Treatment Effects of Electroconvulsive Therapy (ECT) on the Hippocampus in Major Depressive Disorder

S. H. Joshi[1], R. Espinoza[2], T. Pirnia[1], J. Shi[4], Y. Wang[4], Brandon Ayers[3], A. Leaver[1], R. P. Woods[1, 2], and K. L. Narr [1, 2]

[1]Ahmanson-Lovelace Brain Mapping Center, Department of Neurology, University of California at Los Angeles, Los Angeles, CA; [2]Department of Psychiatry and Biobehavioral Sciences, University of California at Los Angeles, Los Angeles, CA; [3]Department of Computational and Systems Biology, University of California at Los Angeles, Los Angeles, CA; [4]School of Computing, Informatics, and Decision Systems Engineering, Arizona State University, AZ

Introduction

Major depressive disorder (MDD) has a high prevalence among psychiatric disorders, with occurrence rates between 4%-14% across the US adult population [1]. Electroconvulsive therapy (ECT) is an effective and rapidly acting treatment for patients with severe depression who fail to respond to antidepressants or psychotherapy. Growing evidence supports that some structural brain abnormalities represent trait or state markers of MDD. Particularly, meta-analytic studies [2] show reduced hippocampal volumes, among other implicated brain abnormalities in patients with MDD. In this work, we investigated effects of ECT treatment on hippocampal structure in a longitudinal cohort of MDD patients and age and gender matched healthy controls.

Methods

Subjects included N=25 (16F/9M) patients (age range 20 – 64 years), and N=27 (15F/12M) controls (age range 20 – 74 years). High-resolution T1-weighted MRI images were acquired on a Siemens 3T Allegra system (Erlangen, Germany) using a 3D EPI-navigated multiecho magnetization prepared rapid gradient echo (MEPRAGE) sequence [3] optimized for morphometric analysis with real-time motion correction. Patients were scanned prior to ECT (T1), after their 2nd ECT (T2) and within one week of completing their ECT index series (T3) at transition to maintenance therapy. Controls were scanned twice, at intervals similar to the patient T1 and T3 scans. Images were processed, automatically segmented [5], and hippocampus extracted for each hemisphere after manual correction of any segmentation errors. Both volumetric and surface-based morphometric analyses were performed where radial distances from each point on the surface to the medial axis of the hippocampus were compared to determine local changes in hippocampal shape [4]. Statistical analyses used a mixed model treating subject as a random effect, time point as a fixed categorical effect, and including intracranial volume (ICV) as a covariate. An ANOVA compared models with and without time point to establish longitudinal effects of hippocampal volume or surface morphometry within each diagnostic group. Follow-up tests compared each of the three time points pairwise in patients.

Results

Patients showed significant volumetric enlargements (Figure 1) of the hippocampus in association with ECT (left hemisphere: $X^2(8)=38.49,\ p=0.000006$, right hemisphere: $X^2(8)=18.331,\ p=0.0188$), and significant treatment effects between T1 and T3 (left

hemisphere: $X^2(4)=24.68$, $p=0.00005$, right hemisphere: $X^2(4)=14.32$, $p=0.006$), and T2 and T3 (left hemisphere: $X^2(4)=15.743$, $p= 0.003$, right hemisphere: $X^2(4)=11.21$, $p=0.02$). There was no significant difference in hippocampal volumes across time in controls. For local shape, significant (corrected for multiple comparisons using FDR, $p<0.00397$) ECT-related surface expansions (controlling for ICV) were observed within anterior CA1 and CA2-3 sub-regions, and the anterior subiculum. Morphometric results are tabulated in Figure 2.

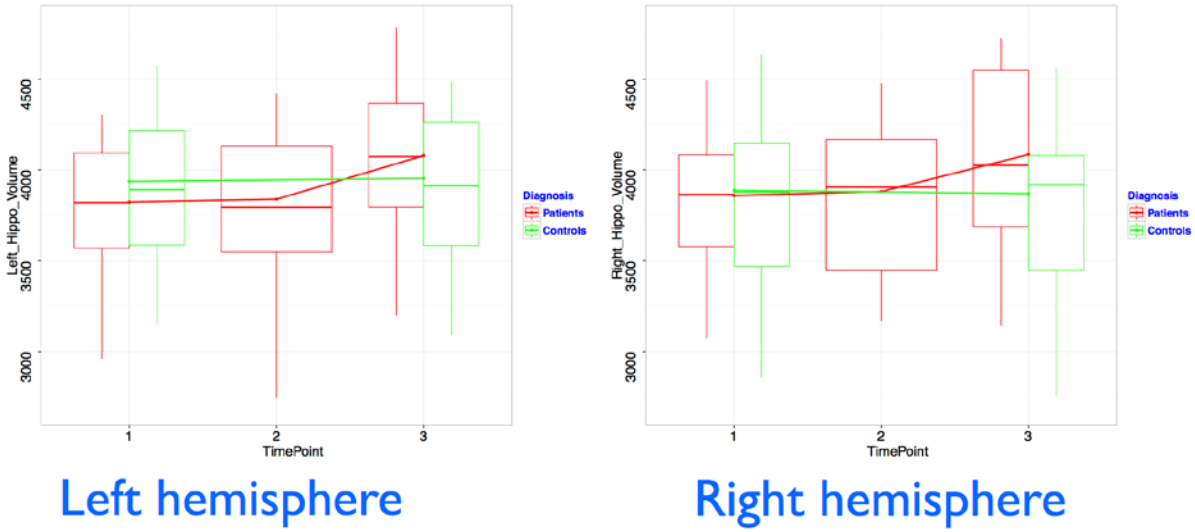

Figure 1. Change in hippocampal volume at each time point in patients (red) and controls (green). An enlargement of the hippocampus is observed in patients following treatment.

Discussion

Results confirm preliminary findings from two independent groups [7, 9] showing hippocampal enlargements in patients with MDD following ECT treatment. We further show that effects of ECT are more localized to anterior hippocampal regions linked with stress response and emotional behavior [10]. Neurotrophic factors and synapto- and neurogenesis may contribute to ECT-related neuroplasticity. For example, animal studies show ECT-related cell proliferation effects [8], while ECT modulated serum BDNF levels are reported in human subjects [6]. Examination of relationships between ECT-related changes in hippocampal morphometry and clinical and neurocognitive variables will clarify the functional significance of regional changes in hippocampal structure with treatment.

a	Patients T1 vs T2	Patients T2 vs T3	Patients T1 vs T3	Controls T1 vs T2
Left Hippo	$\chi^2(4) = 2.4894$ $p = 0.645$	$\chi^2(4) = 15.7453$ $p = 0.003368$	$\chi^2(4) = 24.86$ $p = 5.367e-05$	$\chi^2(4) = 0.2908$ $p = 0.9904$
Right Hippo	$\chi^2(4) = 1.216$ $p = 0.8755$	$\chi^2(4) = 11.213$ $p = 0.02427$	$\chi^2(4) = 14.32$ $p = 0.006341$	$\chi^2(4) = 0.2272$ $p = 0.994$

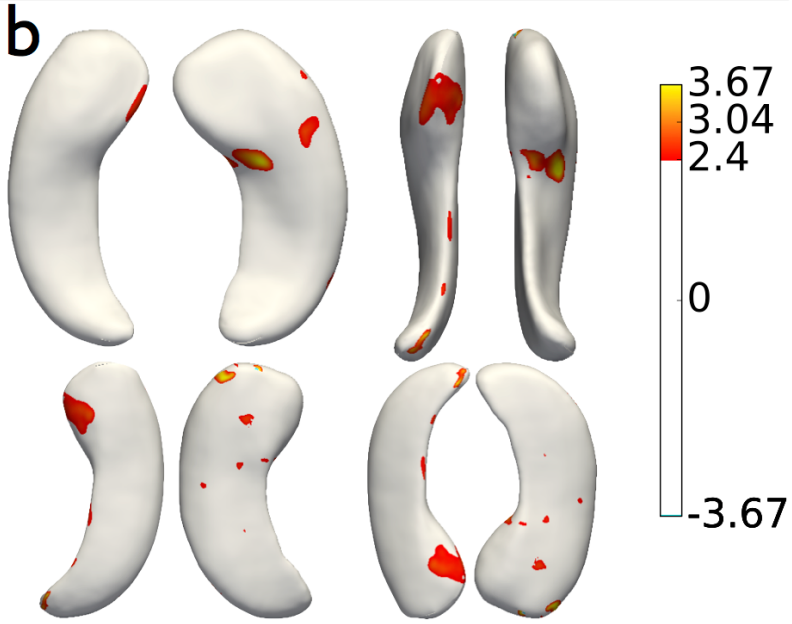

Figure 2. Effects of ECT treatment on (a) hippocampal volume for pairwise comparisons between time points T1 and T3, and (b) hippocampal shape. (p-values FDR corrected; p<0.00397).

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