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Hippocampal subfield volumes in children and adolescents with mood disorders

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A B S T R A C T

The hippocampus has been implicated in various mood disorders, with global volume deficits consistently found in patient populations. The hippocampus, however, consists of anatomically distinct subfields, and examination of specific subfield differences may elucidate the possible molecular mechanisms behind psychiatric pathologies. Indeed, adult studies have reported smaller hippocampal subfield volumes in regions within the cornu ammonis (CA1 and CA4), dentate gyrus (DG), and hippocampal tails in both patients with Major Depressive Disorder (MDD) and Bipolar Disorder (BD) compared to healthy controls. Subfield differences in pediatric patients with mood disorders, on the other hand, have not been extensively investigated. In the current study, magnetic resonance imaging scans were acquired for 141 children and adolescents between the ages of eight and eighteen (57 with BD, 30 with MDD, and 54 healthy controls). An automated segmentation method was then used to assess differences in hippocampal subfield volumes. Children and adolescents with BD were found to have significantly smaller volumes in the right CA1, CA4, and right subiculum, as well as the bilateral granule cell layer (GCL), molecular layer (ML), and hippocampal tails. The volume of the right subiculum in BD patients was also found to be negatively correlated with illness duration. Overall, the findings from this cross-sectional study provide evidence for specific hippocampal subfield volume differences in children and adolescents with BD compared to healthy controls and suggest progressive reductions with increased illness duration.

1. Introduction

About 2.4% of people worldwide have been diagnosed with bipolar disorder (BD). The U.S. in particular has a high lifetime prevalence of BD at 4.4% (Kessler et al., 2005; Merikangas et al., 2011). Concurrently, and alarming 16.6% of people over the age of thirteen in the U.S are diagnosed with major depressive disorder (MDD) (Kessler et al., 2012). Both disorders are associated frequently with neurocognitive impairment, suicide attempts, and other psychiatric comorbidities, all of which place a huge burden on public health (Greenberg et al., 2015; Keck et al., 2008; Passos et al., 2016).

During childhood and adolescence, children are exposed to a diverse array of biological and environmental factors that may shape their mental health for years to come (Paus et al., 2008). Mood disorders, such as BD and MDD, may arise during development and are frequently associated with memory impairment as well as other neurocognitive deficits (Glahn et al., 2005; Jemeleddine et al., 2009). In turn, many studies have found grey matter volume differences between patients and controls in the hippocampus, which plays an important role in memory consolidation, retrieval, and other complex processes, such as stress and emotion (Frodl et al., 2010; McDonald et al., 2004; Strasser et al., 2005; Videbech and Ravnkilde, 2004).

In line with the memory deficits observed in BD and MDD populations, hippocampal volume is heavily associated with several mood disorders and has been reported as a potential metric to diagnose and track progression of BD (Cao et al., 2016a,b; Cao et al., 2016a,b; Zeni et al., 2016) and MDD (Bremner et al., 2000; Frodl et al., 2010). Although many studies have found global hippocampal volume differences between patients and controls (McDonald et al., 2004; Videbech and Ravnkilde, 2004), the hippocampus consists of morphologically distinct subfields, such as the cornu ammonis (CA) subfields CA1–4, the dentate gyrus (DG), the fimbria, and the adjacent subiculum and presubiculum (Small et al., 2011), which may in turn play different roles in BD and MDD pathologies. Indeed, adult studies based on structural brain scans have found that both BD and MDD patients have smaller hippocampal volumes in certain subfields when compared to healthy

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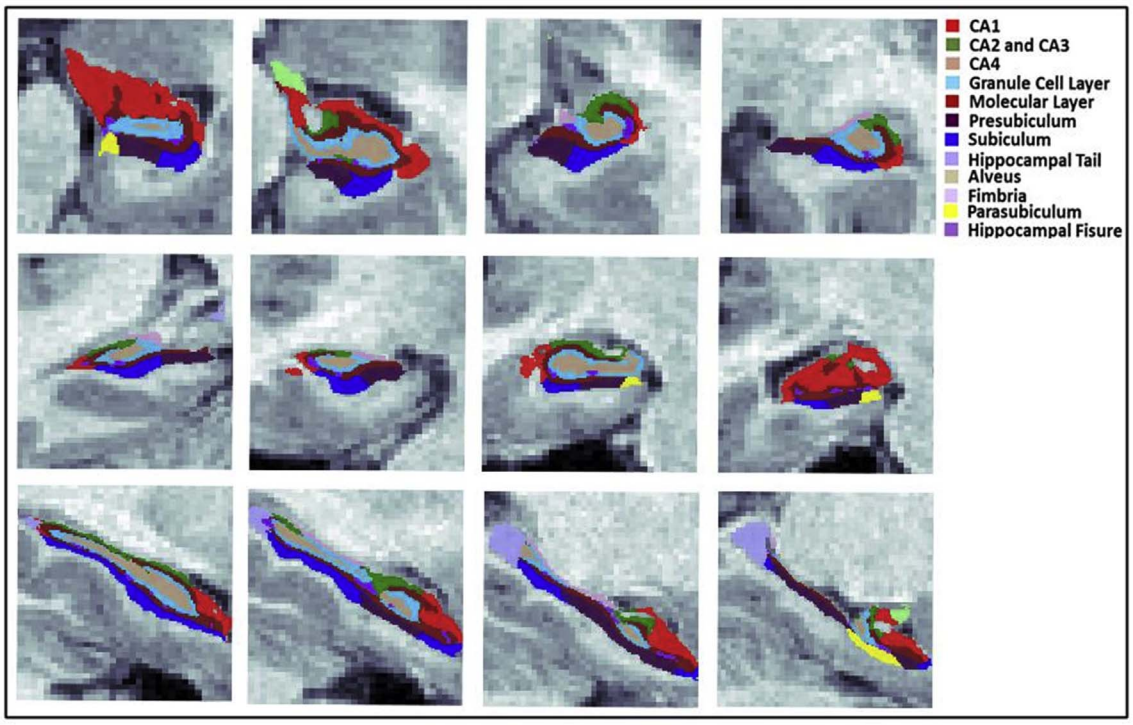

Fig. 1. A sample segmentation of the left hippocampal subfields of a healthy control using the novel method. Abbreviation: CA, cornu ammonis.

controls (HC) (Aas et al., 2014; Cao et al., 2017; Haukvik et al., 2015; Samuels et al., 2015). On the other hand, subfield changes in the pediatric population have not been extensively investigated. In addition, distinct differences in subfield volumes between the BD and MDD groups have yet to be explored and are of interest due to their possible diagnostic implications.

Computational advancements have allowed for automatic segmentation of brain structures and for the development of high resolution atlases for the segmentation of hippocampal subfields. A method based on *ex vivo* hippocampal tissues scanned with ultra-high field strength can provide reliable segmentation of hippocampal subfields and has been proven to have a higher accuracy of segmentation than the previous *in vivo* atlas method (Ho et al., 2016; Iglesias et al., 2015). This new method will help us to better observe the localized changes within the hippocampus related to mood disorders and their progression.

This study presents a comparison of the hippocampal subfield volumes in pediatric patients with BD, MDD, and healthy subjects. We hypothesized that the volumes of hippocampal subfields would be smaller in pediatric patients with mood disorders than in healthy subjects.

2. Materials and methods

2.1. Participants

Subjects were recruited through flyers, radio, and newspaper advertisements from the local community and psychiatric clinics. To meet the inclusion criteria for the clinical sample, subjects needed to be between the ages of eight and eighteen and have a diagnosis for bipolar I disorder, bipolar II disorder, or MDD. All subjects and their parent or legal guardian gave written informed consent. This study was approved by the local IRB. Exclusion criteria included head trauma with residual effects, neurological disorders, and uncontrolled major medical conditions. Healthy controls were excluded if they had a history of any Axis I disorders, had a first-degree relative with any Axis I disorder, or used psychoactive medication less than two-weeks before the study. Subjects were evaluated through a socio-demographic history form for age, gender, and years of education. Axis-I diagnoses and clinical characteristics were assessed with the K-SADS-PL (Kaufman et al., 1997) administered by fully trained research assistants or postdoctoral fellows who were supervised by an experienced research psychiatrist. Current mood symptoms were assessed with the Hamilton Depression Scale (HAMD) (Hamilton, 1960), the Children's Depression Rating Scale (CDRS) (Poznanski et al., 1985), and the Young Mania Rating Scale (YMRS) (Young et al., 1978).

2.2. MRI data acquisition

A Philips 1.5 T MRI scanner (Philips Medical System, Andover, MA, USA) was used to acquire T1-weighted structural brain image for each subject. This magnetic field strength has been used to evaluate hippocampal subfield by previous studies, including an adult study from our group (Cao et al., 2017; Haukvik et al., 2015). A hippocampal 3D axial fast field echo sequence was applied with the following specifications: repetition time (TR) = 24 ms, echo time (TE) = 5 ms, flip angle of 40°, field of view (FOV) = 256 mm, thickness = 1 mm, voxel resolution = 1 mm^3, and matrix size = 256 × 256 for 150 slices.

2.3. Preprocessing and segmentation

After a thorough visual inspection of all the brain images for visual artifacts, MRI scan preprocessing was performed for motion correction, intensity normalization, automated topology corrections and fully automatic segmentations of cortical and subcortical regions using the FreeSurfer suite version 5.3.0 (Dale et al., 1999; Fischl et al., 2002; Jovicich et al., 2006).

For the segmentation of the hippocampal subfields, we used a new FreeSurfer software (v. 6.0) algorithm. This technique provides a high resolution atlas that was acquired by scanning post-mortem hippocampal tissues at ultrahigh field strength and has been shown to substantially increase the segmentation accuracy of the hippocampal subfields (Iglesias et al., 2015).

The algorithm, as is shown in Fig. 1, results in the segmentation of twelve distinct hippocampal subfields. In order to optimize the power