Psychiatry Research: Neuroimaging 259 (2017) 54–59

Contents lists available at ScienceDirect

Psychiatry Research Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

Structural differences in hippocampal subfields among schizophrenia patients, major depressive disorder patients, and healthy subjects

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ARTICLE INFO

Keywords:
Automatic Segmentation of Hippocampal Subfields
Cornu ammonis
Dentate gyrus
Perirhinal cortex

ABSTRACT

Many MRI studies have reported a volume reduction of the hippocampus in psychiatric diseases. However, disease-related volume differences in hippocampus subfields remain unclear. Here we compared the volumes of hippocampus subfields in patients with schizophrenia, patients with major depressive disorder (MDD), and healthy subjects as controls. T2-weighted images were acquired in 20 patients with schizophrenia, 36 with MDD, and 35 healthy volunteers by 3-Tesla MRI. Hippocampal subfields were segmented using an automatic algorithm, Automatic Segmentation of Hippocampal Subfields (ASHS). Schizophrenia patients exhibited significant volume reductions in the cornu ammonis (CA)1 compared to the controls, and in the dentate gyrus compared to the controls and MDD patients without medication, whereas there was no significant difference between the MDD patients and controls. There was a nominal negative correlation between the perirhinal cortex volume and depression severity in the MDD patients without medication, whereas there were negative correlations between CA2 volume and both negative symptoms and the duration of illness in the schizophrenia patients. We identified differing volume reductions in hippocampal subfields and varying correlations between disease severity and subfield volumes depending on diagnosis, suggesting that volume differences in hippocampus subfields may provide important information regarding the pathophysiology of schizophrenia and MDD.

1. Introduction

The hippocampus, located within the medial temporal lobe, is associated mainly with memory, particularly long-term memory. However, the hippocampus is also an important part of the limbic system, and in this capacity it contributes to the regulation of emotion (for review see Phillips et al., 2003). Numerous studies have suggested that the hippocampus is one of the key brain regions involved in the pathophysiology of psychiatric diseases, and many magnetic resonance imaging (MRI) studies have reported hippocampal volume loss in psychiatric diseases; these findings have been consolidated by several meta-analyses of structural MRI studies on major depressive disorder (MDD) (McKinnon et al., 2009; Videbech and Ravnkilde, 2004) and schizophrenia (van Erp et al., 2016).

Most of these MRI studies reported differences in the global hippocampus volume. However, the hippocampus can be further subdivided along its longitudinal axis into subfields. These subfields are anatomically and functionally different subregions (Duvernoy, 2005), and they are suggested to be differentially affected depending on the individual diagnosis (Malykhin and Coupland, 2015; Geuze et al., 2005). Several manual segmentation protocols have been developed for 3- to 7-Tesla MRI, and at 7-Tesla, the ability to distinguish subfield layers improves the segmentation of hippocampal subfields (Wisse et al., 2012). Although manual segmentation was originally time-consuming and required extensive training and evaluation, recent developments in automated subfield segmentation techniques and a freely available, easy-to-use set of automated brain MRI analysis tools (Fischl, 2012; Iglesias et al., 2015; Van Leemput et al., 2009; Yushkevich et al., 2010) have made the segmentation much easier. Among these tools, the “automated segmentation of hippocampal subfields (ASHS)” technique, targeting high-resolution, T2-weighted oblique coronal images of the hippocampal region, showed excellent inter-rater reliability and validity compared to manual segmentation (Yushkevich et al., 2010).

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http://dx.doi.org/10.1016/j.pscychresns.2016.11.002
Received 8 July 2016; Received in revised form 31 October 2016; Accepted 6 November 2016
Available online 22 November 2016

Several research groups have focused on the disease-related changes of hippocampal subfields in schizophrenia (Haukvik et al., 2015; Ho et al., 2016; Kawano et el., 2015; Kuhn et al., 2012; Maller et al., 2012; Mathew et al., 2014; Zierhut et al., 2013), and these investigations revealed volume reductions in the cornu ammonis (CA)1 (Haukvik et al., 2015; Ho et al., 2016; Kuhn et al., 2012; Mathew et al., 2014; Narr et al., 2004; Zierhut et al., 2013), the CA 2/3 (Haukvik et al., 2015; Ho et al., 2016; Kawano et al., 2015; Mathew et al., 2014), and the dentate gyrus (DG) (Haukvik et al., 2015; Kawano et al., 2015; Mathew et al., 2014). One study without control subjects reported that schizophrenia patients with stronger positive symptoms had smaller CA2/3 and CA1 (Kuhn et al., 2012). The previous studies on schizophrenia have thus yielded mixed results.

In regard to MDD and the hippocampal subfields, the several available studies (Han et al., 2016; Huang et al., 2013; Lim et al., 2012; Lindqvist et al., 2014; Maller et al., 2012; Malykhin et al., 2010; Neumeister et al., 2005; Travis et al., 2014; Treadway et al., 2015; Wisse et al., 2015) yielded mixed results. In terms of analytical technique, the majority of these studies used manual segmentation (Huang et al., 2013; Lindqvist et al., 2014; Maller et al., 2012; Malykhin et al., 2010; Narr et al., 2004; Neumeister et al., 2005; Travis et al., 2014; Wisse et al., 2015; Zierhut et al., 2013) and 1.5-Tesla MRI data (Han et al., 2016; Haukvik et al., 2015; Kawano et al., 2015; Maller et al., 2012; Narr et al., 2004). Moreover, only one study estimated the differences among three diagnostic groups using 1.5-Tesla MRI data and the manual segmentation method (Maller et al., 2012), and there was no study focusing on the volume difference of hippocampal subfields between the MDD and schizophrenia patients using 3-Tesla MRI and the automated segmentation method. Further, an automated hippocampal segmentation technique developed by van Leemput in 2009 was later found to be inaccurate (Ho et al., 2016). In the present study, we compared the volumes of hippocampal subfields individually across three diagnostic groups, i.e., patients with schizophrenia, patients with MDD, and healthy controls, using 3-Tesla MRI data and automated segmentation by the ASHS technique. We hypothesized that there would be disease-specific volume differences of hippocampal subfields among these diagnostic groups, especially in CA1 and DG, and that the characteristic distribution of hippocampal subfield changes would be effective for discriminating among these conditions. Additionally, we performed a correlational analysis between the severity of disease and each volume of the hippocampal subfield.

2. Methods

2.1. Subjects

The subjects were 20 patients with schizophrenia, 36 with MDD, and 35 healthy controls (Table 1). A consensus diagnosis by at least two psychiatrists (MO, SH, or TT) was made according to the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5) criteria (American Psychiatric Association (APA), 2013), on the basis of information obtained by the Japanese version of the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), additional unstructured interviews, and medical records.

All MDD patients were rated with the 21-item version of the Hamilton Depression Rating Scale (HAMD-21) to determine their depressive symptoms (Hamilton, 1960), and all schizophrenia subjects were assessed with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). Because a previous meta-analysis showed larger hippocampal volumes among remitted patients than currently depressed patients (Kempton et al., 2011), we excluded all remitted MDD patients, as defined by a total HAMD-21 score of < 8 (Mayberg et al., 2005), from the present study. Daily doses of antidepressant were converted to fluoxetine equivalents, and daily doses of antipsychotics (including depot antipsychotics) to chlorpromazine equivalents, using published guidelines (American Psychiatric Association (APA), 1997; Inada and Inagaki, 2015). Patients were excluded if they had a medical history of central nervous system disease or severe head injury. The mean time interval between the MRI-scanning and the clinical assessment was 20.4 ± 25.2 days.

Healthy subjects were interviewed for enrollment by a research psychiatrist using the Japanese version of the MINI. Participants were excluded if they had a medical history of central nervous system disease, psychiatric illness, or severe head injury, or if they met the criteria for substance abuse or dependence.

Written informed consent was obtained for participation in the study. The study was approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan.

2.2. MRI data acquisition and processing

The MR studies were performed on a 3-Tesla MR system (Trio, Siemens, Erlangen, Germany) using an 8-channel array coil. For the measurement of hippocampal subfields, we used a high-resolution T2-weighted fast spin echo sequence (TR/TE: 5310/92 ms, echo train length 15, 15 ms echo spacing, 150° flip angle, 0% phase oversampling, 0.47×0.47 mm in plane resolution, 2-mm slice thickness, 30 interleaved slices with 0.6 mm gap), angulated perpendicular to the long axis of the hippocampal formation.

Three-dimensional (3D) T1-weighted images were scanned in the sagittal plane (echo time [TE]/repetition time [TR], 2.6/1380 ms; flip angle, 15°; slab thickness, 192 mm; matrix, 256×256; 1 NEX; field of view [FOV], 260×260 mm^2; slice thickness, 1 mm), yielding 192 contiguous slices through the head. In addition to high-resolution T2-weighted images and 3D T1-weighted images, conventional axial T2-weighted images (TE/TR: 106/5000 ms; flip angle, 159°; slice thickness, 5 mm; intersection gap, 1.5 mm; matrix, 456×512; FOV, 196×220 mm^2; acquisitions, 1) and fluid attenuation inversion recovery (FLAIR) images in the axial plane (TE/TR: 106/1000 ms; flip angle, 150°; slice thickness, 5 mm; intersection gap, 1.5 mm; matrix, 240×320; FOV, 166×220 mm^2; acquisition, 1) were acquired to exclude cerebrovascular disease. On conventional MRI, no abnormal findings were detected in the brain in any subject.

We computed the intracranial volume (ICV) from the T1 image by performing a high-dimensional diffeomorphic registration of each subject to a custom brain image template in which a binary mask of the intracranial region was defined. The inverse of the subject to the template mapping was used to transform this mask to the space of the subject. The ICV was then calculated as the volume of each subject-specific mask. Registration and segmentation were performed using the Advanced Normalization Tools (ANTs) package (Avants et al., 2008). Segmentations of the hippocampal formation were generated using the ASHS method described elsewhere (Yushkevich et al., 2010). We were then able to obtain the volumes of the CA (CA1, CA2, CA3), DG, subiculum, entorhinal cortex, and perirhinal cortex (Brodmann areas [BAs] 35 and 36) (Fig. 1). We combined the left and right hippocampal volumes to increase stability.

2.3. Statistical analysis

The differences in age, education years, body mass index (BMI) and ICV among the two patient groups and the healthy controls were evaluated by an analysis of variance (ANOVA). Gender differences were evaluated by the chi-square test, and the differences in age at onset were analyzed by a two-sample *t*-test. Antidepressants may have neuroprotective and neurotoxic effects (Haller et al., 2007; Lavretsky et al., 2005), and we therefore analyzed the differences in hippocampal subfield volumes among four groups—i.e., schizophrenia patients, MDD patients with or without medication, and healthy subjects—using a two-way analysis of covariance (ANCOVA) in which the diagnosis was a fixed factor, and age, ICV, and gender were covariates.