

## RAPID COMMUNICATION

## Navigational Skills Correlate With Hippocampal Fractional Anisotropy in Humans

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**ABSTRACT:** Individuals vary widely in their ability to orient within the environment. We used diffusion tensor imaging to investigate whether this ability, as measured by navigational performance in a virtual environment, correlates with the anatomic structural properties of the hippocampus, i.e., fractional anisotropy. We found that individuals with high fractional anisotropy in the right hippocampus are (a) faster in forming a cognitive map of the environment, and (b) more efficient in using this map for the purpose of orientation, than individuals with low fractional anisotropy. These results are consistent with the role of the hippocampus in navigation, and suggest that its microstructural properties may contribute to the intersubject variability observed in spatial orientation. © 2008 Wiley-Liss, Inc.

**KEY WORDS:** hippocampus; diffusion tensor imaging; topographical orientation; virtual environment; cognitive map

### INTRODUCTION

Evidence from human and non-human animals (O'Keefe and Nadel, 1978; Mellet et al., 2000) has shown that successful orientation within familiar and unfamiliar surroundings relies on a mental representation of the environment, namely a cognitive map (Tolman, 1948). The cognitive map includes the environmental landmarks and their spatial relationships, and allows individuals to reach any target location by any one of a number of routes available within the environment (Maguire et al., 1998; Iaria et al., 2003). Thus, the use of a cognitive map is critical for orientation allowing an efficient navigation irrespective of the individuals' actual spatial location (O'Keefe and Nadel, 1978).

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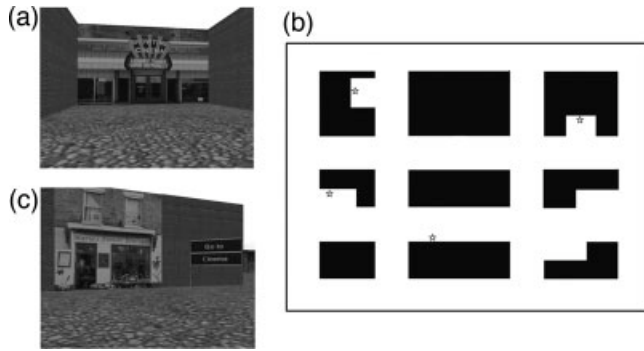
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In accordance with evidence from pioneer experiments in rodents (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978) and human neuropsychological studies (Bohbot et al., 2004), we recently reported that the hippocampus plays a fundamental role during both the formation and subsequent use of a cognitive map in humans (Iaria et al., 2007). However, although all normal human subjects possess this anatomical structure, individuals vary widely in their ability to orient within the environment (Ohnishi et al., 2006). The reasons for this normal variability remain unknown. It is possible that at least some of this normal variation reflects individual differences in the neuroanatomic structures involved in navigation and environmental orientation. If so, an "individual differences" approach might be used to examine whether anatomic indices vary with behavioral indices of navigational ability.

In this study, we used diffusion tensor imaging (DTI) (Basser et al., 1994) and a behavioral navigational test (Iaria et al., 2007) to examine the hypothesis that the structural integrity of the hippocampus, as expressed by fractional anisotropy (FA), correlates with the individuals' ability to form and use a cognitive map of the environment. DTI is a recent magnetic resonance imaging (MRI) technique used to explore and characterize the structure of the brain tissues in vivo by quantifying the diffusion of water molecules along a sampled axis. Diffusion within each voxel is characterized by a diffusion tensor and the FA is a scalar index representing the diffusion anisotropy for that voxel. Anisotropies indicate a deviation from the normally random distribution of the direction of diffusion, and thus reflect microstructural properties of neural elements (particularly axons) that impart order and organization within given brain regions. FA values range between zero and +1, where values nearer +1 reflect high anisotropy, thus confirming integrity of the tissue.

We asked 12 healthy participants to undergo MRI scanning for the acquisition of DTI data, and then to perform a computerized navigational test using a virtual environment. This navigational test was designed to quantify individuals' orientation skills for both the



**FIGURE 1.** The figure displays a view of one of the landmarks available within the environment (a), and the structure of the virtual city in which the participants performed both the learning and the retrieval tasks (b). On the map (b), \* indicates the locations of the four landmarks; the same map, but with no indications of landmarks' locations, was used to assess individuals' formation of the cognitive map. The figure also shows a view of the participants' starting position while performing one trial of the retrieval task (c): in this example, subjects were asked to reach the cinema (target location) from the flower shop (starting position).

formation and subsequent use of a cognitive map (Iaria et al., 2007): hence it consisted of two tasks, a learning and a retrieval task (Fig. 1). In the learning task participants were required to navigate within the environment to form a mental representation of it (i.e., a cognitive map) including the landmarks and their spatial relationships. The degree of success in forming the cognitive map was assessed by asking the subjects to report on a survey-map the location of each landmark. After the cognitive map was formed, participants were given the retrieval task. This consisted of 12 trials: in each trial, participants started facing a landmark and a sign that indicated the target location that they needed to reach, and were asked to reach the target location as quick as possible by following the shortest pathway. Since both target place and starting location varied across trials, the use of the cognitive map was the only way to solve the task. The time that the participants spent to solve the learning and retrieval tasks were taken to be measures of the individuals' ability to form and use a cognitive map, respectively.

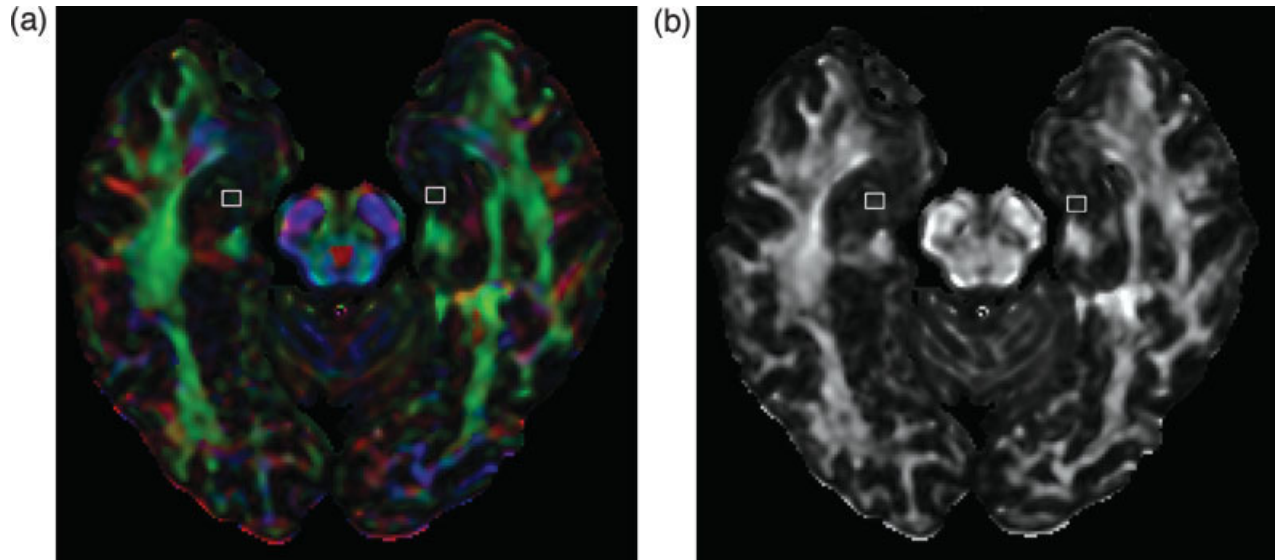
The DTI images were processed offline using DTIstudioV2 software (Johns Hopkins University, Baltimore, MD) to create FA and color-coded directionality maps of diffusion. For each participant, regions of interest (ROI) were drawn bilaterally on the axial slices (Fig. 2), based on the identification of the hippocampi on the structural images. In each hemisphere, the hippocampal ROI included two areas in the anterior and posterior gray matter regions, respectively. Hippocampal FA values resulted from the average of these two regions in each hemisphere. This approach has been adopted in several studies assessing hippocampal abnormalities in different clinical populations (Assaf et al., 2003; Chen et al., 2007; Manoach et al., 2007), and it has been recently shown to be a reliable technique to assess the structural integrity of the hippocampus (Muller et al., 2006). It should be noted, however, that the diffusion tensor model (Basser et al., 1994) provides an estimate

of overall diffusion within the voxel but does not explicitly describe complex tissue organization where multiple fiber directions are present within a voxel. Nevertheless, this model provides useful insights regarding the in vivo structural organization of the brain, and FA has been used to investigate correlations between behavioral performance and anisotropic diffusion in various cognitive domains (Klingberg et al., 2000; Tuch et al., 2005).

We correlated the FA values of the right and left hippocampus with the time the participants spent to solve both the learning and the retrieval tasks. For all subjects, the ROI sizes were kept fixed. The results revealed a statistically significant correlation between the FA in the right hippocampus and the time the participants spent to perform both the learning ( $r = -0.74$ ,  $P = 0.006$ ) and retrieval ( $r = -0.82$ ,  $P = 0.001$ ) tasks. Subjects with higher FA values in the right hippocampus required less time to form a cognitive map (Fig. 3a) and were more efficient in using the map during navigation in the subsequent retrieval task (Fig. 3b). No significant correlations were found between the FA of the left hippocampus and the individuals' performance on either the learning ( $r = 0.24$ ,  $P = 0.45$ ) or retrieval ( $r = 0.06$ ,  $P = 0.85$ ) tasks.

We also investigated whether a relationship between microstructural integrity and navigational performance could be found in other brain regions involved in spatial processing. We correlated the time required by the subjects to solve the navigational tasks with the FA values of two different brain regions in the orbitofrontal cortex and the precuneus in the posterior parietal region of both hemispheres. These regions were selected because of their critical role in the attentional and perceptual mechanisms involved in spatial processing, as supported by evidence from functional neuroimaging (Kastner and Ungerleider, 2000), human lesion studies (Posner et al., 1984), and lesion and single neuron recording studies in the monkey (Bushnell et al., 1981; Petrides, 1996). ROIs within the orbitofrontal cortex and the precuneus were drawn similarly to the hippocampal ones. No significant correlations were found between the performance at the learning and retrieval tasks and the FA of the ROIs in either the orbitofrontal (left hemisphere: learning,  $r = 0.19$ ,  $P = 0.55$ , retrieval,  $r = 0.002$ ,  $P = 0.99$ ; right hemisphere: learning,  $r = -0.22$ ,  $P = 0.49$ , retrieval,  $r = -0.20$ ,  $P = 0.53$ ) or the parietal cortex (left hemisphere: learning,  $r = -0.11$ ,  $P = 0.73$ , retrieval,  $r = -0.34$ ,  $P = 0.28$ ; right hemisphere: learning,  $r = -0.15$ ,  $P = 0.64$ , retrieval,  $r = -0.53$ ,  $P = 0.08$ ).

Finally, we looked at the relation of age and gender with respect to both hippocampal microstructure and behavioral performances. We found no relationship between age or gender with FA in either the left (age:  $r = 0.05$ ,  $P = 0.88$ ; gender:  $t_{(10)} = 1.26$ ,  $P = 0.24$ ) or the right (age:  $r = -0.23$ ,  $P = 0.47$ ; gender:  $t_{(10)} = -1.73$ ,  $P = 0.11$ ) hippocampus. Likewise, no correlations were found between the age of the individuals and their navigational skills (learning,  $r = 0.51$ ,  $P = 0.09$ , retrieval,  $r = 0.04$ ,  $P = 0.90$ ); however, our subjects were relatively young (the oldest being 37 yr) and this result does not mean that differences in behavior or FA would not

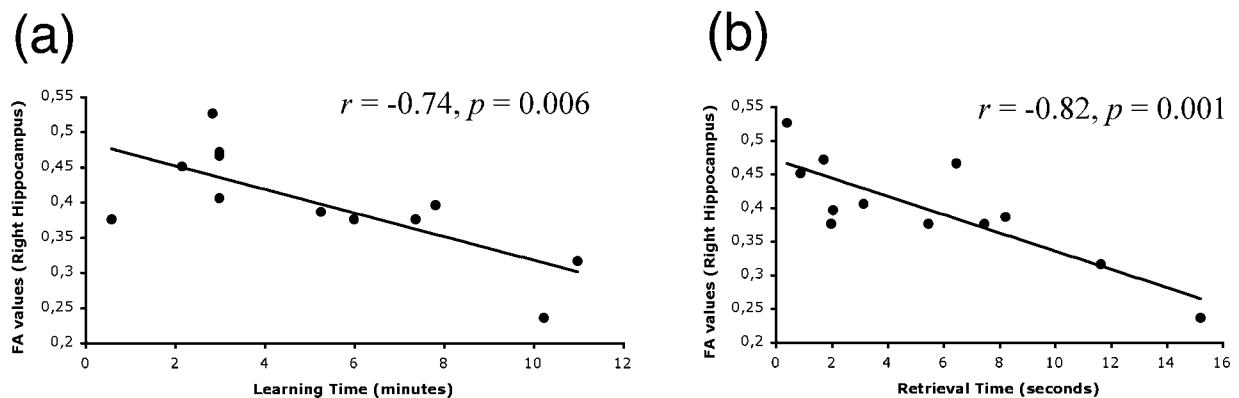


**FIGURE 2.** (a) ROIs at the bilateral hippocampal regions overlaid on the color-coded directionality maps of diffusion (red: left-to-right direction, green: anterior-to-posterior direction, blue: superior-to-inferior direction), and (b) on the FA maps.

emerge in a sample including much older participants (Moffat and Resnick, 2002). On the other hand, we found a statistically significant difference between males and females in the learning task ( $t_{(10)} = 2.63, P = 0.02$ ), with males (mean time, 190 s; standard deviation (SD), 136 s) faster than females (mean time, 434 s; SD, 184 s) in forming a cognitive map of the environment. No statistically significant differences were found between females (mean time, 7.8 s; SD, 5.3 s) and males (mean time, 3.1 s; SD, 2.5 s) while performing the retrieval task ( $t_{(10)} = 1.98, P = 0.08$ ).

In summary, we showed that the human ability to form and use a cognitive map of the environment is highly correlated with the FA of the hippocampus. These findings are consistent with the proposed role of the hippocampus in navigation as

previously shown by functional neuroimaging (Maguire, 1997; Maguire et al., 1999; Iaria et al., 2007) and neuropsychological (Maguire et al., 1996, 2006; Bohbot et al., 2004) studies in humans. In addition, our findings are consistent with previous studies showing increased gray matter volume of the hippocampus in individuals with selective navigational expertise such as taxi drivers (Maguire et al., 2000), as well as in individuals showing a spontaneous bias in using environmental landmarks for the purpose of orientation (Bohbot et al., 2007). These studies made use of standard 3D structural MRI to provide evidences of macrostructural changes within the hippocampus. Here, by using a new neuroimaging technique such as DTI, we shed more light on the role of hippocampus in navigation, showing that its microstructural properties may contribute to



**FIGURE 3.** The diagrams display the negative correlations found between FA values of the right hippocampus and the time spent by the participants to form a cognitive map of the environment (learning task) (a), and the average delayed time they spent to reach the target locations (retrieval task) (b).

some of the variability in spatial orientation observed in a healthy population (Iaria et al., 2003; Etchamendy and Bohbot, 2007). The advantage of using DTI to detect microstructural changes within the hippocampus, as compared with the use of a more traditional 3D structural MRI for detecting changes at a more macroscopic level, may be extremely relevant for the detection of neural degeneration before it becomes apparent macroscopically. For example, detecting microstructural changes within the hippocampus of patients affected by mild cognitive impairment may help to predict the future occurrence of Alzheimer's disease.

In addition to hippocampal properties, other sources of variability likely exist too: while behavioral performance did show gender differences, this did not appear to be due to gender differences in hippocampal FA. Hence, while the behavioral findings regarding gender are in agreement with previous studies (Astur et al., 1998; Moffat et al., 1998), the results suggest that, in addition to the hippocampal FA, other factors may contribute to normal interindividual variability in navigational skills.

Similar correlations between FA and behavioral performance have been recently found in healthy young individuals in other cognitive domains such as reading abilities (Klingberg et al., 2000), visuo-spatial attention (Tuch et al., 2005), visual target detection (Madden et al., 2004), and mental rotation skills (Wolbers et al., 2006). These studies reveal a functional relationship between diffusion anisotropy of selective brain regions and the cognitive skills of an individual. Our study extends this relationship to the domain of navigation and orientation within the environment. Together, this growing body of work points to an emerging relationship between microstructural differences in brain morphology and individual differences in behavior, and illuminate a potentially important source of variation in the human condition.

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exploration the examiner would stop them occasionally (every minute) to ask them to report the locations of the landmarks on similar maps. The learning task was considered completed at the moment when a participant was first able to indicate the correct locations of all four landmarks, either during one of the every-minute interrogations of the examiner or at the terminal moment when the participant felt that he/she had formed the mental map. The time spent to reach this point was taken to be the time required to form the cognitive map. Immediately after learning, participants were administered the retrieval task. This task consisted of 12 trials in which the subjects were asked to use the mental representation that they had formed to reach the location of specific landmarks. On each trial, the subjects started by facing a landmark and a sign indicating the target location they needed to reach as quick as possible by following the shortest pathway. The duration of each trial was recorded as a measure of behavioral performance.

## APPENDIX: DETAILED METHODS

### Subjects

Twelve right-handed healthy individuals (6 males; mean age, 27 yr; range, 18–37 yr) with no history of neurological disorders provided informed consent to participate in this study.

### Behavioral Navigational Tasks

Participants used a three-button keypad to navigate in a virtual city, which included a cinema, a restaurant, a hotel, and flower shop. During the learning task, the participants were instructed to explore freely the environment to create a mental representation of the city including the landmarks' locations. Subjects were asked to report when they felt that they had completed that mental representation, and were told that at that "terminal moment" the examiner would ask them to report the locations of the landmarks on a schematic map representing the city from a top-view perspective. In addition to this terminal assessment, participants were also aware that during their

### Diffusion Tensor Imaging Data

DTI was performed with an echo planar imaging sequence (55 slices, voxel size:  $2.2 \times 2.2 \times 2.2$  mm<sup>3</sup>, *b* value: 700 s/mm<sup>2</sup>, TE = 69 μs, TR = 6,074 μs) on a 3.0 Tesla Philips scanner. Diffusion-weighted images were sensitized for diffusion along 32 directions, and two measurement replications served to improve signal-to-noise (S/N) ratio in the tensor maps. In addition, for each participant, we acquired a structural image with a T1-weighted sequence, recording 170 axial slices of 1.1 mm thickness (1-mm gap) with an in-plane resolution of 1.1 mm × 1.1 mm (FOV = 256). FA and color-coded directionality maps of diffusion were created off-line by processing the DTI images using DTIstudioV2 software (Johns Hopkins University, Baltimore, MD). ROIs were drawn after localization of the hippocampi gray matter on the anatomical images of each individual. Similarly, gray matter ROIs within the orbitofrontal cortex and the precuneus were localized according to neural activity found in previous functional neuroimaging studies (Iaria et al., 2003, 2007) and neuroanatomy atlas as displayed on the individuals' anatomical images.