Title:

Intrinsic Hippocampal-Caudate Interaction Correlates with Human Navigation

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Abstract

Spatial navigation is a crucial ability in daily life. Previous neuropsychological and neuroimaging studies suggested that two spatial representation systems with either the hippocampus or the caudate nucleus at the core play an important but distinct role underlying navigation. However, it remains unclear whether and how these two systems interact during rest, and how the intrinsic interactions support human navigation. Here we investigated the intrinsic hippocampal-caudate interactions using resting-state fMRI and functional connectivity analysis, and related the interactions to individual variability in navigation performance across a large group of healthy young adults (N = 190). We found that the hippocampus showed predominantly positive functional connectivity with the caudate (especially in good navigators), suggesting an efficient hippocampal-caudate cross talk during rest, which may facilitate stronger functional integration of two systems of spatial representations underlying navigation. As expected, we found positive correlations between the hippocampal-caudate interactions and better navigation ability as measured with the Santa Barbara sense of direction scale (SBSOD). Moreover, prediction analysis with machine learning algorithm and a cross-validation procedure showed that individual's behavioral performance in a virtual reality 3D pointing task were generally well predicted by the hippocampal-caudate interactions. Taken together, these results suggest a cooperative interaction between two representation systems underlying navigation, and further study on the dynamic interaction between the two core structures would help us identify previously ignored effects and advance our understanding of normal aging and psychiatric disorders.

Keywords: Spatial navigation; Hippocampus; Caudate nucleus; Functional connectivity

Introduction

To navigate the world is crucial for human in everyday life. Currently, spatial navigation is modeled as a process supported by allocentric and egocentric spatial representations (O'Keefe & Nadel, 1978), which have been suggested to largely depend on the hippocampus (Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978) and the striatum (in particular the caudate nucleus) (Brasted, Humby, Dunnett, & Robbins, 1997; Cook & Kesner, 1988), respectively. The allocentric representations allow navigation from new starting locations (Hartley, Maguire, Spiers, & Burgess, 2003) based on the large-scale environmental configuration (Doeller, King, & Burgess, 2008; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003) or recognition of places from a new viewpoint (King, Burgess, Hartley, Vargha-Khadem, & O'Keefe, 2002; Lambrey et al., 2008), while the egocentric representations allow navigation via a fixed route (Hartley, et al., 2003; Iaria, et al., 2003) or relative to a single landmark (Doeller, et al., 2008). Although there are considerable individual preferences in use of one or the other of these representations, it is expected that, during real-world navigation, switching between them adaptively would facilitate accurate navigation (Andersen, 1997; Bremmer, Schlack, Duhamel, Graf, & Fink, 2001). Actually, emerging behavioral and neuroimaging evidence has demonstrated the cooperative nature of interactions between two systems of spatial representation underlying navigation (Brown, Ross, Tobyne, & Stern, 2012; Rice, Wallace, & Hamilton, 2015; Voermans et al., 2004). For example, in patients with Huntington's disease, the hippocampus compensates for gradual caudate nucleus dysfunction with a gradual activity increase during route recognition to maintaining normal behavior (Voermans, et al., 2004). However, it is still unclear whether and how these two systems interact during rest, especially in healthy population, and how the intrinsic interaction supports human navigation.

Recently, resting-state functional magnetic resonance imaging (fMRI) combined with functional connectivity analysis has been widely used to examine the intrinsic interactions among brain areas and their roles in behavioral variability. It is suggested that positive functional connectivity between two brain areas during rest may represent an efficient

inter-regional cross talk, which may facilitate certain functional processes. For instance, our recent study has shown that there is positive functional connectivity between two well-established face-selective regions (i.e., FFA and OFA), the strength of which predicts individual variability in face recognition ability (Zhu, Zhang, Luo, Dilks, & Liu, 2011). Within the navigation network, for another instance, functional connectivity between the parahippocampal gyrus and hippocampus has been shown to be positively related to participants' self-reported navigation ability (Wegman & Janzen, 2011). These suggest that, by examining the functional connectivity between two brain areas with rest-state fMRI, we would be able to reveal the nature of functional interaction between them and its role in certain functions.

Here, we proposed to address three open questions in this paper by combining resting-state fMRI, functional connectivity analysis and behavioral tests. First, how does the hippocampus interact with the caudate during rest? Because these two structures are involved in the same task (i.e., navigation), albeit in different ways, we hypothesized that there would be a positive functional connectivity between them. Second, whether the intrinsic hippocampal-caudate interaction correlates with individual variability in navigation ability? With Santa Barbara Sense of Direction scale (SBSOD) score which is considered as a reliable proxy of people's general navigation ability (Janzen, Jansen, & van Turennout, 2008; Wegman & Janzen, 2011), we hypothesized that the intrinsic hippocampal-caudate interaction would positively correlate with SBSOD scores. That is, the positive nature of the hippocampal-caudate interaction would be more prominent in good navigators. Third, if specific association between the hippocampal-caudate interaction and navigation ability exists, to what extent the interaction could predict individual's performance in navigation tasks such as the 3D pointing task in a virtual environment? We predicted that the observed associations would be well replicated with the specific navigation task, and that individual's behavioral performance in the 3D pointing task could be well predicted with the hippocampal-caudate interaction.

Materials and Methods

Participants. One hundred and ninety college students (117 females; mean age = 20.3 years, standard deviation (SD) = 0.91 years) from Beijing Normal University (BNU), Beijing, China, participated in the study. The dataset is part of the Brain Activity Atlas Project (BAA, http://www.brainactivityatlas.org/). All participants had normal or corrected-to-normal vision. The study was approved by the Institutional Review Board of BNU. Written informed consent was obtained from all participants before they took part in the experiment.

All participants (N = 190) underwent the resting-state fMRI scanning and no participant was excluded due to excessive head motion (2 mm in translation or 2 degree in rotation from the first volume in any axis) or visually detected registration errors (X.-z. Kong, Song, Zhen, & Liu, 2015; Zhen et al., 2015). In addition, most of these participants (N = 167; 104 females; mean age = 20.2 years, SD = 0.90 years) participated four behavioral assessments, including a standard questionnaire on general navigation ability in daily life, a computer test on small-scale spatial ability, a Raven task for general ability, and a 3D pointing task in a virtual environment task on a specific navigation performance. Seven participants (2 females) failed to complete the 3D pointing task and were therefore excluded from the corresponding analyses.

MRI scanning. Scanning was conducted at BNU Imaging Center for Brain Research, Beijing, China, on a Siemens 3T scanner (MAGENTOM Trio, a Tim system) with a 12-channel phased-array head coil. Participants were instructed to relax without engaging in any specific task and to remain still with their eyes closed during the scan. The resting-state scan lasted 8 min and consisted of 240 contiguous echo-planar-imaging (EPI) volumes (TR=2000 ms; TE=30 ms; flip angle=90°; number of slices=33; matrix=64 × 64; FOV=200 × 200 mm^2; acquisition voxel size=3.125 × 3.125 × 3.6 mm^3).

High-resolution T1-weighted images were acquired with magnetization prepared gradient echo sequence (MPRAGE: TR/TE/TI=2530/3.39/1100 ms; flip angle=7°; matrix=

256 × 256) for spatial registration. One hundred and twenty-eight contiguous sagittal slices were obtained with 1 × 1 mm^2 in-plane resolution and 1.33-mm slice thickness.

Imaging data analysis: data preprocessing. For each participant, image preprocessing was performed with FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl/). Preprocessing included head motion correction (by aligning each volume to the middle volume of the image with MCFLIRT), spatial smoothing (with a Gaussian kernel of 6-mm full-width half-maximum), intensity normalization, and removal of linear trend. Next, a temporal band-pass filter (0.01–0.1 Hz) was applied with *fslmaths* to reduce low frequency drifts and high-frequency noise.

Registration of each participant's high-resolution anatomical image to a common stereotaxic space (the Montreal Neurological Institute (MNI) 152-brain template with a resolution of 2 × 2 × 2 mm^3, MNI152) was accomplished using a two-step process. Firstly, a 12-degrees-of-freedom linear affine was carried out with FLIRT (Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001). Second, the registration was further refined with FNIRT nonlinear registration (Andersson, Jenkinson, & Smith, 2007). Registration of each participant's functional images to the high-resolution anatomical images was carried out with FLIRT to produce a 6-degrees-of-freedom affine transformation matrix.

To eliminate physiological noise, such as fluctuations caused by motion or cardiac and respiratory cycles, nuisance signals were regressed out using the methods described in previous studies (Biswal et al., 2010; Fox et al., 2005). Nuisance regressors included averaged cerebrospinal fluid signal, averaged white matter signal, global signal averaged across the whole brain, six head realignment parameters obtained by rigid-body head motion correction, and the derivatives of each of these signals. The 4-D residual time series obtained after removing the nuisance covariates were registered to MNI152 standard space by applying the previously calculated transformation matrix.

Imaging data analysis: quality control. Two predefined criteria were used to access the qualities of functional MR images. First, to minimize the artifacts due to motion during scanning, the participants with excessive head motion (greater than 2.0 ° or 2.0 mm throughout the rs-fMRI scan) would be excluded from the further analysis. Second, to minimize the error caused by misalignment of functional and anatomical volumes, the participants with large error of registration would be excluded. Specifically, the registration quality was checked visually by overlaying the normalized volume on the MNI152 template. No participant showed excessive head motion or visually detectable registration errors; that is, no participant was excluded and the data from all participants were included in the following analyses.

Imaging data analysis: ROI selection. Anatomical ROIs of the hippocampus and caudate (in each hemisphere) were derived using the Harvard-Oxford probabilistic atlas that was included with FSL. We defined our ROIs to only include voxels that had 50% or higher probability of being as corresponding anatomical label (left hippocampus: 4016 mm^3; right hippocampus: 4248 mm^3; left caudate: 3328 mm^3; right caudate: 3672 mm^3; Fig. 1). All subsequent analyses were performed separately for these ROIs.

Imaging data analysis: resting-state functional connectivity. After the preprocessing, a continuous time course for each ROI was extracted by averaging the time courses (from resting-state fMRI; 240 TRs; TR = 2000 ms) of all voxels in each of that ROI. Thus, we obtained a time course consisting of 236 data points (removed the first 4 data points) for each ROI and for each participant. Temporal correlation coefficients between the extracted time course from a given ROI and those from other ROIs were calculated to determine which regions were functionally correlated at rest. Correlation coefficients (r) were transformed to Gaussian-distributed z scores via Fisher's transformation to improve normality, and these z scores were then used for further analyses (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006).

Behavioral tests: sense of direction scale. Navigational ability was operationalized as scores on the Santa Barbara Sense of Direction scale (SBSOD) (Hegarty, Richardson, Montello, Lovelace, & Subbiah, 2002), which is a standard test on sense of direction in a large-scale environment, increasingly used as a reliable proxy for actual navigation ability (Janzen, et al., 2008; Wegman & Janzen, 2011). SBSOD consists of 15 items. Example items are "I very easily get lost in a new city" and "I can usually remember a new route after I have traveled it only once". Participants were instructed to indicate the extent to which they agreed or disagreed with each statement in a 5-point Likert-type scale. The total score was used to index one's navigation ability, with higher scores indicating better performance in daily navigation.

Note that previous studies have shown that people have explicit and accurate knowledge on their own navigation ability (Kozlowski & Bryant, 1977; Sholl, 1988; Wolbers & Hegarty, 2010) , and therefore it is not surprising that the scale, which is based on navigation experiences in daily life, has been found highly reliable (test-retest reliability: 0.91). Another reason of choosing the SBSOD is that it can be easily administrated and thus has been widely used as a reliable proxy for real-world navigation performance in a variety of neuroimaging studies (Auger, Mullally, & Maguire, 2012; Epstein, Higgins, & Thompson-Schill, 2005; Janzen, et al., 2008; Wegman et al., 2014; Wegman & Janzen, 2011). For instance, with structural MRI and DTI data, Wegman et al. (2014) have demonstrated that the gray and white matter of the caudate nucleus and medial temporal regions correlates with navigation ability measured by the SBSOD. With task fMRI, the strength of fMRI adaptation effect in the PPA correlates with SBSOD score (Epstein, et al., 2005), and the effect of memory consolidation of landmarks in the hippocampus is observed only in good navigators who are screened by the SBSOD (Janzen, et al., 2008), whereas poor navigators

who are also screened by the SBSOD are less reliable at identifying landmarks with reduced activation in the RSC and anterodorsal thalamus (Auger, et al., 2012). With resting-state fMRI, Wegman and Janzen (2011) have demonstrated that the functional connectivity at rest between the PHG and the hippocampus/caudate is related to participants' navigational ability measured by the SBSOD. Taken together, the SBSOD is valid to be used as a proxy of real-world navigation performance in neuroimaging studies.

Behavioral tests: Raven's advanced progressive matrices (RAPM). To eliminate the possible influence of the general ability on the relationship between navigation ability and the intrinsic interaction connectivity of interest, individual's general intelligence was measured using the standard RAPM (Raven, 1995). The number of correct responses to the test items of RAPM was used to index intelligence for this study.

Behavioral tests: mental rotation task (MRT). To investigate the navigation-specific nature of the observed brain-behavior association, we also measured individual's small-scale spatial ability. Participants were administered the MRT (Shepard & Metzler, 1971), consisting of 40 trials. Each trial started with a blank screen for 0.5 s, followed by the first cube stimulus presented at the center of the screen. The three-dimensional asymmetrical assemblages of cube image were presented for 0.7s. After an ISI of 0.5 s, the second stimulus appeared for the same duration as the first one, with the viewpoint being changed. Subjects were instructed to indicate whether the second stimulus was the first one rotated or another stimulus as quickly as possible. Participants were given 3 min to finish all 40 trials, including 20 trials for 'rotated' condition and 20 for 'another' condition. The accuracy was used to index individual's mental rotation ability.

Behavioral tests: 3D pointing task. An objective measure of navigation ability was measured with a 3D pointing task in virtual mazes (Lawton & Morrin, 1999). Mazes were created using Unity3D, which was used to present and control the experiment as well. Each maze consisted of a series of hallways of equal length and uniform texture and color (Fig. 4A, 4B). There was only one path that could be taken through each maze. No landmarks were present in the hallways, except for two words 'Start' and 'Finish' on the start and end of the pathway respectively. The point of view while moving through the mazes was approximately eye-level.

Mazes consisted of either one turn, two turns, four turns, or six turns. All turns were right angles (90º). There were two variations of the one-turn maze (either a right-hand turn or left-hand turn), which were used as practice mazes, and four variations of each of the two-, four-, and six-turn mazes used in experimental trials. These mazes were configured such that there were no more than two consecutive turns in the same direction (i.e., no loop). There were a total of 24 mazes, consisting of a set of 12 mazes repeated twice but in a different order. Each set of 12 mazes contained four blocks of mazes, each block consisting of a different two-turn, four-turn, and six-turn maze, randomly ordered.

Participants were first given practice on the computer pointing task using the two one-turn mazes. Movement through the mazes was controlled by the computer with same speed (5 s per maze hallway). Participants controlled view direction at the end of the mazes using the computer mouse to pointing the start point. In practice trials, feedback would be given about the accuracy of their responses. Then, participants continued with the 24 experimental mazes and were given no feedback on these mazes. Participants were asked not to draw out a map of the mazes. Pointing error scores were computed as the absolute difference between the participant's answer and the correct answer, with error scores up to 180º possible in either direction.

To rule out the possible influence of video game playing, participants were also asked to rate the frequency with which they have played the video games requiring navigation through an environment on a 5-point scale, ranging from *Not at All Frequently* to *Very Frequently*.

Statistical analyses: Hippocampal-caudate functional connectivity correlates with spatial navigation ability. To investigate the association between the intrinsic hippocampal-caudate interaction and navigation ability, we performed partial correlation analyses between navigation ability measured by SBSOD and the functional connectivity between the hippocampus and caudate, with age and sex controlled. Spearman correlation analysis was also performed to confirm the correlations observed. In this study, we investigated both the ipsilateral and contralateral connectivity between the hippocampus and caudate, including the connectivity between left hippocampus and left caudate (HippL-CaudL), connectivity between right hippocampus and right caudate (HippR-CaudR), connectivity between left hippocampus and right caudate (HippL-CauR), and connectivity between right hippocampus and left caudate (HippR-CaudL). False Discovery Rate (FDR) correction for multiple comparisons (as described in (Huang, Kong, Zhen, & Liu, 2013), see also (Hastie et al., 2009)) was used to control the false positive rate. Associations with a corrected p value of < 0.05 were considered statistically significant.

Further, we investigated the directionality (i.e., positive or negative nature) of the resting-state functional connectivity between hippocampal and caudate in good and poor navigators. We first divided the participants into good (N = 81) and poor (N = 86) navigator groups using a mediation split (median SBSOD = 47), and then conducted one-sample t-test analysis on the hippocampal-caudate functional connectivity separately for each group.

Statistical analyses: seed-based functional connectivity between hippocampal subfields and caudate correlates with navigation ability. Given both the hippocampus and caudate are anatomically and functionally heterogeneous (Gilbert, Kesner, & Lee, 2001; Robinson et al., 2012; Yassa & Stark, 2011), we further conducted seed-based voxel-wise functional connectivity analyses to investigate the observed brain-behavior association. Specifically, the hippocampus subfields, including CA1, CA2/3, CA4/DG, presubiculum, subiculum, fimbria and the hippocampal fissure, were defined using a new automated

procedure (Van Leemput et al., 2009) based individual's T1-weighted MRI data. Segmentation results were visually inspected for errors in all datasets, and no manual edits were done. Since the procedure was based on a probabilistic model, a 50% threshold was used to define the hippocampal subfield ROIs to ensure that there was no overlap between the ROIs. Then, a continuous time course for each ROI was extracted by averaging the time courses of all voxels in each of that ROI. For each voxel within the caudate, the functional connectivity with each hippocampal subfield ROI was calculated with a Pearson correlation analysis followed by a Fisher's transformation. We conducted voxel-based multiple regression with SBSOD score as the independent variable. The confounding variables (i.e., age and sex) were controlled as mentioned above. We used a stringent threshold of $p < 0.05$ family-wise error (FEW) corrected for multiple comparisons.

Statistical analyses: Hippocampal-caudate functional connectivity predicts individual's performance in the 3D pointing task. To investigate whether the hippocampal-caudate functional connectivity at rest could predict individual's performance in specific navigationally-relevant tasks, we conducted a 3D pointing task, in which participants were asked to point to the starting point of the route just taken at the end of a maze (see *Behavioral tests*). Initially, to replicate the brain-behavior association found with SBSOD, partial correlation analyses were performed between pointing error and the resting-state functional connectivity between the hippocampus and caudate, with age, sex and game playing frequency. The game playing frequency was controlled to rule out the possible influence of video game playing on the 3D task performance. In addition, given that we has a priori hypotheses about the direction of the correlation (as shown below), we used one-tail significance threshold $p < 0.05$. Moreover, to estimate to what extent these hippocampal-caudate interactions together could predict individual's performance in the pointing task, we used support vector regression (SVR) and leave-one-out cross-validation (LOOCV) procedure. The Pearson correlation coefficient between observed performance and the predicted score was calculated to provide measure of prediction accuracy.

Results

Resting-state interaction between the hippocampus and the caudate. We found that the hippocampus showed predominantly positive functional connectivity with the caudate in both hemispheres (HippL-CaudL: 0.08 ± 0.017, $t(189) = 4.66$, $p < 0.001$; HippR-CaudR: 0.05 ± 0.015, $t(189) = 3.01$, $p = 0.003$) (Fig. 1B). The positive functional connectivity suggested a cooperative functional relationship at rest (though the strength was relatively weak; see below for more discussion). Although the present study mainly focused on the hippocampal-caudate interactions in ipsilateral hemisphere, we included the hippocampal-caudate interactions between contralateral regions in this study. We found the left hippocampus showed positive functional connectivity with the right caudate (HippL-CauR: 0.05 ± 0.016, $t(189) = 3.20$, $p = 0.002$), while the functional connectivity between the right hippocampus and left caudate only showed a weak positive trend but no significant difference from zeros (HippR-CaudL: 0.02 ± 0.017, $t(189) = 1.30$, $p = 0.20$) (Fig. 1B). No sex difference was found (ps > 0.50).

Hippocampal-caudate interaction correlates with navigation ability. Next, we investigated whether individuals with higher hippocampal-caudate connectivity at rest reflected individual variability in navigation ability.

To link the intrinsic hippocampal-caudate interaction to human navigation, we measured individual's general navigation ability with the SBSOD. As expected, navigation score showed wide variability (from 27 to 74; 48.72 ± 9.55) across participants (X. Z. Kong et al., 2016). Consistent with previous studies (Astur, Ortiz, & Sutherland, 1998; X.-z. Kong et al., submitted; Moffata, Hampsona, & Hatzipantelisa, 1998), males showed significantly higher scores than females ($t(165) = 2.69$; $p = 0.008$), suggesting better navigation ability in males on average. Further, we conducted correlation analyses between navigation ability and the functional connectivity between hippocampus and caudate, controlling for sex and age.

Results showed that both ipsilateral and contralateral hippocampal-caudate interaction showed significantly positive correlation with individual's navigation ability (Fig. 2; HippL-CaudL: $r = 0.25$, $p = 0.001$; HippR-CaudR: $r = 0.19$, $p = 0.014$; HippL-CaudR: $r = 0.22$, $p = 0.004$; HippR-CaudL: $r = 0.24$, $p = 0.002$). These results were confirmed with Spearman correlation analysis (HippL-CaudL: *rho* = 0.26, $p = 0.001$; HippR-CaudR: *rho* = 0.17, $p = 0.027$; HippL-CaudR: *rho* = 0.23, $p = 0.003$; HippR-CaudL: *rho* = 0.26, $p = 0.001$). That is, individuals with higher hippocampal-caudate interaction tend to possess better navigation ability, suggesting that the hippocampal-caudate interaction at rest would benefit individual's daily navigation.

Based on these findings, we further evaluated the directionality of the functional connectivity values by dividing the subjects into good (N = 81) and poor (N = 86) navigator groups using a mediation split (median SBSOD = 47). Results showed that the good navigator group, as expected, had positive functional connectivity between the hippocampus and the ipsilateral caudate (Hipp_L-Caud_L: $t(80) = 5.56$, $p < 0.001$; Hipp_R-Caud_R: $t(80) = 3.58$, $p = 0.001$), whereas the poor navigator group did not show the relationship (Hipp_L-Caud_L: $t(85) = 0.46$, $p = 0.65$; Hipp_R-Caud_R: $t(85) = -0.35$, $p = 0.731$) (Fig. 3). Similarly, the good navigator group showed positive functional connectivity between the hippocampus and the contralateral caudate (Hipp_L-Caud_R: $t(80) = 5.11$, $p < 0.001$; Hipp_R-Caud_L: $t(80) = 2.75$, $p = 0.007$), whereas the poor navigator group did not show the relationship (Hipp_L-Caud_R: $t(85) = -0.64$, $p = 0.525$; Hipp_R-Caud_L: $t(85) = -0.17$, $p = 0.098$) (Fig. 3). Hence, the positive interaction between the hippocampus and caudate was more prominent in good navigators, which suggests a positive link between the hippocampal-caudate interaction and navigation ability.

Navigation-specific nature of the findings. The hippocampus and caudate have been implicated as the cores of two systems of spatial representation underlying navigation. Next, we hypothesized that the associations between the hippocampal-caudate interaction and

behavioral variability would show a navigation-specific nature. To test our hypothesis, we conducted further analyses.

First, to investigate the navigation-specific nature of the observed brain-behavior association, we asked whether the hippocampal-caudate interaction was related to non-navigation performance, including general ability and small-scale spatial ability. First, to rule out the possibility that general ability contributed to the observed associations, we measured individual's general intelligence using the standard RAPM (Raven, 1995). We found that when the general intelligence was controlled, the observed associations remained significant (HippL-CaudL: $r = 0.25$, $p = 0.002$; HippR-CaudR: $r = 0.19$, $p = 0.015$; HippL-CaudR: $r = 0.22$, $p = 0.004$; HippR-CaudL: $r = 0.23$, $p = 0.003$), suggesting the observed associations were independent to general ability. Second, to further investigate the specificity of the observed associations, we measured individual's small-scale spatial ability with MRT and found no significant correlations between small-scale spatial ability and the hippocampal-caudate interactions in the HippR-CaudR ($r = 0.09$, $p = 0.230$), HippL-CaudL ($r = 0.13$, $p = 0.088$) and the HippR-CaudL ($r = 0.06$, $p = 0.412$). Although interaction in the HippL-CaudR showed a significant correlation with small-scale spatial ability ($r = 0.17$, $p = 0.023$), when the small-scale ability was controlled, the observed associations between navigation ability and hippocampal-caudate interactions remained significant ($r = 0.21$, $p = 0.006$). In sum, these findings suggest that the associations are specific to large-scale spatial ability (i.e, navigation ability).

Furthermore, as a control experiment for neural specificity, we conducted similar correlation analysis with functional connectivity between contralateral regions for the hippocampus and the caudate separately. We found that functional connectivity between contralateral analogs for either the hippocampus ($r = 0.02$, $p = 0.757$) or caudate ($r = -0.09$, $p = 0.246$) showed no correlation with navigation ability, suggesting the neural specificity of the observed associations between navigation and the hippocampal-caudate interaction.

Finally, given both the hippocampus and caudate are anatomically and functionally heterogeneous (Gilbert, et al., 2001; Robinson, et al., 2012; Yassa & Stark, 2011), we further

conducted seed-based functional connectivity analyses with hippocampal subfields as seeds. These seeds, including CA1, CA2/3, CA4/DG, presubiculum, subiculum, fimbria and the hippocampal fissure (Fig. 4A), were defined using a new automated procedure (Van Leemput, et al., 2009) based individual's T1-weighted MRI data. The results showed that resting-state functional connectivity of all hippocampal subfields with the caudate showed similar correlation with navigation ability, and in caudate it was mainly the dorsal medial caudate contributing to this association (Fig. 5).

Taken together, these findings showed a considerable navigation-specific nature of the association between the hippocampal-caudate interaction and spatial navigation, suggesting a critical role of this intrinsic interaction in supporting people's navigation.

Hippocampal-caudate interaction predicts pointing performance in the 3D pointing task. Based on these findings, we asked that whether the hippocampal-caudate interaction would predict individual's behavioral performance in out-of-scanner navigation task. Here, we used a pointing task in a virtual environment (Fig. 6A, 6B). As expected, the pointing error showed significant correlation with self-reported navigation ability (Fig. 6C: r = -0.22, p = 0.010). Similarly, males showed significantly smaller pointing error than female ($t(158)$ = -5.14, $p < 0.001$). To rule out the possible influence of video game playing, participants were also asked to rate the frequency with which they played the video games requiring navigation through an environment. The mean self-rating of experience with video games was significantly lower for women (M = 1.47, SD = 0.77) than for men (M = 2.41, SD = 1.02), $t(154) = 6.48$, $p < 0.001$. A simple correlation analysis showed that higher video game experience was associated with lower overall pointing error in the experimental mazes, r = -0.31, $p < 0.001$. Thus, video game experience, as well as sex and age, were controlled in the following analyses. Initially, we conducted correlation analyses between hippocampal-caudate interaction and pointing error, and found significant correlations in both ipsilateral and contralateral hippocampal-caudate interaction (Fig. 7) (HippL-CaudL: r = -0.20, p = 0.010; HippR-CaudR: r = -0.15, p = 0.039; HippL-CaudR: r = -0.18, p = 0.017;

HippR-CaudL: r = -0.22, p = 0.005), which replicated our findings above. Moreover, we used SVR and LOOCV procedure to predict individual's performance in the 3D pointing task based on these hippocampal-caudate interactions. As is shown in Fig. 8, the correlation between predicted and actual scores was 0.38 ($p < 0.001$), indicating that individual's navigation performance could be well predicted using the measures of hippocampal-caudate interaction at rest.

Discussion

In sum, we investigated the intrinsic interaction between the hippocampus and caudate with resting-state fMRI, and confirmed its behavioral importance in human navigation. Specifically, we found predominantly positive functional connectivity between the hippocampus and caudate (in particular in good navigators), suggesting a cooperative interaction between two systems of spatial representation underlying navigation. Moreover, we found that the strength of the intrinsic hippocampal-caudate interaction was positively correlated with people's general navigation ability measured with SBSOD, and that the observed associations could not be accounted for by non-navigation abilities (e.g., general ability and small-scale spatial ability), which suggests a navigation-specific nature. Finally, we found that the observed brain-behavioral associations could be replicated with a 3D pointing task in virtual reality, and more importantly, prediction analysis with machine learning algorithm and a cross-validation procedure showed that the specific navigation performance for each individual could be well predicted using the hippocampal-caudate interaction measures. Our findings support the hypothesis that in human the hippocampus and caudate interact in a cooperative manner to support flexible navigation.

Our findings advanced previous studies linking the two spatial representation systems (i.e., the allocentric and egocentric systems) to spatial navigation. As a complex cognitive process, flexible navigation relies on proper coupling between multiple brain regions including the hippocampus and the caudate. Though these two systems function differently

in navigation (Cook & Kesner, 1988; Morris, et al., 1982) as discussed in Introduction, the cooperative interaction between them has been strongly highlighted for its behavioral significance during navigation tasks (Brown, et al., 2012; Rice, et al., 2015; Voermans, et al., 2004). For example, in patients with Huntington's disease, the hippocampus compensates for gradual caudate dysfunction with a gradual activity increase during route recognition to maintaining normal behavior (Voermans, et al., 2004). Our results advanced our understanding of the hippocampal-caudate interaction in the following senses. First, with a large dataset of resting-state fMRI, we investigated the intrinsic interaction between the hippocampus and the caudate without any task modulation. To the best of our knowledge, this study is the first report of a positive interaction between the hippocampus and caudate at rest, which suggested intrinsic cooperative dynamics of two systems underlying navigation. Second, the cooperative interaction was further supported by the findings that the hippocampal-caudate functional connectivity varies as a function of both general navigation ability (measured by the SBSOD) and specific navigation performance (measured by the 3D pointing task), showing the behavioral importance in supporting human navigation of the hippocampal-caudate interaction. Finally, our findings that the intrinsic interactions of interest predicted each individual's performance in the out-of-scanner pointing task, suggest that the interaction between the hippocampus and caudate would be intrinsically involved in shaping human navigation behaviors. That is, the hippocampal-caudate interaction not only benefits human navigation during navigation (Brown, et al., 2012), but also cooperatively prepares for upcoming navigation tasks.

There are also studies suggesting a competitive interaction between the hippocampus and caudate, one or the other being optimal for specific tasks. For example, with task fMRI, a previous study has identified a caudate region whose activity was negatively correlation with the medial temporal regions, including the hippocampus, suggesting a negative relationship between these structures (Poldrack et al., 2001). In addition, a recent structural study has

showed that the gray matter in the hippocampus was negatively correlated to the gray matter in the caudate nucleus, suggesting a competitive interaction between these two brain areas (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007). There is also evidence from animal studies (Eichenbaum, Fagan, Mathews, & Cohen, 1988; Packard, 1999) showing that the hippocampus and caudate acquire different types of information during learning: the hippocampus appears to acquire spatial relationships whereas the caudate acquires stimulus-response associations. This proposed competition between hippocampus and caudate may reflect an adaptive mechanism for optimizing behavior depending upon task demands (Poldrack, et al., 2001). It's important to note that this does not contradict our findings. Unlike these studies, the present study examined the hippocampal-caudate interaction with individual resting-state fMRI data, which allows us to explore inter-regional interaction within each individual and independent to any specific task. Human navigation is a complex behavior and engages interactions of multiple processes. Thus, together with the different roles of these two systems in navigation (Doeller, et al., 2008; Hartley, et al., 2003), out findings suggest that the cooperative interaction between hippocampus and caudate may reflect the intrinsic flexibility to switch navigation strategies according to the external environment which would do benefit for accurate navigation. This conjecture is largely supported by the positive functional connectivity between the hippocampus and caudate (in particular in good navigators), and the positive association between the intrinsic hippocampal-caudate interaction and navigation performance. Our findings also coincide with previous neurophysiological evidence (Voermans, et al., 2004) that the hippocampus compensates for the functional degradation of the caudate to maintain normal behavior in

route recognition. Taken together, our findings provide novel evidence for cooperative contribution of the hippocampal-caudate interaction to human navigation.

Note that the strength of the functional connectivity of interest was relatively weak (~ 0.10). However, the weak connections could reliably predict individual differences in behavioral performance, suggesting a critical functional role of weak connections in human brain. Previous brain network studies have generally focused on strong connectivity patterns (e.g., top 5% connections or connections larger than 0.20), for both diagnostic purposes (Bassett et al., 2008; Wang, Wang, He, Yu, & Wang, 2015), and the understanding of the organization (Achard, Salvador, Whitcher, Suckling, & Bullmore, 2006; Sporns & Zwi, 2004) and developmental trajectories (Cao et al., 2014; Meunier, Achard, Morcom, & Bullmore, 2009) of human brain. In most of previous studies, weak connections are usually considered spurious and assigned a value of zero, resulting in the fact that the role of weak connections has remained obscure for years. This is somehow surprising, given that the relevance of weak connections in other complex systems had already been stressed many years ago. For instance, Granovertter (1973) has pointed out the importance of weak relationships (edges) between members (nodes) in complex social networks, for the maintenance of overall system dynamics, and the spreading of new ideas and information (Granovetter, 1973). Only recently, new evidence has suggested that weak connections may be a useful marker for general cognitive functioning (Santarnecchi, Galli, Polizzotto, Rossi, & Rossi, 2014) and specific pathological conditions (Bassett, Nelson, Mueller, Camchong, & Lim, 2012). Our findings provide strong support for the hypothesis that weak connectivity reflects meaningful individual differences rather than simply a technical artifact, which could have substantial implications for functional connectivity study. This could also put forward the need to characterize the functional properties and dynamics of both weak and strong connections in order to obtain a comprehensive understanding of their role in considerable individual variability.

The exact mechanism underlying the observed hippocampus-caudate interaction during rest and its role in human spatial navigation is not clear yet. Previous studies suggest that the hippocampus and caudate do not share direct anatomical connections, but the medial prefrontal cortex (MPFC) receives direct projections from the hippocampus and sends direct projections to the medial caudate nucleus (Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinoso-Suarez, 2000; Haber, Kim, Mailly, & Calzavara, 2006; Roberts et al., 2007). A recent study suggests that MPFC might internally simulate alternative strategies (Schuck et al., 2015), and in navigation researches, the MPFC has been suggested as a coordinator between striatal and hippocampal systems in rodents (Killcross & Coutureau, 2003) and humans (Doeller, et al., 2008). Further studies are needed to reveal the exact role of the MPFC in the hippocampus-caudate interaction. In addition, both genetic and environmental factors could contribute to the considerable individual differences in the hippocampal-caudate interaction. On the one hand, genetic factors predispose individual differences in the spontaneous brain function (Glahn et al., 2010) including the hippocampal-caudate interaction and in the task-evoked activity related to human navigation (X.-z. Kong, et al., 2015). On the other hand, environmental factors such as acquired experience may be critical to reinforce these differences (Maguire et al., 2000; Woolley et al., 2015). Better navigation ability may reflect more navigation experience, which may boost the functional synchronization between the hippocampus and caudate. This could be supported by greater functional connectivity between the hippocampus and the caudate revealed when participant uses contextual information to aim navigation (Brown, et al., 2012). Finally, regardless of the mechanism or pathway(s) involved, our results indicate that the two memory systems interact cooperatively during rest, and that this interaction shapes individual's navigation ability. The exact underlying physiological, genetic, and developmental mechanisms of the relation will be an important topic for further studies.

In sum, our findings provide first evidence for cooperative interaction of the hippocampus and caudate during rest, and its critical role in human navigation. Further research is needed to examine the dynamics of this interaction in response to different spatial

tasks (e.g., spatial encoding and retrieval) and early development. Moreover, spatial navigation impairment is associated with both normal aging (Gazova et al., 2012) and different psychiatric disorders, such as mild cognitive impairment (MCI) (Delpolyi, Rankin, Mucke, Miller, & Gorno-Tempini, 2007; Hort et al., 2007) and Alzheimer's disease (AD) (Lithfous, Dufour, & Despres, 2013). Previous studies have linked the deficit to some structural and/or functional alteration of the hippocampus and caudate (Chetelat et al., 2002; Dai et al., 2009; Rombouts, Barkhof, Witter, & Scheltens, 2000). Systematic studies on the dynamic interaction between related structures would help us identify the previously ignored impact from altered inter-regional interaction, thus advance our understanding of the neural mechanisms underlying normal aging and psychiatric disorders. Finally, given the complex nature of human navigation, functional connectivity analysis of whole brain and/or multiple navigation-related regions would lead to better understanding of the dynamic interactions between multiple systems in spatial navigation.

Acknowledgments

This study was funded by the National Natural Science Foundation of China (31230031), the National Basic Research Program of China (2014CB846101), the National Natural Science Foundation of China (31221003, 31471067 and 31470055), the National Social Science Foundation of China (13&ZD073, 14ZDB160), and Changjiang Scholars Programme of China.

Author Contributions

X.K., Y.P. and J.L. conceived and designed the experiments, X.K., X.W, and Z.Z conducted the experiments, X.K., Y.P. and X.W. analyzed the data, X.K., Y.P., S.X., X.H., and J.L. wrote the paper.

Competing Financial Interests

The authors declare no competing financial interests.

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Figure Legends

Fig. 1. Functional connectivity between the hippocampus and caudate. (A) Anatomical ROIs of the hippocampus and caudate (in each hemisphere). Yellow: Hippocampus; Blue: Caudate. (B) Functional connectivity between the hippocampus and caudate in both ipsilateral and contralateral hemispheres revealed with resting-state fMRI. Error bars represent ± standard error of the mean (SEM). HippR-CaudR/ HippL-CaudL, functional connectivity between the hippocampus and caudate in the same hemispheres; HippR-CaudL/ HippL_CaudR, functional connectivity between the hippocampus and caudate in the different hemispheres; R, right; L, left. ** $p < 0.01$, *** $p < 0.001$.

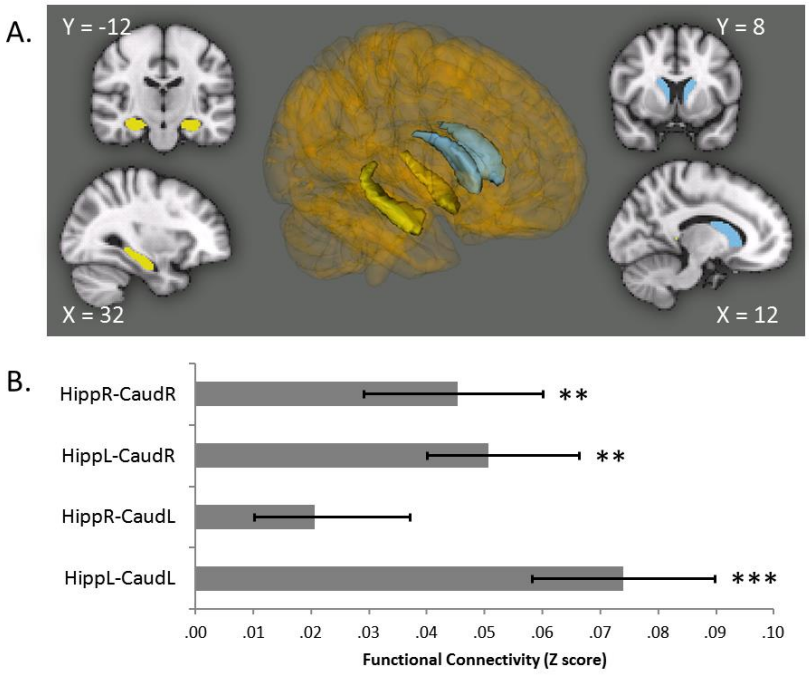

Fig. 2. Correlations between the hippocampal-caudate functional connectivity and navigation ability measured with SBSOD. Shaded regions depict 95% confidence intervals. HippR-CaudR/ HippL-CaudL, functional connectivity between the hippocampus and caudate in the same hemispheres; HippR-CaudL/ HippL_CaudR, functional connectivity between the hippocampus and caudate in the different hemispheres; R, right; L, left. ** $p < 0.001$; *** $p < 0.001$.

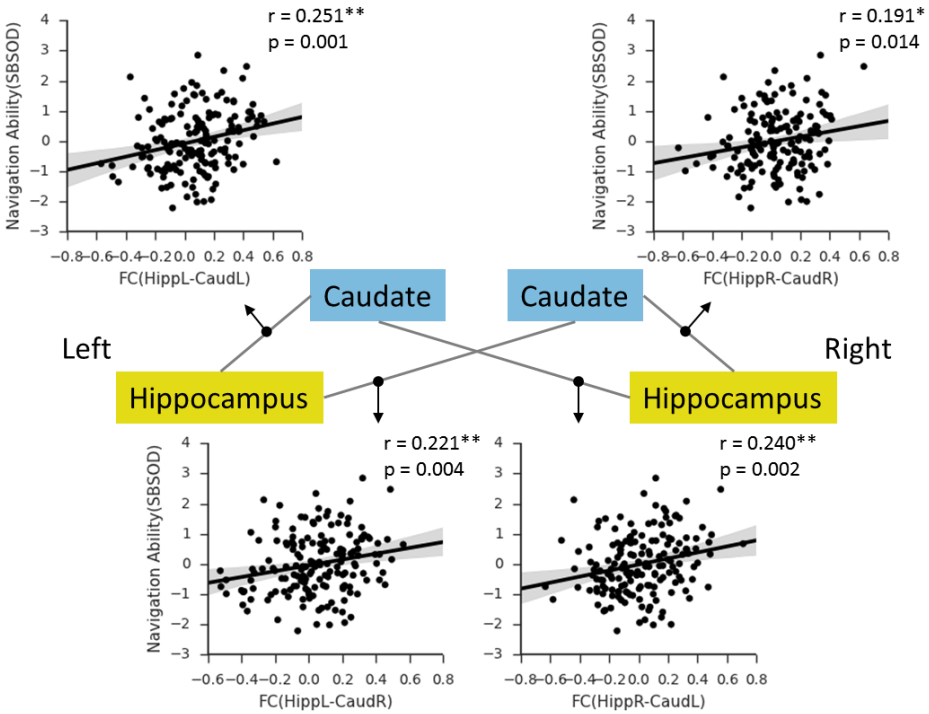

Fig. 3. Functional connectivity between the hippocampus and caudate in good navigators and poor navigators. HippR-CaudR/ HippL-CaudL, functional connectivity between the hippocampus and caudate in the same hemispheres; HippR-CaudL/ HippL_CaudR, functional connectivity between the hippocampus and caudate in the different hemispheres; R, right; L, left. $^{+}$ $p < 0.10$; ** $p < 0.01$; *** $p < 0.001$.

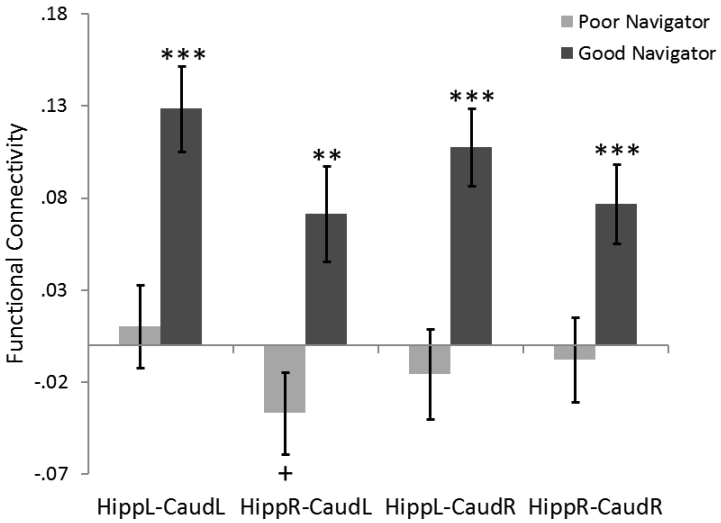

Fig. 4. Anatomical ROIs of hippocampal subfields and caudate for seed-based analysis.

(A) The hippocampus segmentation for one subject superimposed on the subject's T1-weighted scan in coronal view. (B). Region boundary of the ROI of caudate (blue) in sagittal and axial views, respectively and the region reference for Fig. 5 (gray).

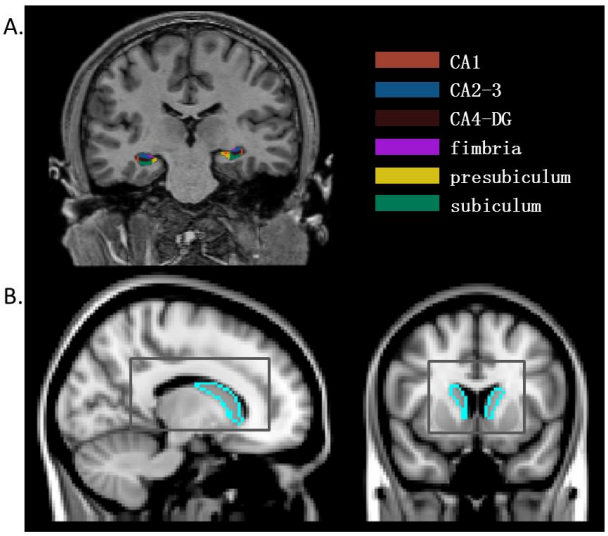

Fig. 5. Association between navigation ability and seed-based functional connectivity in the caudate with each hippocampal subfield. The first six columns show the association results ($p < 0.05$, FWE-corrected) with CA1, CA2-3, CA4-DG, fimbria, presubiculum and subiculum, respectively. The last column shows the conjunction map of these associations.

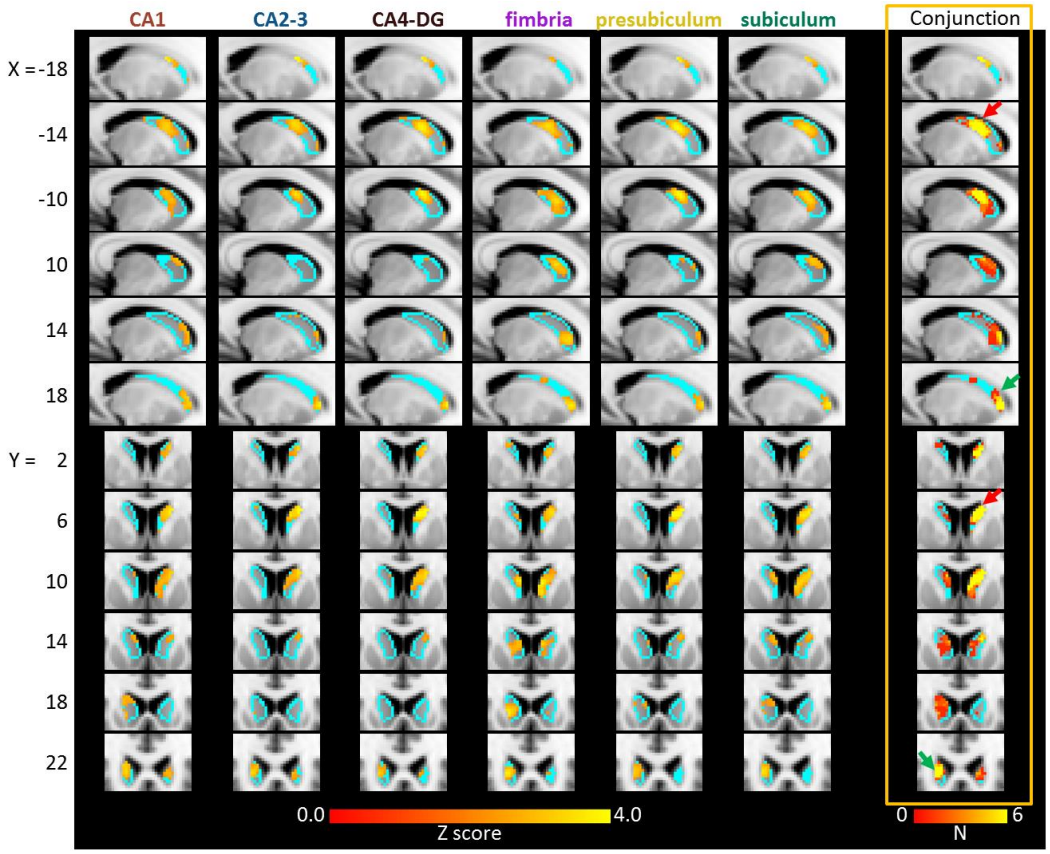

Fig. 6. The 3D pointing task. (A) Screenshots from the task in the virtual environment, and (B) exemplar routes used in this study. (C) Correlation between pointing error in this task and navigation ability measured with SBSOD. Shaded regions depict 95% confidence intervals. * $p < 0.05$.

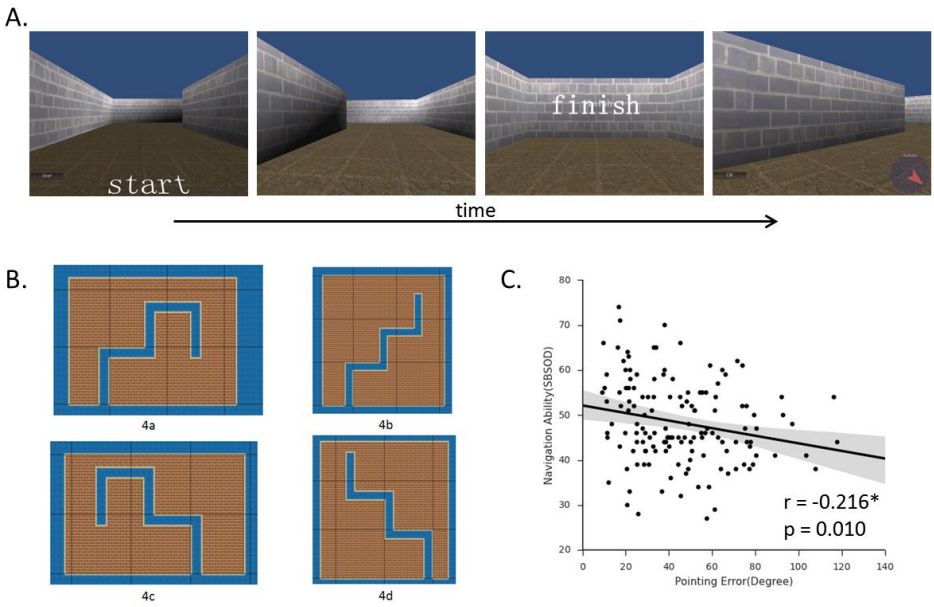

Fig. 7. Correlations between the hippocampal-caudate functional connectivity and pointing error measured with 3D pointing task. Shaded regions depict 95% confidence intervals. HippR-CaudR/ HippL-CaudL, functional connectivity between the hippocampus and caudate in the same hemispheres; HippR-CaudL/ HippL_CaudR, functional connectivity between the hippocampus and caudate in the different hemispheres; R, right; L, left. * $p < 0.05$; ** $p < 0.01$

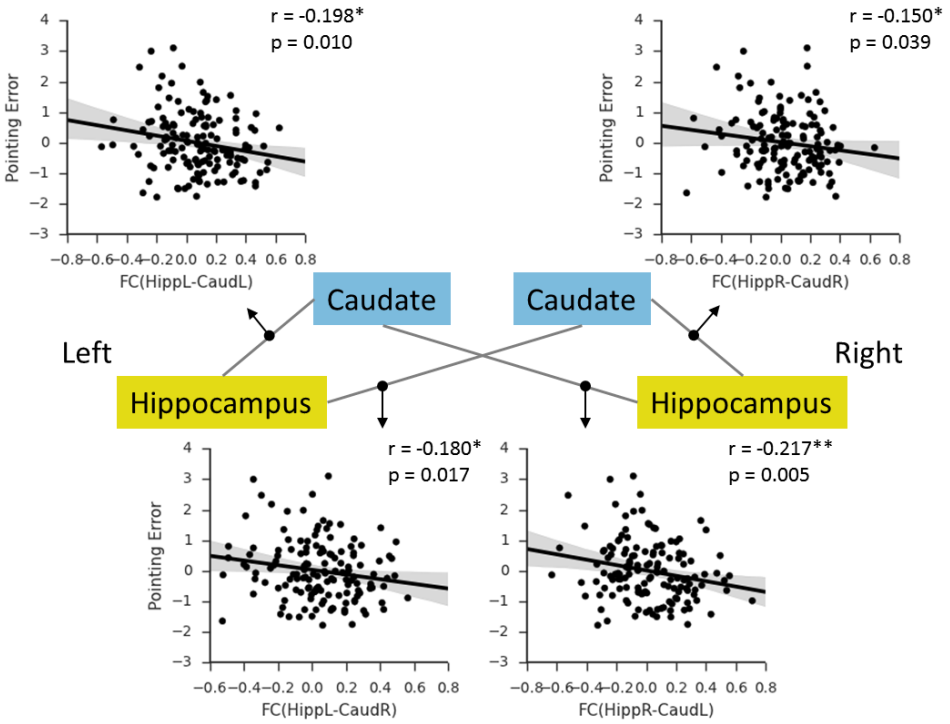

Fig. 8. Scatterplot represents the linear association between predicted pointing error and actual pointing error. Shaded regions depict 95% confidence intervals. *** $p < 0.001$.