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Variations in myo-inositol in fronto-limbic regions and clinical response to electroconvulsive therapy in major depression

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ABSTRACT

Though electroconvulsive therapy (ECT) is an established treatment for severe depression, the neurobiological factors accounting for the clinical effects of ECT are largely unknown. Myo-inositol, a neurometabolite linked with glial activity, is reported as reduced in fronto-limbic regions in patients with depression. Whether changes in myo-inositol relate to the antidepressant effects of ECT is unknown.

Using magnetic resonance spectroscopy (^{1}H-MRS), we measured dorsomedial anterior cingulate cortex (dmACC) and left and right hippocampal myo-inositol in 50 ECT patients (mean age: 43.78, 14 SD) and 33 controls (mean age: 39.33, 12 SD) to determine cross sectional effects of diagnosis and longitudinal effects of ECT. Patients were scanned prior to treatment, after the second ECT and at completion of the ECT index series. Controls were scanned twice at intervals corresponding to patients' baseline and end of treatment scans. Myo-inositol increased over the course of ECT in the dmACC ($p = 0.042$). A significant hemisphere by clinical response effect was observed for the hippocampus ($p = 0.003$) where decreased myo-inositol related to symptom improvement in the left hippocampus. Cross-sectional differences between patients and controls at baseline were not detected. Changes in myo-inositol observed in the dmACC in association with ECT and in the hippocampus in association with ECT-related clinical response suggest the mechanisms of ECT could include gliogenesis or a reversal of gliosis that differentially affect dorsal and ventral limbic regions. Change in dmACC myo-inositol diverged from control values with ECT suggesting compensation, while hippocampal change suggested normalization.

1. Introduction

Electroconvulsive therapy (ECT) remains the most effective acute treatment for severe depression (Pagnin et al., 2004, Petrides et al., 2001) and is the modality of choice for patients failing standard therapeutic approaches (Janicak et al., 1985; Pagnin et al., 2004). However, the neurobiological events accounting for clinical response to ECT are still debated (Fosse and Read, 2013; Ishihara and Sasa, 1999). Renewed emphasis has been placed on the role of glial cells in antidepressant response as converging evidence suggests glia pathology and perturbations in glia number in depression. For instance, *reductions* in glia in major depressive disorder (MDD) are reported in post-mortem samples within regions widely implicated in depression such as the subgenual anterior cingulate (Öngür et al., 1998), dorsolateral prefrontal (Cotter et al., 2002) and orbitofrontal cortex (Rajkowska et al., 1999). Conversely, *increased* glial density has been reported in the hippocampus (Stockmeier et al., 2004).

Myo-inositol is a stereoisomer of inositol, a compound that is largely (though not solely) produced by the phosphoinositide second messenger signaling system (Moore et al., 2000). Although neurons contain measurable myo-inositol, the myo-inositol signal detected by ^{1}H-MRS is considered to reflect glial myo-inositol where much higher concentrations are present (Brand et al., 1993). Reduced levels of myo-inositol, a putative glial marker (Hattingen et al., 2008), are indicated in the cerebral spinal fluid (CSF) and in the frontal cortex in post-mortem data of individuals with affective disorders (Barkai et al., 1978; Shimon et al., 1997). Further, several independent proton magnetic resonance

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spectroscopy (^{1}H-MRS) studies report reduced resonance of myo-inositol in the prefrontal cortex (PFC) (Coupland et al., 2005), the anterior cingulate cortex (ACC) (Chen et al., 2014, Chiappelli et al., 2015, Frey et al., 1998) and hippocampus (Husarova et al., 2012) of depressed patients.

Oral supplementation of inositol has been tested in randomized controlled trials where at least two studies have shown reductions in depressive symptoms in association with inositol administration (Elizur et al., 1995, Levine, 1997). However, research addressing links between traditional antidepressant therapies and myo-inositol is sparse and conflicting. One ^{1}H-MRS study reported significantly *reduced* ACC myo-inositol in patients taking different classes of antidepressants relative to unmediated patients (Frey et al., 1998). Conversely, a recent study indicated *increased* ACC myo-inositol concentration in depressed patients following administration of a selective serotonin reuptake inhibitor (Chen et al., 2014). Transcranial magnetic stimulation (TMS) has been shown to increase prefrontal myo-inositol in depressed adolescents (Zheng et al., 2010). One report also shows elevated myo-inositol in the ACC of depressed patients in remission (Taylor et al., 2009). In sharp contrast to standard pharmacotherapies that take weeks to months to elicit a full therapeutic response, ECT has a relatively rapid onset of action. Animal studies using electroconvulsive shock (ECS) as a model for ECT show increased markers of glial cells in regions important in depression such as the PFC (Jansson et al., 2009), hippocampus (Wennström et al., 2003, 2006; Kaae et al., 2012), and amygdala (Wennström et al., 2004). However, whether changes in myo-inositol associate with response to ECT has not been addressed or documented.

Using single voxel ^{1}H-MRS, we sampled myo-inositol levels from the dorsomedial ACC, right and left hippocampus to determine whether changes in myo-inositol occur in association with ECT and ECT-related clinical response. Patients with DSM-IV major depression scheduled to receive ECT were scanned at three time points: within 24 h prior to the first ECT treatment (T1), after the second and prior to the third ECT session (T2) and at the end of the ECT treatment index series (T3). To establish normative myo-inositol values and variance, demographically similar healthy controls were assessed at two time points (C1 and C2). Based on initial evidence from previous ^{1}H-MRS studies that mostly suggest increased myo-inositol in association with other antidepressant therapies (Chen et al., 2014; Zheng et al., 2010), we hypothesized that myo-inositol values would increase in association with ECT and that patients would exhibit lower myo-inositol relative to controls at baseline.

2. Methods

2.1. Subjects

All study participants provided written informed consent as approved by the UCLA Institutional Review Board. The study was conducted in accordance with the latest version of the Declaration of Helsinki. Exclusion criteria for all participants included history of alcohol or substance abuse within the past 6 months and/or dependence within the past 12 months, any neurological disorder, and contraindication to MRI scanning. Demographic and clinical information for all subjects is provided in Table 1.

Fifty patients (23 males, 27 females) experiencing a major depressive episode were recruited from individuals scheduled to receive ECT at the University of California, Los Angeles (UCLA) Resnick Neuropsychiatric Hospital. A board certified psychiatrist determined diagnosis using Diagnostic Statistical Manual (DSM)-IV criteria. Diagnostic status was additionally confirmed with the

Table 1
Demographic and clinical characteristics.

	Patients with MDD, N = 50			Controls, N = 33	
Age, mean (SD), y	43.78 (14)			39.33 (12)	
Gender (M/F)	23/27			14/19	
Race/ethnicity[b]					
African American	2			3	
Asian	4			3	
Hispanic	6			2	
White	36			24	
Multi-ethnic	1			1	
Adjusted education, years	15.78 (2.70)			16.94 (2.30)	
Dextral/non-dextral [a,b,c]	37/12			28/4	
ECT Index sessions, mean (SD) [b]	9.96 (4.05)				
Patients receiving RUL/bilateral [b]	34/14				
Unipolar/bipolar	43/7			–	
Responders/remitters	20/8				
Age at onset [b], mean (SD), y	27.75 (12.23)			–	
Current episode [b], mean (SD), y	1.81 (2.82)			–	
Lifetime illness [b], mean (SD), y	17.78 (13.31)			–	
Time point	**T1 = 50**	**T2 = 42**	**T3 = 33**	**T1 = 33**	**T2 = 31**
HAM-D-17	24.91 (5.89)	20.92 (6.19)	12.46 (7.97)	–	
MADRS	39.04 (9.17)	32.66 (8.62)	30.64 (13.29)	–	
Tissue segmentations [d]					
Dorsomedial ACC gray/white matter volume mean (SD), cm^3	3135.43 (398.75)/ 555.08 (201.31)	3162.850 (403.29)/ 580.88 (198.21)	3061.00 (437.29)/ 582.53 (232.12)	3218.69 (453.78)/ 696.41 (447.88)	3265.03 (326.46)/ 609.45 (180.95)
Left hippocampus gray/white matter volume mean (SD), cm^3	2452.33 (272.40)/ 1749.35 (325.40)	2469.44 (370.22)/ 1737.81 (391.38)	2469.27 (247.72)/ 1758.06 (284.04)	2501.76 (227.42)/ 1730.06 (263.04)	2547.13 (227.42)/ 1669.58 (183.48)
Right hippocampus gray/white matter volume mean (SD), cm^3	2450.06 (418.78)/ 1643.51 (365.83)	2392.86 (496.84)/ 1745.60 (444.53)	2464.24 (256.82)/ 1745.60 (259.13)	2542.49 (236.80)/ 1689.36 (263.06)	2479.55 (411.24)/ 1735.58 (387.32)

[a] Handedness was estimated using the modified Edinburgh Handedness Inventory [57] where a laterality quotient of < .7 defined non-dextrals.
[b] Data for 1 patient each was missing for race/ethnicity, handedness, education, age of onset, duration of current episode and duration of lifetime illness; Data for 2 patients missing for lead placement and number of ECT sessions.
[c] Data for 1 control missing for handedness. Response defined as >50% improvement in HAM-D or MADRS scores over the course of treatment. Remitters defined as patients with HAMD <7 at the end of ECT.
[d] Total volume for all voxels equaled 4320 cm^3.