p=0.001*) in the left hippocampus compared to controls.

Discussion: Though prior studies have shown changes in neurochemistry with ECT, this is the first study to our knowledge to simultaneously investigate changes in 'over reactive' dorso-medial (anterior cingulate) and 'under-reactive' ventral limbic (hippocampus) regions linked with mood regulation and emotional response respectively. Results showed a significant increase and normalization of Glx in the dorsal cingulate with ECT suggesting increased excitatory neurotransmission in line with prior findings [7]; changes in creatine and mI suggest glial function and/or second messenger-mediated neurotrophic factors also account for therapeutic effects. In contrast, Glx decreased with ECT in the left hippocampus, findings that may suggest changes in hypo- and hyperactive dorsal and ventral cortico-limbic networks and relate to ECT-induced neurogenesis or synaptogenesis [7, 8]. Patients showed decreased levels of NAA in the left hippocampus compared to controls at baseline. Since NAA is an MRS marker of neuronal integrity, these suggest neuronal dysfunction in MDD.

References: [1] Hasler, G et al. *Arch of Gen Psychiatry* 64.2 (2007): 193-200. [2] Ende, G, et al. (2000), *Arch Gen Psychiatry*, 57(10), pp. 937-43. [3] Obergriesser, T. et al. (2003), *J Clin Psychiatry*, 64(7), pp. 775-80. [4] Hess, A.T,et al. (2011), *Magn Reson Med*, 66(2), pp. 314-23. [5] Marquina, A. et al. (2000) *SIAM J. Sci. Comp.* 22, no. 2 (2000): 387-405. [6] Yuksel, C. et al. (2010), *Biol Psychiatry*, 68(9), pp. 785-94. [7] Zhang, J. et al. (2012), *Mol Psychiatry*, 18(3), pp. 268-70. [8] Merkl, A. et al. (2011) *Biol Psychiatry* 69(8): 772-779.

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