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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.

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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, 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 (Rajkowska and Miguel-Hidalgo, 2007a). 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, 1978, Shimon et al., 1997). Further, several independent proton magnetic resonance spectroscopy (^{1}H-MRS) studies report reduced resonance of myo-inositol in the prefrontal cortex (PFC) (Coupland et al., 2005), the 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 prefrontal-cortex (Jansson et al., 2009), hippocampus (Wennström et al., 2006, Kaae et al., 2012, Wennström et al., 2003), 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 hours 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.

Methods

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 Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). Of the 50 patients completing baseline assessments, 33 patients (19 females, 14 males; mean age: 41.87, 3.54 SD) completed all study time points.

Thirty-three healthy controls (14 males, 19 females) similar in age and gender were recruited from the Los Angeles area using advertisements. Controls were administered the M.I.N.I. (Sheehan, 1998) to exclude subjects for history of depression, other psychiatric or medical illness, and or a history of antidepressant use. Controls were scanned at two time points, C1 and C2, which occurred 2–5 weeks apart. Of the 33 control participants, 31 controls (18 females, 13 males; mean age: 39.32, 3.5 SD) completed both study time points.

In an earlier and related study including an overlapping sample of research participants (Njau et al., 2016), we addressed whether changes in glutamate, NAA, creatine and choline occur in relation to ECT. These results are discussed in the context of the current findings in the Discussion section.

ECT treatment

ECT followed the seizure threshold (ST) titration method where after establishing the seizure threshold, treatments were delivered at 5× ST for right unilateral (RUL) d'Elia lead

placement, using an ultrabrief pulse-width (0.3msec), and at 1.5× ST for bilateral placement, using a brief pulse-width (0.5msec). For the index series, ECT (5000Q MECTA Corp.) was administered three times a week, using a standard protocol for anesthesia (methohexital at 1mg/kg dosage) and paralysis (succinylcholine at 1mg/kg dosage). All patients were tapered off psychotropic medications (including antidepressants and benzodiazepines) prior to starting ECT and participating in this study.

Clinical measures

To measure clinical response we administered the Hamilton (HAM-D-17) (Hamilton, 1976) and Montgomery-Asberg (MADRS) (Montgomery and Asberg, 1979) depression rating scales at the same time points as ^{1}H MRS acquisition. Since HAMD and MADRS scores display high concordance, HAMD ratings were chosen as the primary measure of clinical response and used to determine relationships with myo-inositol concentration. Patients also provided information concerning their clinical histories, education and handedness, which is presented in Table 1.

MRS acquisition and analysis

Magnetic resonance single-voxel point resolved spectroscopy (PRESS) sequences were acquired on a Siemens 3T Allegra (Erlangen, Germany) system with (TR/TE: 2200/30 ms; spectral width 2000 Hz; 1024 samples) and without (128/1 averages) water suppression. A volumetric navigator was used to correct for motion and B0 inhomogeneities in real time (Hess et al., 2011). High resolution motion-corrected multi-echo MPRAGE images (Tisdall et al., 2012) were acquired on the same scanner (TEs/TR= 1.74, 3.6, 5.46, 7.32/2530 ms, TI=1260 ms, FA=7°, FOV=256 × 256 mm, 192 sagittal slices, voxel resolution = 1.3 × 1.0 × 1.0 mm^3) and resliced to position ^{1}H-MRS voxels of interest (12 × 30 × 12 mm) in midsagittal dorsal ACC and in (20 × 18 × 12 mm) left and right hippocampal gray matter [Figure 1]. Voxel positioning was determined based on previous evidence in an overlapping as well as an independent sample indicating that ECT affects neurochemistry in the ACC and hippocampus (Njau et al., 2015, Zhang et al., 2013) and structural neuroplasticity in the hippocampus (Joshi et al., 2015), which associate with positive clinical response to ECT. Work from our own group has also shown alterations in the functional (Leaver et al., 2015) and structural pathways (Lyden et al., 2014) that connect the cortical and limbic networks that encompass the ACC and hippocampus, respectively.

To calculate myo-inositol signal relative to the unsuppressed water signal, we used LCmodel software (Provencher, 1993) (Version 6.2). Computed myo-inositol concentrations were corrected for CSF contributions using tissue classified T1-weighted images (Gussew et al., 2012).

Statistical Analyses

Prior to statistical analysis, we excluded myo-inositol data with a Cramer-Rao lower bound value of > 10 % as this indicates poor model fit. The *adjusted sample sizes utilized in specific statistical tests are denoted in parentheses*. For all analyses, right and left hippocampal myo-inositol values were examined by modeling hemisphere as a repeated

measure; ACC myo-inositol values were analyzed separately since the ACC voxel was placed at midline.

Cross sectional analyses—For each region [Figure 1], we used the General Linear Model (GLM) to explore differences in myo-inositol concentration between ECT patients and controls assessed at baseline for the ACC (*24 controls, 44 patients*) and hippocampi (*27 controls and 45 patients*).

Longitudinal analyses (Effects of ECT)—General Linear Mixed Modeling (GLMM) was used to explore changes in myo-inositol concentration in the ACC (*44 patients*) and hippocampus (*45 patients*) over the course of ECT by modeling time as a repeated measure (T1, T2, T3), to account for within-subject correlations between repeated measurements and to allow for unbiased parameter estimates despite missing data points resulting from participant attrition or exclusionary Cramer-Rao bound values. For those voxels displaying significant changes in myo-inositol over the course of ECT, in follow-up analyses, we investigated whether T3 metabolite values in patients differ from T1 myo-inositol values in controls to explore indications or counter indications of normalization. Post-hoc analyses were performed to confirm ECT effects in the subsample of patients (*n=33*) completing all study time points.

Longitudinal analyses (Associations with clinical response)—Including patients who completed ECT index series only (*n=33*), relationships between change in myo-inositol levels and change clinical response were determined with the GLM using difference scores between baseline and the end of the ECT index for myo-inositol and HAMD scores (delta-delta correlations). Decreased HAMD ratings after treatment reflect improved mood, while increased HAMD ratings represent an increase in symptoms. For all analyses, age was used as a covariate as age is shown to correlate with myo-inositol concentration in previous ^{1}H-MRS studies (Chiappelli et al., 2015, Frey, 1998) as was also the case in our sample (Patients: dorsal ACC r(44) = 0.367, p =0.014, right hippocampus: r(45) = 0.464, p = 0.001 and left hippocampus r(44) = 0.345, p = 0.022; Controls: dorsal ACC r(24) = 0.511, p = 0.011, left hippocampus r(27) = 0.382, p = 0.041 and right hippocampus r(27) = 0.665, p = 0.001).

To assess predictive effects of baseline myo-inositol concentrations on clinical response, we determined associations between the difference scores for HAMD ratings between baseline and the end of the ECT index (T3 – T1) and myo-inositol concentrations *prior to treatment* (T1).

Lastly, post-hoc comparisons were performed to address possible interactions between ECT-related myo-inositol changes and clinical-response between 1) unipolar and bipolar depression patients and 2) lead placement locations (measured as a continuous measure of % of ECT sessions utilizing right unilateral leads). As lead placement is clinically determined such that those whom fail to show a clinical response to RUL lead placements are switched to bilateral leads, baseline HAMD ratings prior to treatment were controlled for in this analysis.

Results

Demographics

ECT patients and controls did not differ in sex, X^2 (1,82) = .35, p = .55, or age, F(1, 82) = 2.19, p = .14.

Longitudinal Analyses: Effects of ECT

In patients, HAMD and MADRS rating improved significantly with ECT, F(2, 12.20) = 30.05 and F(2, 37.24) = 30.04, both p < .0001. The GLMM indicated a significant increase in dorsomedial ACC myo-inositol F(2, 32.34) = 3.497, p = .042 over the course of ECT treatment [Figure 2]. Pairwise comparisons indicated significant differences in myo-inositol content between T1 and T3 (p = 0.021) and T2 and T3 (p = 0.025). Overall changes in myo-inositol over the course of ECT were not significant for the hippocampi. These results were similar when including only patients completing all three study time points for analysis and main effects of ECT for the left or right hippocampus were not observed (p<.05). However, results showed an interaction with hemisphere for relationships with HAMD change, F(1,27.148)=11.009, p = 0.003 [Figure 3]. Follow-up Pearson's correlations indicated decreases in left hippocampus myo-inositol were associated with improved HAMD ratings r(28) = 0.458, p = 0.014.

Predictors of clinical response

Associations between myo-inositol values prior to treatment and improvements in mood, as measured by percent change in HAMD ratings over the course of ECT, were not significant.

Cross-sectional analyses—There were no differences in myo-inositol concentration between MDD patients and controls at baseline for the dorsal ACC or the left and right hippocampus, all p>0.05. Follow-up analyses investigating whether myo-inositol values in patients at the end of treatment (T3) differ from baseline values in controls (C1) for the dorsal ACC were also not significant p >0.05.

Effects of electrode lead placement, diagnostic and response category

No differences were identified for post-hoc analysis exploring interactions between changes in myo-inositol concentrations and lead placement, diagnosis of unipolar or bipolar depression, all p>0.05.

Discussion

Several lines of evidence suggest that glial pathology contributes to the pathophysiology of major depression and may play a role in the mechanisms of successful treatment (Rajkowska and Miguel-Hidalgo, 2007b). Since myo-inositol is considered a ^{1}H-MRS marker of glial cell integrity, the current study sought to determine whether changes in myo-inositol occur with ECT and relate to therapeutic response. Study results provide the first evidence of ECT-related increases in myo-inositol concentration in the dorsomedial ACC [Figure 2]. We also show relationships between myo-inositol concentration and improvements in mood for the hippocampus, which interacted with hemisphere [Figure 3]. Follow-up analysis showed that

decreased left hippocampal myo-inositol associated with improvements in mood suggesting these effects are not solely due to seizure therapy. These findings also suggest ECT-related changes in myo-inositol differ across dorsal and ventral limbic regions. Differences in the direction of effects may relate to an imbalance between dorsal and ventral limbic systems and may also explain previous findings of both increases and decreases in myo-inositol in patients with depression treated with other therapies (Chen et al., 2014, Frey et al., 1998). In the current study we did not detect significant overall diagnosis-related differences myo-inositol in the ACC (Coupland et al., 2005, Chiappelli et al., 2015) at baseline as indicated in other studies.

Neural glia are involved in an amalgam of neural processes as signal transducers, inflammatory and homeostatic regulators and modulators of neurotransmission (Newman, 2003). For example, astrocytes, which are highly abundant in the central nervous system, directly affect glutamate neurotransmission and calcium signaling mechanisms (Volterra et al., 2014. Newman, 2003). Astrocytes can increase their levels of intracellular calcium following stimulation via glutamate and other neurotransmitters, brain-derived neurotrophic factors or synaptic activity. These events may be followed by a release of signaling factors such as inositol 1,4,5-triphosphate (IP3), which can further induce increase in internal calcium in other glia or neurons. Consequently, increases in intracellular calcium within neurons can lead to increased neurotransmitter release and neuronal activity. An internal increase in glial calcium can also spur neuronal activity through the action of astrocyte secreted transmitters. These glia released transmitters have been shown to partake in critical neuronal activities such as long term (Perea et al., 2009) and short-term (De Pittà et al., 2011) synaptic plasticity as well as other critical synaptic changes (Volterra, 2014, Halassa and Haydon, 2010).

Based on the above, the reported reductions in glia and independent reports of altered myo-inositol concentrations in the frontal cortex in patients with depression could indicate altered glutamate neurotransmission in the ACC/PFC (Zhang et al., 2013, Auer et al., 2000, Pfleiderer et al., 2003, Rosenberg et al., 2005). The observed increases in myo-inositol content in the ACC following ECT might similarly reflect changes in glial density or function linked with glutamate neurotransmission. Notably, in both an independent and an overlapping sample, we have shown that glutamate increases in association with ECT treatment in the dorsal (Zhang et al., 2013) and subgenual ACC (Njau et al., 2016). Further, in the same study showing increased subgenual ACC glutamate with ECT, we have also shown decreased glutamate in the left hippocampus, where reductions in glutamate associate with positive clinical response to ECT (Njau et al., 2016). These findings are compatible with the relationships between reductions in myo-inositol and clinical outcome observed in current study for the left hippocampus, suggesting a link with glutamatergic neurotransmission. Our finding also suggest that reductions in neuronal or glial activity in the hippocampus occurring with ECT is specifically involved in treatment-related clinical response.

Our results suggest that the neural processes occurring in dorsal and ventral limbic systems with ECT differ, but are potentially related to the same underlying processes. The divergent changes in ACC and left hippocampus myo-inositol over the course of ECT appear

supportive of treatment-related normalization of hyperactive ventral-limbic and hypoactive cortical-dorsal activity in depression, a model that is supported by other studies. For instance, Mayberg and colleagues (Mayberg et al., 2014) demonstrated depressive symptoms associated with increased activity in limbic networks and decreased activity in the dorsolateral prefrontal and inferior parietal regions. Following successful recovery from depression, these patterns of cortico-limbic activity were reversed. Together, these findings advance current cognitive models of depression which support impaired emotional regulation as a function of increased limbic circuitry contributions and reduced cortical influences (Disner et al., 2011).

The current findings indicating changes in myo-inositol with ECT suggest that the mechanisms associated with treatment response are not solely a consequence of neuronal integrity or plasticity, but also involve glial function. Glial cells are also involved in the regulation of inflammatory responses. Specifically, increased myo-inositol is shown as a clinical marker of astrocyte and microglial activation resulting from neuronal inflammation (Chang et al., 2013). In this context, it is possible that the convulsive effects of ECT (Fosse and Read, 2013) and associated changes in myo-inositol signal may be indicative of increased inflammatory response by glia.

Conclusion and Limitations

$^{1-}$H-MRS provides the opportunity to probe *in vivo* changes in neurochemistry and neural transmission resulting from depression and underlying successful antidepressant response to ECT. The changes in myo-inositol within the ACC and hippocampus reported here support that ECT is associated with changes in fronto-limbic circuitry and that these changes are detectable through alterations in the resonance of myo-inositol, a metabolite that is critical to glial functioning, and that may consequently also affect neural processes. Observations of increased ACC myo-inositol following ECT suggest a down regulation of gliosis or up-regulation of gliogenesis contribute to successful antidepressant response. The significant myo-inositol changes in the left hippocampus only might warrant further investigation in larger samples. Hemispheric differences may be attributable to methodological factors such as increased variance in one hemisphere or to lateralized effects of ECT. Notably, at least three previous structural imaging studies have reported marginally greater left relative to right hippocampus volume reductions in depressed subjects (Sheline et al., 1999, Sheline et al., 1996, Frodl et al., 2006), suggesting potential hemispheric differences in the hippocampus in depression. Though we did not find effects of ECT lead placement in the current study, lateralized effects of myo-inositol for the hippocampus could reflect effects of electrode placement. Since only a minority of patients received bilateral lead placement, we were not able to fully explore this hypothesis in the current investigation.

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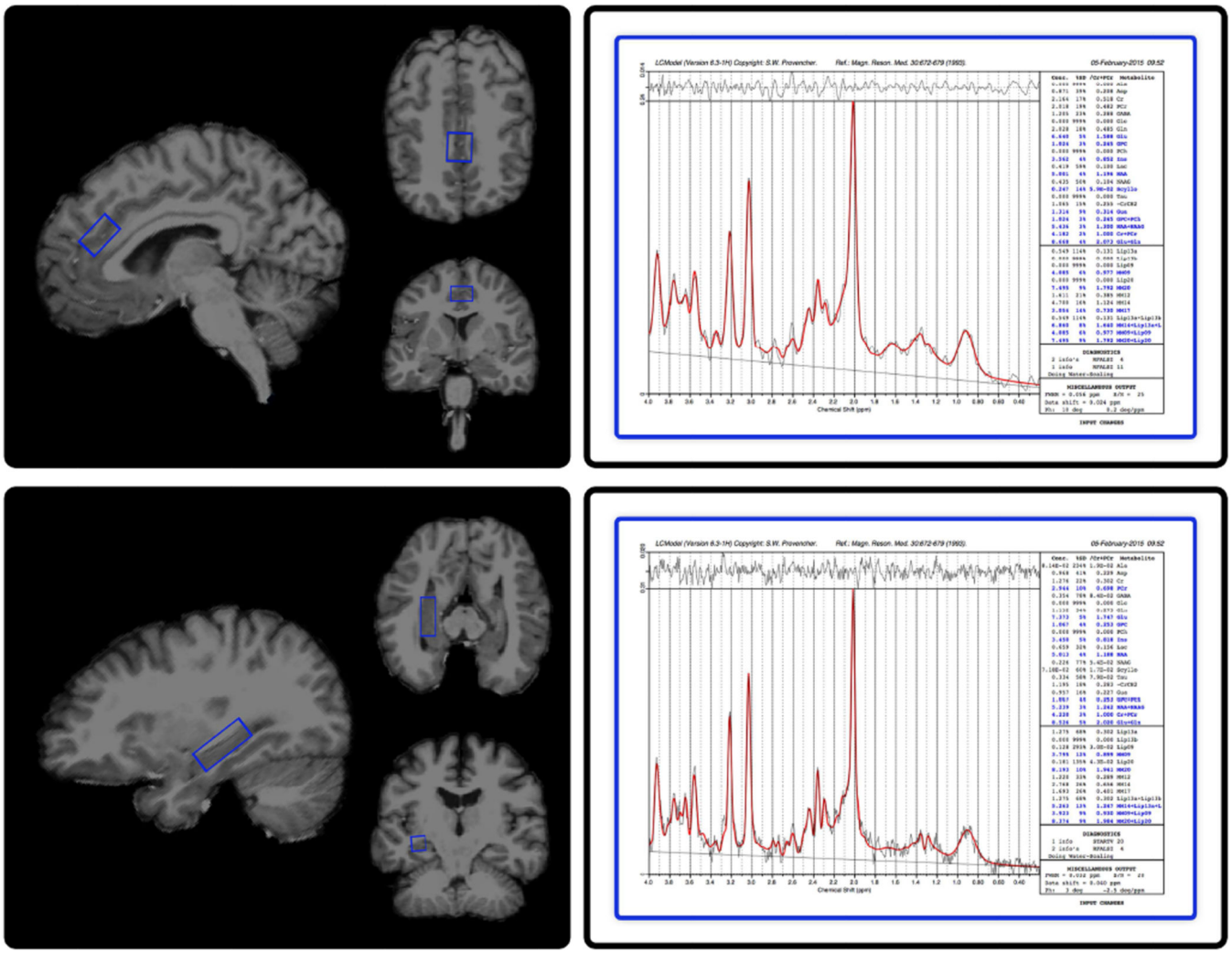

Figure 1.
Sample voxel positioning and LC model output for the dorso-medial anterior cingulate and right hippocampus. Left hippocampus placement is not shown to avoid redundancy.

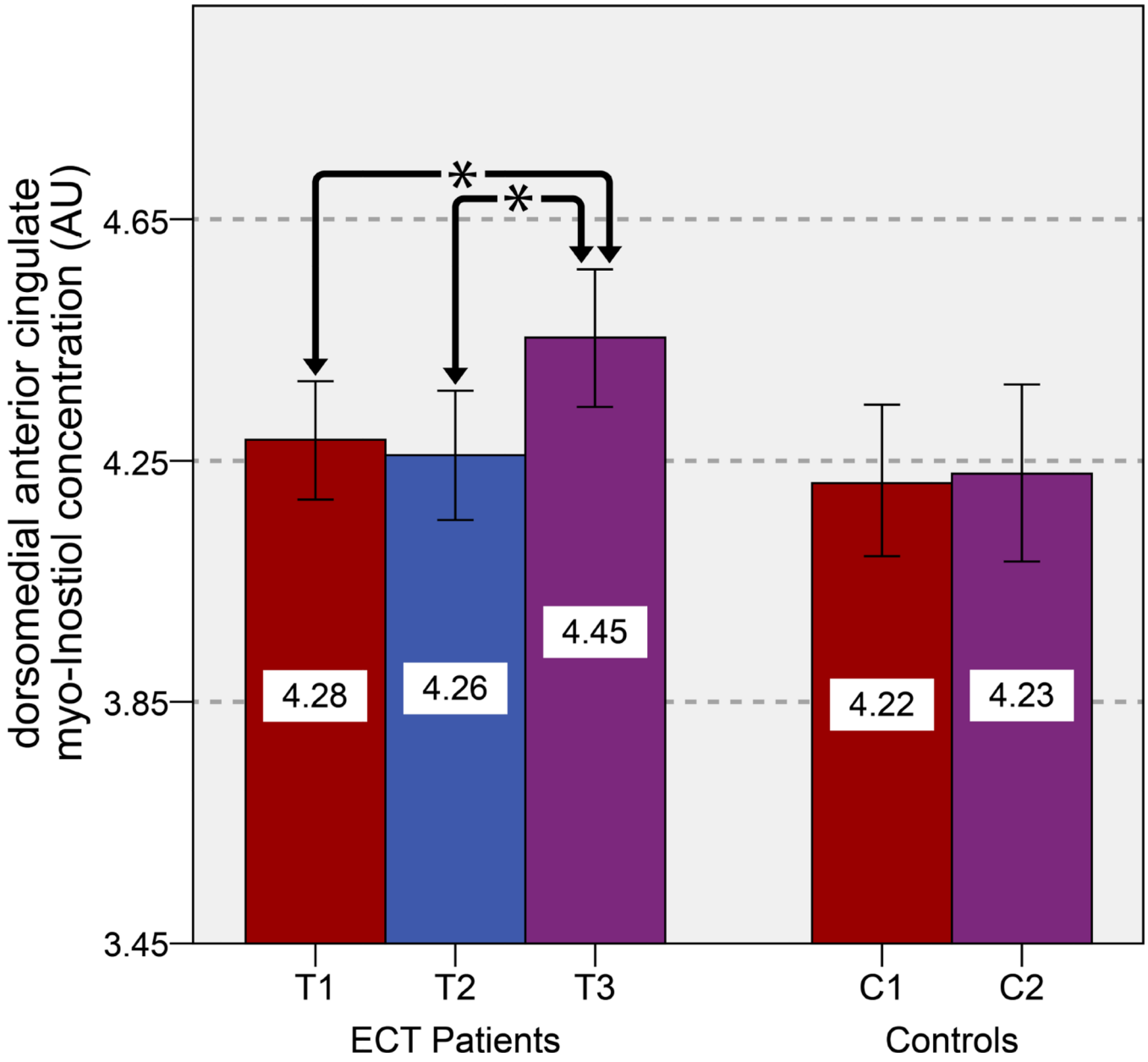

Figure 2.

Graph of means show changes in CSF-adjusted ^{1}H-MRS myo-inositol concentration in the dorso-medial anterior cingulate for ECT patients scanned prior to treatment (T1), after two ECT sessions (T2) and at the end of the ECT index series (T3) and controls scanned twice (C1 and C2), corresponding to patient baseline and end of ECT index scans. AU indicates arbitrary units. Arrows and asterisks indicate significant changes in myo-inositol content for patients over the course of ECT. See text for p-values.

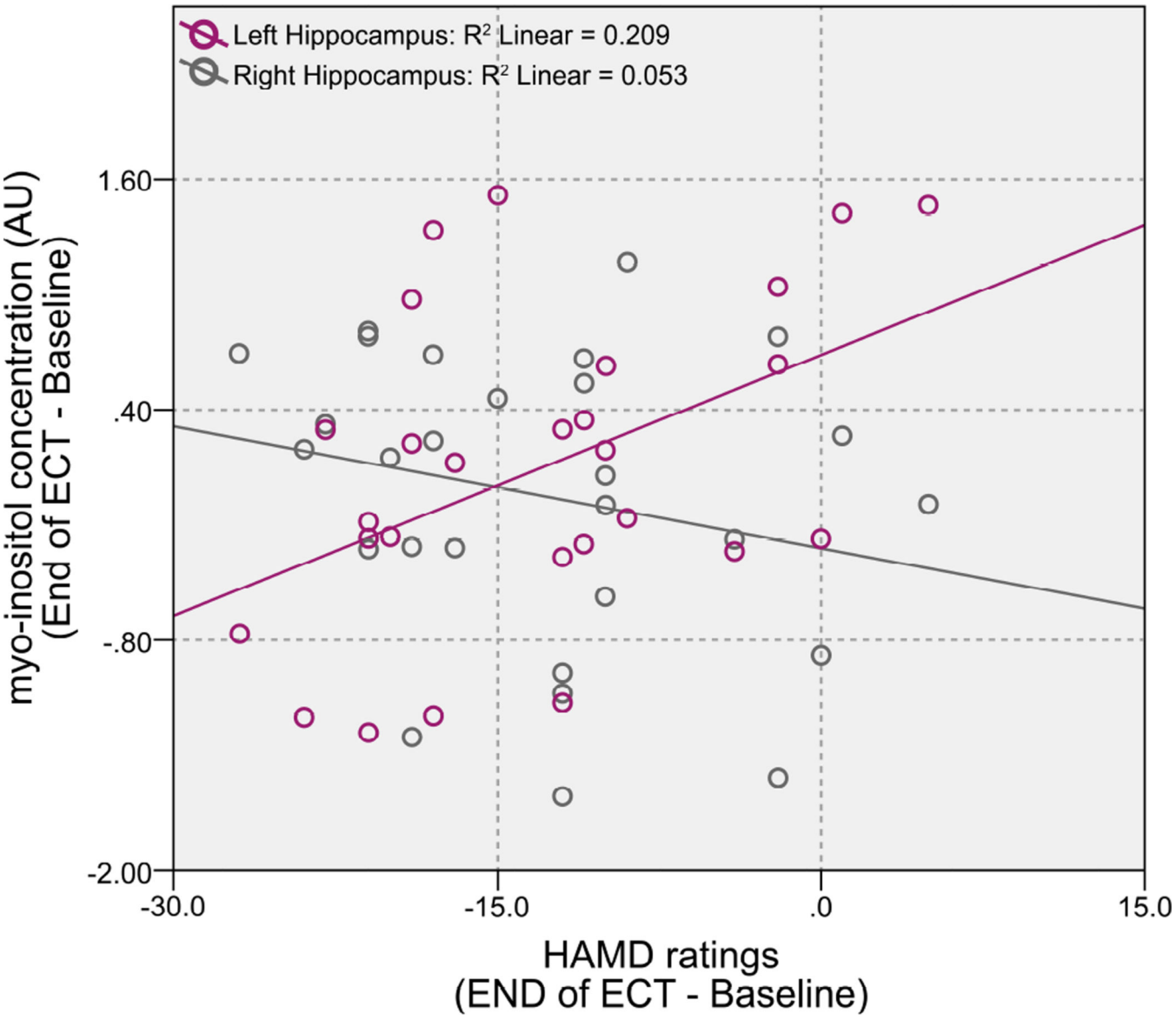

Figure 3.

Scatter plots display changes in myo-inositol concentration and HAMD ratings over the course of ECT treatment (T3-T1) for the right and left hippocampus. Graph shows regression lines for both hippocampi.

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]	9.25 (4.54)				
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.