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Hippocampal subfields' volumes are more relevant to fluid intelligence than verbal working memory

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ABSTRACT

The hippocampus plays an important role in learning and memory. Poor segmentation tools of hippocampal subfields, however, have hindered our understanding of their specific roles. Using FreeSurfer 6.0, which provides more accurate segmentation than previous versions (especially for Cornu Ammonis [CA] subfields), the current study examined the 12 hippocampal subfields' contributions to fluid intelligence (measured with Raven's Advanced Progressive Matrices, RAPM) and working memory (measured with n-back visual and verbal working memory tasks) in a sample of 417 healthy young adults. Results showed that RAPM and visual n-back working memory had similar correlations with hippocampal subfields' volumes, but RAPM was more highly correlated with the volumes of the right hippocampus as well as three of its subfields (CA1, molecular layer of the hippocampus, and hippocampal tail) than was verbal n-back working memory (after correcting for multiple comparisons). In addition, sex moderated the correlation between left hippocampal fissure volume and n-back working memory. These results suggest both shared and distinct neural substrates for fluid intelligence and visual and verbal working memory, and highlight the role of CA1 in visuospatial cognition.

1. Introduction

The hippocampus plays a critical role in learning and memory as shown in both animal and human studies (Zatorre, Fields, & Johansen-Berg, 2012). Previous studies further showed that hippocampal volumes were positively associated with cognitive performance on the Raven's Advanced Progressive Matrices (RAPM) and n-back working memory (WM) tasks after controlling for sex, age, and the intracranial volume (Li et al., 2013; Zhu et al., 2014). Their shared neural basis may explain the positive correlation between RAPM and WM performance (Jaeggi et al., 2010; Kane, Conway, Miura, & Colflesh, 2007), and the positive effect of training with the dual n-back WM task on matrix reasoning (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). On the other hand, there are also differences between matrix reasoning (as a measure of fluid intelligence) and n-back WM (Au et al., 2015), with the former focusing on solving novel problems and the latter on updating and manipulating remembered information. Given that the hippocampus is a heterogeneous structure with subfields that can subserve different aspects of cognition (de Flores, La Joie, & Chetelat, 2015), it is likely that different subfields may be differentially linked to matrix reasoning and n-back WM. Indeed, using a sample of 104 healthy young adults, a recent study reported that spatial n-back WM performance was mainly associated with posterior areas of bilateral hippocampal structures, whereas RAPM performance was significantly associated with right hippocampal structure (Colom et al., 2013). Colom et al. (2013) further found that the correlations between cognitive performance and hippocampal structures were mostly positive for the 45 males in their sample, but negative for the 59 females. The current study aimed to extend previous research by examining hippocampal subfields' associations with RAPM and n-back (visual and verbal) WM in a large sample of Chinese young adults. The most recent technique to segment the hippocampus, FreeSurfer 6.0, was used in order to gain a better understanding the roles of specific hippocampal subfields.

Among the various segmentation methods of the hippocampus, FreeSurfer 6.0 has proven to be effective and reliable in hippocampal subfield segmentation and volume estimation in large samples of healthy subjects or patients (Ho et al., 2016; Iglesias et al., 2015; Whelan et al., 2016). The volumes of hippocampal subfields from FreeSurfer 6.0 showed a significantly higher level of agreement with those from histological studies than did the volumes from FreeSurfer 5.3. For example, both histological studies and FreeSurfer 6.0 have shown that the volume of CA1 is largest and that of CA2/3 is relatively small, but FreeSurfer 5.3 shows that the volume of CA1 is the smallest

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and that of CA2/3 is the largest (Iglesias et al., 2015). This discrepancy might have explained why most studies using FreeSurfer 5.3 found that Alzheimer's disease (AD) affected the volume of CA2/3 but not CA1, whereas most studies using manual segmentation methods found that AD affected CA1 volume (de Flores et al., 2015). In sum, FreeSurfer 6.0 has been shown to be a reliable tool for hippocampal subfield segmentation in large samples of subjects, especially for an accurate estimation of CA1 volume.

The current study tested three hypotheses. First, we hypothesized that CA1 volume, especially in the right hemisphere, would be associated positively with RAPM performance. This hypothesis was based on the results of several previous structural and functional neuroimaging studies. As suggested by Colom et al. (2013), the association between RAPM performance and right hippocampus structure may reflect the visual spatial requirements of RAPM. Another functional magnetic imaging (fMRI) study further found that right hippocampal CA1 played an essential role in spatial cognition (Suthana, Ekstrom, Moshirvaziri, Knowlton, & Bookheimer, 2009). Finally, using high-resolution fMRI, researchers found that the CA1 was the only hippocampal subfield that functioned as a visual spatial match/mismatch detector (Duncan, Ketz, Inati, & Davachi, 2012).

Second, we hypothesized that hippocampal subfields' volumes would have lower correlations with overall n-back WM (but mainly verbal n-back WM) than with RAPM performance. Previous studies suggested that hippocampal structures were associated with visual spatial information processing, but not with verbal information updating. For example, Colom et al. (2013) found that hippocampal structures were associated with both RAPM and visual spatial n-back WM performance, but not with verbal intelligence. An earlier neurosurgical hippocampectomy study showed that the hippocampectomy group had significant impairment in visual WM but not in verbal WM (Owen, Morris, Sahakian, Polkey, & Robbins, 1996). These findings of differentiated roles of the hippocampus in visual and verbal WM expand on the broader neural similarities and differences involved in the two types of WM (Owen, McMillan, Laird, & Bullmore, 2005). They further supported Baddeley's three-component WM model, which includes the contextual executive and two subsidiary systems of a phonological loop and a visuospatial sketchpad (Baddeley, 2000). The above-mentioned studies, however, focused on the overall hippocampal structures, without delineating the specific roles of hippocampal subfields in visual and verbal n-back WM. Based on the earlier discussion, it seems likely that particular hippocampal subfields (e.g., CA1) may play a more important role in solving novel visual spatial problems as measured by RAPM than in updating verbal information as measured by verbal n-back WM tasks.

Third, we hypothesized that sex would moderate the relationship between some hippocampal subfields' volumes and cognitive performance, with positive correlations between hippocampal subfields' volumes and cognition for males but negative correlations for females. Sex is an important factor in the relationships between brain structures and cognitive ability (Haier, Jung, Yeo, Head, & Alkire, 2005). Males and females may achieve similar intellectual performance using different brain regions. Most relevant to our hypothesis, Colom et al. (2013) used a statistical map of local differences in radial hippocampal distance and found mostly positive associations between hippocampal structures and cognition for males but negative correlations for females. The current study extended the hypothesis to identify hippocampal subfields' structures (e.g., CA1) whose correlations with cognitive performance would be moderated by sex.

2. Materials and methods

2.1. Participants

Participants were 417 healthy Chinese college students (age: 20.24 ± 0.86, range 18–24 years old; 237 females and 180 males, 98% right handed), who completed RAPM and n-back WM tasks. This sample expanded upon the previous 330 subjects used in our previous studies (Li et al., 2013; Zhu et al., 2014) after additional imaging data were secured. They had normal or corrected-to-normal vision and had no history of psychiatric or neurological diseases, head injuries, or stroke/seizure. Handedness did not influence any results in the current study, so all subjects were included in the analyses. Written consent was obtained from each participant after a full explanation of the study procedure. This study was approved by the Institutional Review Board of Beijing Normal University, China.

2.2. Behavioral assessments

Raven's Advanced Progressive Matrices was used to measure general fluid intelligence (Raven, Raven, & Court, 1998). Participants were given 30 min to complete as many items as possible. For each item, abstract shapes and patterns were presented in a 3-by-3 matrix with a missing piece in the bottom right, and participants were asked to identify the missing piece from eight choices. The test had 48 items. Each item was presented in black ink on a white background. This test is appropriate for adults and adolescents of above-average intelligence (Raven et al., 1998). It has been used widely in China with good reliability and validity (the split-half reliability was 0.86) (Zhai, 1999). Cronbach's alpha in this study was 0.75. The total score on this test was used as the measure of fluid intelligence.

WM was tested with the typical 2-back paradigm (Owen et al., 2005; Xue, Dong, Jin, & Chen, 2004). Participants were asked to continuously judge whether the current character was related to the one presented two characters earlier. There were three judgment tasks, including semantic judgment (whether Chinese characters were from the same semantic category), phonological judgment (whether Chinese characters rhymed), and morphological judgment (whether two Tibetan characters were the same). Tibetan letters were unfamiliar and meaningless to participants. Each judgment task consisted of four blocks, with 10 trials in each block. The average score (accuracy) of three tasks was used as the index of overall n-back WM. In addition, because morphological judgment on Tibetan characters can be performed only on visual features, we used the accuracy of morphological judgment task as the index for visual n-back WM, and the average score (accuracy) of the other two tasks (i.e., semantic and phonological judgment tasks) as the index for verbal n-back WM. Cronbach alpha for visual, verbal, and overall n-back WM in this study was 0.66, 0.77, and 0.82, respectively.

2.3. MRI data collection and analysis

MRI scans were performed on a 3.0 T Siemens Magnetom Trio scanner equipped with a 12-chanel head coil at Beijing Normal University Brain Imaging Center. Structural MRI data were acquired with the T1-weighted, three-dimensional, MPRAGE pulse sequence, using the following imaging parameters: TE = 3.75 ms, TR = 2530 ms, flip angle = 7°; FOV = 256 mm × 256 mm, voxel size = $1 \times 1 \times 1.33$ mm^3, number of partitions = 128. To extract volumetric measures of the whole hippocampus and its 12 subfields (Fig. 1A), MRI data were analyzed automatically with atlas-based FreeSurfer segmentation software (http://surfer.nmr.mgh.harvard.edu, version 6.0) (Iglesias et al., 2015). Volumes of hippocampal subfields (i.e., parasubiculum, presubiculum, subiculum, CA1, CA2/3, CA4, granule cells in the molecular layer of the dentate gyrus [GC-ML-DG], hippocampal-amygdaloid transitional area [HATA], fimbria, molecular layer of the hippocampus, hippocampal fissure, and hippocampal tail) were generated according to a refined probabilistic atlas. This new automated algorithm provided by FreeSurfer 6.0 was based on a computational atlas built upon a combination of ex vivo MRI data (manual delineation of the hippocampal substructures from 15 subjects using ultra-high resolution scanner) and in vivo MRI data (manual annotation of the adjacent extrahippocampal structures from a separate dataset of 39 subjects).

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