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Hippocampal volume and verbal memory performance in late-stage bipolar disorder

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ABSTRACT

Studies about changes in hippocampal volumes in subjects with bipolar disorder (BD) have been contradictory. Since the number of manic episodes and hospitalization has been associated with brain changes and poor cognitive outcomes among BD patients, we have hypothesized that these variables could clarify this issue. We stratified subjects with BD in early (BD-Early), intermediate (BD-intermediate) and late (BD-Late) stages as a function of number of manic episodes and prior hospitalization. Then, we compared their hippocampal volumes and California Verbal Learning Test-II (CVLT-II) scores with healthy controls (HC) using the general linear model. A total of 173 subjects were included in the study (112 HC, 15 BD-Early, 30 BD-Intermediate, and 16 BD-Late). We found a significant group effect on hippocampus volume ($F(3,167) = 3.227$, $p = 0.024$). *Post-hoc* analysis showed that BD-Late subjects had smaller hippocampus than HC ($p = 0.017$). BD-Early and BD-Intermediate subjects showed no significant difference in hippocampus volume compared to HC and BD-Late subjects. The CVLT trial 1 to 5 scores were significantly different across the groups ($F(3,167) = 6.371$, $p < 0.001$). *Post-hoc* analysis showed that BD-Intermediate ($p = 0.006$) and BD-Late ($p = 0.017$) subjects had worse memory performance during immediate recall than HC, while the performance difference between BD-Early subjects and HC was not significant ($p = 0.208$). These findings add to the notion that BD is a neuroprogressive disorder with brain changes and cognitive impairment according to prior morbidity (number of manic episodes and hospitalization). Also, they suggest that hippocampus is a brain marker and a potential therapeutic target for patients at late stage.

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1. Introduction

Lifetime prevalence of bipolar disorder (BD) is 2.1% worldwide, with subthreshold forms affecting another 2.4% (Merikangas et al., 2007). BD is associated with cognitive impairment even during periods of euthymia (Martínez-Arán et al., 2004; Barrett et al., 2009). Emergent evidence from systematic reviews in the field suggests an association between the number of manic episodes as well as psychiatric hospitalizations with neurocognitive decline (Robinson and Ferrier, 2006), particularly verbal memory impairment (Martínez-Arán et al., 2004). Not only cognition seems to be impaired in portion as a function of number of mood episodes in BD. There is evidence of overall brain atrophy in bipolar patients with multiple-episodes and a cross-sectional study showed that lateral ventricles were significantly larger in bipolar patients with multiple-episodes as compared to first-episode patients or healthy controls (Strakowski et al., 2002). Also, a recent study showed decreased volume of corpus callosum in BD women with more than 10 episodes and at least one psychiatric hospitalization (Lavagnino et al., 2015).

Hippocampus is essential for the acquisition, consolidation and retrieval of memory (Eichenbaum, 2000), which places it as an interesting structure to study the relations among cognitive impairment, brain changes, and number of manic episodes. However, studies of hippocampal volumes in BD patients have been

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contradictory so far, showing no changes (Brambilla et al., 2003; Altshuler et al., 2000; Bertolino et al., 2003), smaller volumes (Blumberg et al., 2003; Bearden et al., 2008), and even larger volumes in BD patients as compared to controls (Javadapour et al., 2010; van Erp et al., 2012). In addition, six meta-analyses did not show changes in hippocampal volumes in patients with BD (McDonald et al., 2004; Videbech and Ravnkilde, 2004; Kempton et al., 2008; Arnone et al., 2009; Bora et al., 2010; Ellison-Wright and Bullmore, 2010).

Thus we hypothesize that reduced hippocampal volumes and poorer verbal memory performance can be identified in patients with multiple episodes and hospitalizations but not in patients with fewer and less severe episodes. We set forth to assess hippocampal volume and verbal memory according to number of manic episodes and hospitalization in BD.

2. Methods

We performed a cross-sectional study to assess hippocampal volume and verbal memory in subjects with BD type 1 according to prior number of episodes and hospitalizations. Because the distribution of the number of episodes was not normal, we previously stratified subjects into subgroups. A similar approach was used in a recent paper in major depressive disorder (Treadway et al., 2015). Also, the grouping approach is less sensitive to variability in the retrospective report of number of episodes, especially when the number of episodes experienced by the subject are high (Treadway et al., 2015). Therefore, we classified subjects as “BD-Late” if they had 10 or more manic episodes and 1 or more hospitalizations due to manic or depressive episodes. Similar definitions were used in previous studies (Magalhães et al., 2012; Lavagnino et al., 2015). We classified subjects as “BD-Early” when subjects had 3 or less manic episodes. The remaining subjects were classified as “intermediate-stage” (BD-Intermediate). The study was approved by the Institutional Review Boards of the University of Texas Health Science Center at San Antonio. Subjects signed informed consent before any study-related procedures after a complete description of the study with ample time for questions.

2.1. Participants

Subjects were recruited from the community and psychiatric clinics through flyers, radio, and newspaper advertisements. Inclusion criteria were subjects with BD type I according to DSM-IV, and age between 18 and 65. Exclusion criteria were head trauma with residual effects, neurological disorder, and uncontrolled major medical conditions. Healthy controls (HC) with a history of any Axis I disorder or with any first-degree relative with any Axis I disorder or use of psychoactive medication less than two-weeks prior to the study were also excluded. Subjects were evaluated through a socio-demographic history form to assess age, gender, years of education, and occupational status. Axis-I diagnoses and clinical characteristics were assessed with the Structured Clinical Interview for DSM-IV axis-I Disorders (SCID-I), which was administered by fully trained staff. Current dimensional mood symptoms were assessed with the Hamilton Depression Scale (HAM-D) (HAMILTON, 1960) and the Young Mania Rating Scale (YMRS) (Young et al., 1978). Verbal memory was measured using California Verbal Learning Test-II (CVLT-II) (Elwood, 1995).

2.2. MRI data acquisition

We acquired structural T1-weighted scans using a Philips 1.5 T MRI scanner (Philips Medical System, Andover, MA, USA) with a three-dimensional axial fast field echo sequence. The parameters are as follows: repetition time (TR) = 24 ms, echo time (TE) = 5 ms, flip angle = 40°, field of view (FOV) = 256 mm, slice thickness = 1 mm, matrix size = 256 × 256 and 150 slices.

2.3. MRI data preprocessing

All scans were visually inspected to rule out gross artifacts. Cortical and subcortical reconstruction and segmentation were performed with the Freesurfer software suite version 5.3.0 (http://surfer.nmr.mgh.harvard.edu). The whole procedure including motion correction, intensity normalization, automated topology corrections and automatic segmentations of cortical and subcortical regions was documented elsewhere (Dale and Sereno, 1993; Dale et al., 1999; Fischl et al., 1999a, 1999b, 2002; Fischl and Dale, 2000; Ségonne et al., 2004; Jovicich et al., 2006). Regions labeled as left and right hippocampus were extracted, and the corresponding volumes were calculated according to the voxel numbers contained within the regions and the voxel volume. Six subjects (4 HC and 2 BD-Early) were excluded as outliers in either of the hippocampus volumes (threshold: 3 standard deviations) and a total number of 173 subjects were further analyzed. The left and right hippocampus volumes were then averaged, because we did not find significant laterality effect in the preliminary analysis ($F = 0.191$, $p = 0.663$). The average hippocampus volume was then scaled by the estimated total intracranial volume (ICV) for each subject.

2.4. Memory performance

All participants were administered the Wechsler Abbreviated Scale of Intelligence (WASI), which is a screener of verbal, non-verbal, and general cognitive ability and the Wechsler Test of Adult Reading (WTAR), which is a measure of premorbid intellectual quotient (IQ) (Friedmann, 2013). All participants were administered a revised version of the CVLT – a standardized test measuring verbal learning and declarative memory via a trial list-learning paradigm (Donders, 2008). This version of the CVLT was part of the South Texas Assessment of Neurocognition (STAN) which includes both standardized and computerized neurocognitive tasks (Glahn et al., 2007). In the CVLT task participants are presented orally with 16 words for 5 times and asked to recall as many words as possible in any order. The total number of correctly recalled words from trial 1 to 5 was used to evaluate the memory performance. Furthermore, semantic clustering and series clustering scores were used to evaluate the memory strategy.

2.5. Statistical analyses

Statistical analyses were conducted using SPSS software (Version 21.0). Descriptive analyses were reported as means (standard deviations), median (interquartile range) or absolute and relative frequencies. We have used analysis of variance (ANOVA) to compare demographic and clinical variables. For each hippocampus measurement, we have used a general linear model with one way ANCOVA. Group (BD-Late, BD-Intermediate, BD-Early, and HC) was entered as an independent variable, while hippocampus volume was entered as a dependent outcome variable. We used age and gender as covariates. The education level was significantly different across the groups. However, in a preliminary analysis, we found no significant effect of education level using ANCOVA to test the group effect on hippocampus volumes and CVLT-II scores with age, gender and education as the covariates ($p > 0.1$). In addition, 22 subjects did not have valid education level data (14 HC, 5 BD-Intermediate and 3 BD-Late subjects), which would significantly affect the statistical power for BD subjects, especially for BD-Late subjects, as 18.8% (3 out of 16) BD-Late subjects would be missing in the