Hippocampal Size Predicts Rapid Learning of a Cognitive Map in Humans

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ABSTRACT: The idea that humans use flexible map-like representations of their environment to guide spatial navigation has a long and controversial history. One reason for this enduring controversy might be that individuals vary considerably in their ability to form and utilize cognitive maps. Here we investigate the behavioral and neuroanatomical signatures of these individual differences. Participants learned an unfamiliar campus environment over a period of three weeks. In their first visit, they learned the position of different buildings along two routes in separate areas of the campus. During the following weeks, they learned these routes for a second and third time, along with two paths that connected both areas of the campus. Behavioral assessments after each learning session indicated that subjects formed a coherent representation of the spatial structure of the entire campus after learning a single connecting path. Volumetric analyses of structural MRI data and voxel-based morphometry (VBM) indicated that the size of the right posterior hippocampus predicted the ability to use this spatial knowledge to make inferences about the relative positions of different buildings on the campus. An inverse relationship between gray matter volume and performance was observed in the caudate. These results suggest that (i) humans can rapidly acquire cognitive maps of large-scale environments and (ii) individual differences in hippocampal anatomy may provide the neuroanatomical substrate for individual differences in the ability to learn and flexibly use these cognitive maps. © 2013 Wiley Periodicals, Inc.

KEY WORDS: navigation; spatial learning; volumetry; voxel-based morphometry; caudate

INTRODUCTION

Human spatial behaviour is complex and idiosyncratic. One way that people differ from each other is in their ability to learn and navigate large-scale environments (Wolbers and Hegarty, 2010). Fundamental to this variation in ability may be differences in the propensity to use so-called *cognitive maps* – mental representations of space in an allocentric (i.e., world-centered) format that allow recovery of distances and directions between locations and flexible planning of routes (O'Keefe and

Nadel, 1978; Gallistel, 1990; Bennett, 1996). Ever since Tolman's (1948) seminal work, a vast body of research has explored the use of cognitive maps in animals. Yet, there is still considerable debate in the psychological literature as to whether humans use cognitive maps or simply rely on snapshot memories of locations and route-following response strategies for navigation (Wang and Spelke, 2002; Foo et al., 2005; Shettleworth, 2010).

The large range of individual differences in cognitive mapping ability and strategies may, in fact, account for the persistence of the debate about their existence. Whereas some individuals may encode accurate internal maps, others may encode no cognitive maps at all, relying instead on route-based strategies (Ishikawa and Montello, 2006). Previous neuroscientific work (Packard and McGaugh, 1996) has identified two memory systems whose differential employment might provide a potential neuronal substrate for these individual differences. First, a spatial memory system centered on the hippocampal formation that encodes the allocentric coordinates of different locations (O'Keefe and Nadel, 1978). Second, a response-based memory system centered on the caudate nucleus (Packard and Knowlton, 2002) that encodes procedural knowledge about which action to take at each decision point when following a route (e.g., turn right at the pub). Neuroimaging studies have shown that activation in these two systems during virtual navigation varies across individuals depending on whether the subject uses a space-based or a response-based navigational strategy (Hartley et al., 2003; Iaria et al., 2003). Furthermore, volumetry studies have shown that the hippocampus is larger and the caudate smaller in participants who use a spatial rather than a response-based strategy to recall locations in an 8-arm virtual maze (Bohbot et al., 2007). Anatomical variation has also been observed within the hippocampus, with larger posterior and smaller anterior hippocampal subregions in London taxi drivers compared to control subjects with less navigational expertise (Maguire et al., 2000).

Although these results are suggestive, no previous study has directly examined how individual differences in hippocampal anatomy correspond to individual differences in cognitive map learning per se. Establishing such a connection is essential for linking the neuro-

scientific literature to the extensive cognitive literature on real-world spatial learning (Siegel and White, 1975; Montello, 1998). Here we address this issue by teaching subjects a real-world campus environment that was unknown to them prior to the study. Familiarization took place in three sessions spread out over a period of three weeks. Cognitive map learning was indexed by performance on spatial memory tasks administered after each session. We then related individual differences in behavioral performance to individual differences in gray matter volume assessed through structural MRI scans. We reasoned that if the hippocampus were involved in cognitive map learning, then the size of the hippocampus (or the posterior subregion thereof) would predict performance on tasks that require the recall of an enduring and allocentric representation of the location of different buildings in the campus, such as judgment of the relative direction (JRD) between these buildings. To anticipate, our results suggest that individual differences in hippocampal anatomy may underlie individual differences in cognitive mapping ability.

MATERIALS AND METHODS

Subjects

Sixteen subjects (9 male, 7 female, median age 22 years, range 19–27) with normal or corrected vision participated in the behavioral segment of this study. Thirteen subjects (all right handed, 8 males, 5 females, median age, 22 years, range 20–27) returned for the MRI segment 9–12 months later. All subjects were students from Temple University who had never visited the study area (which was located 25 km from the main campus) prior to testing. Written informed consent was obtained according to the provisions set by the Temple University and the University of Pennsylvania local institutional boards.

Behavioral Segment

Overview

To assess cognitive map learning in a real-world setting, subjects were taught the spatial layout of Temple University's Ambler campus during the behavioral portion of the experiment. A map of the campus is shown in Figure 1. Subjects had never visited the Ambler Campus or inspected a map of the area prior to testing. Training and testing were performed in three sessions spread out over a period of 3 weeks.

In the first session, participants were guided by the experimenter while walking two separated routes and were asked to remember the name and position of four buildings on each route (eight total). Buildings within route "A" were separated by small woodland such that participants standing in front of building "A4" (east most building) could not simultaneously see the other three buildings in the route. All buildings in route "B" were simultaneously visible to participants. More impor-

tantly, the two routes were carefully chosen so buildings from route A would not be visible from route B and vice-versa. When moving between routes, participants were blindfolded, given noise-reducing earphones, disoriented, and pushed in a wheelchair to remove any visual, auditory, or proprioceptive cues that would allow them to integrate the two parts of campus. In the second and third sessions, participants were again guided along the two routes, and they were also guided along 1 of 2 connecting paths that linked the two areas of the campus, one of which was straight (short connection) and the other circuitous (long connection).

Participants' spatial knowledge of the campus and locations was investigated at the end of each session by asking them to complete four spatial tasks specifically designed to probe different aspects of their spatial knowledge of the campus. In accordance with previous work with humans (Ishikawa and Montello, 2006) and animals (Chapuis et al., 1987), we posited that cognitive map learning would be evidenced by the acquisition of an integrated representation in Sessions 2 and 3 that incorporated knowledge of the spatial relationships between buildings along both routes. In contrast, subjects were not expected to develop such an integrated representation in Session 1 because the two segments of campus were learned separately in this session with disorientation in between.

The four spatial tasks administered after each learning session were (in order): onsite direction estimates, offsite direction estimates, distance estimates, and the drawing of a sketchmap of the campus. These tasks were chosen based on their facial ecological validity in accordance with previous research that urged researchers to use multiple converging methods in the analysis of cognitive maps (Kitchin and Blades, 2002). Although all were expected to tap cognitive map learning to some degree, not all of them were expected to provide pure measures of such learning. Of the four tasks, the one that most clearly indexes allocentric spatial knowledge—and hence, cognitive map learning—is offsite direction estimation, as there is no way to perform this task except by accessing allocentric spatial representations (although see Wang and Spelke, 2002). In contrast, the other three tasks can be performed using a mixture of egocentric or allocentric strategies, as we explain further below.

Onsite and offsite direction estimation

Two pointing tasks were used to assess participants' knowledge of the directional relationships between different locations on campus. In the onsite pointing task, participants walked the two routes (subsequent to the training phase), stopped in front of each of the 8 buildings (while still facing in the direction of the route), and they were free to look around before pointing to the other 7 buildings. In the offsite pointing task, participants were blindfolded, disoriented and brought to a testing room where they performed judgments of relative direction (while remaining blindfolded) which required them to imagine their position and facing orientation before pointing (i.e., "you are standing in front of building x, facing building y, now point to the front door of building z"). Pointing judgments
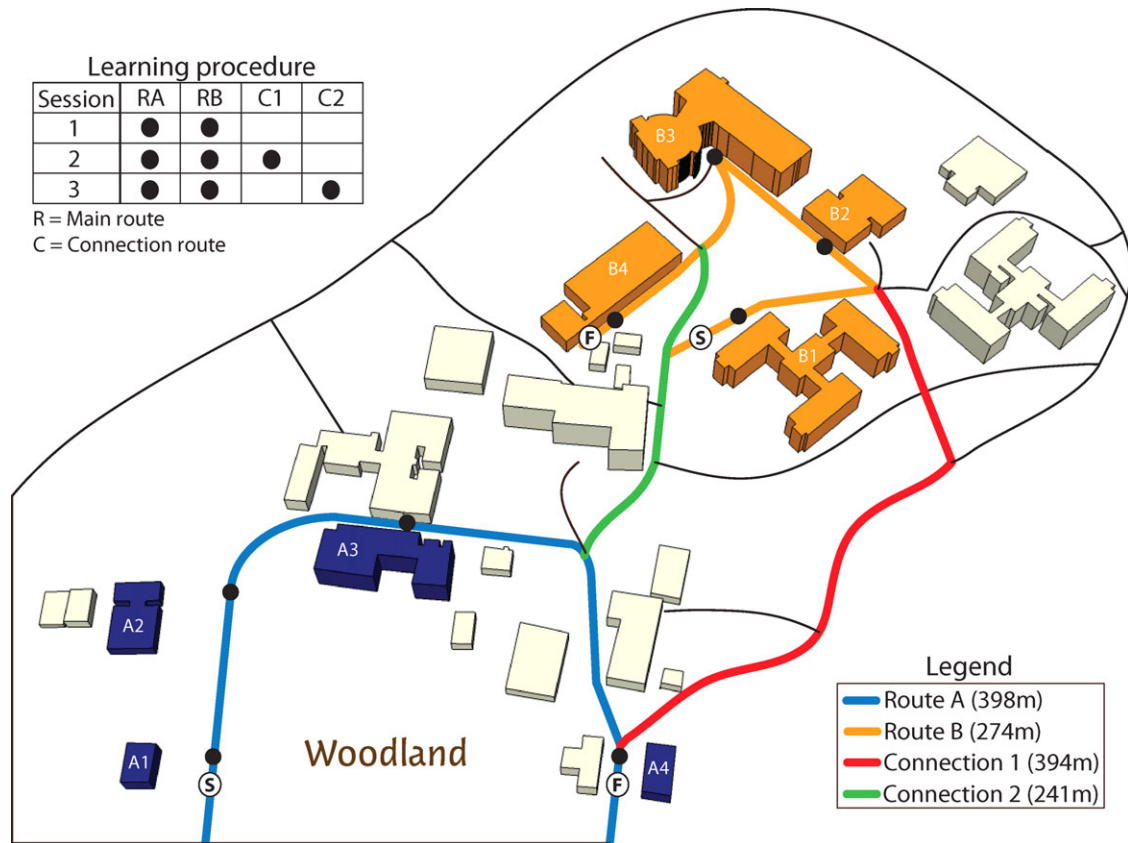
FIGURE 1.   **Study area: Temple University's Ambler campus. Participants learned the campus over a period of three weeks. Buildings from route A were not visible from route B and vice-versa. Buildings within route A were separated by small woodland such that participants standing in building A4 (east most building) could not simultaneously see the other three buildings in the route. All buildings in route B were simultaneously visible to participants. In their first visit, they were guided along two separate routes and were asked to remember the name and position of the four buildings on each route (blue and orange buildings). Specifically, when standing in front of each building (black circles) they memorized the locations of the front door. In the second and third sessions, participants were again guided along the two routes, and they were also guided along 1 of 2 connecting routes that linked the two areas of the campus through a short (green) or longer (red) path. Participants' spatial knowledge of the campus was investigated at the end of each session by asking them to complete onsite and offsite direction estimates, distance estimates, and the drawing of a sketchmap of the campus.**

were acquired for buildings pairs located along the same route (within-route judgments) and also for building pairs located on different routes (between-route estimates). Participants made a total of 56 onsite (24 within route and 32 between routes) and 64 offsite (32 within route and 32 between routes) pointing judgments. All pointing judgments were recorded using a SILVA NOMAD© digital compass with an instrument error of $\pm 5°$. Estimated angles were converted to conform to a circular logic so that the difference between the estimated and the real values was kept under $180°$ (Batschelet, 1981). Performance on pointing judgments was evaluated by calculating the unsigned difference (absolute error) between the real and estimated angles.

Note that although both onsite and offsite pointing require subjects to access spatial representations, there are two important differences between these tasks. The first is that the onsite task is performed while immersed in the training environment whereas the offsite task is performed elsewhere. Thus, the onsite task might rely on a mixture of transient (online/egocen-

tric) and enduring (offline/allocentric) spatial representations, whereas the offsite task must be performed entirely on the basis of enduring (offline/allocentric) representations. Previous work has demonstrated a dissociation (Burgess, 2006; Waller and Hodgson, 2006; although see Wang and Spelke, 2002) between these two kinds of spatial representation which suggests that they might be supported by different neural systems. Consistent with this view, neurophysiological, neuropsychological, and neuroimaging studies indicate that the parietal lobe supports egocentric representations, the hippocampus and the medial temporal lobe support allocentric environmental representations, and the retrosplenial cortex and parieto-occipital sulcus support mechanisms that allow one to switch between these two types of representations (Wolbers and Buchel, 2005; Burgess, 2008; Epstein, 2008). The second difference is that participants faced along the route while performing the onsite task (although they were free to look around), but were asked to imagine facing a variety of different directions during the offsite task. Thus, the offsite task requires participants to mentally

recreate a different point of view for each trial whereas the onsite task does not.

Distance estimation

Knowledge of the relative distance between the eight locations was tested using the method of triadic comparison (Rieser et al., 1980; Ungar et al., 1996). A paper questionnaire was created containing 56 triads representing all possible combinations between the 8 different locations on campus. For each triad, subjects were asked to judge which two of the three locations were the closest together and which two were the furthest apart. Questionnaires were scored relative to a Euclidean baseline acquired by measuring the metric straight-line distances between locations on a map of the campus. Subjects were awarded 1 point for each correct answer and accuracy was calculated as a percentage of a perfect score. Triadic comparison has an advantage over other methods of distance estimation because it does not require participants to produce an exact numerical distance but instead requires them to consider the relative distances between elements in the triad.

Sketch mapping

Participants were asked to draw sketch maps of the two routes and buildings on an 8½ × 11 sheet of a paper. They were encouraged to include as much detail as possible while making sure to indicate with an "x" and a label the position of the 8 test buildings. Data from sketchmaps were analyzed using bidimensional regression (Tobler, 1994; Friedman and Kohler, 2003) where the (r^2) represents the degree of association between two configurations of related coordinate data for the 8 test buildings. Sketchmaps can be useful in the analysis of cognitive maps as participants are given a chance to reproduce from a global perspective the allocentric relationship between different elements in environment (Kitchin and Blades, 2002). This method has been criticized in the past, however, because sketchmaps can be incrementally constructed on the basis of sequentially perceived information that is not necessarily compiled into an allocentric representation. Thus, while the final product may look like the externalization of a cognitive map, the positioning of the different elements in the model may be the product of mentally following learned paths of movement (Appleyard, 1970).

MRI Segment

Once participants had been trained on the Ambler campus and their knowledge of the campus assessed, we then acquired MRI scans of their brains in order to relate individual differences in cognitive map learning to individual differences in the volume of neuroanatomical structures. The MRI segment of the experiment was conducted 9–12 months after the behavioral segment at the Hospital of the University of Pennsylvania. Subjects (13 of the original 16) were scanned on a 3-T Siemens Trio equipped with an 8-channel multiple array Nova Medical head coil. A 3D magnetization prepared rapid gradient-echo

pulse sequence (TR = 1,620 ms, TE = 3 ms, time to inversion = 950 ms, voxel size = 0.976 × 0.976 × 1 mm. matrix size = 192 × 256 × 160) was used to acquire structural T_1-weighted images.

Volumetry

To determine the volume of the hippocampus and caudate in each subject, cortical reconstruction and volumetric segmentation of T1 structural images was performed with FreeSurfer image analysis package (http://surfer.nmr.mgh.harvard.edu). Briefly, the process involves the removal of nonbrain tissue using a hybrid watershed surface deformation procedure, automated Tailarch transformation, segmentation of the subcortical white matter and gray matter volumetric structures, intensity normalization, tessellation of gray matter/white matter boundary, automated topology correction, and surface deformation following intensity gradients that optimally place the gray/white and gray/cerebrospinal fluid borders (Fischl et al., 2002). Subcortical regions were normalized to the total intracranial volume (TIV) using an analysis of covariance approach (Free et al., 1995). Manual segmentation of the hippocampus into subregions was then conducted by importing the automatically generated volumetric masks for each subject to itk-SNAP (www.itksnap.org/pmwiki/pmwiki.php). Hippocampal segmentation into subregions was conducted by a researcher in our lab unaware of the subjects' performance in the behavioral tests. We also calculated the center of mass $\mathcal{R} = \dfrac{\sum m_i r_i}{\sum m_i}$ of the hippocampus for each subject as a continuous measure of within-structure differences, where m_i is the number of voxels in each coronal slice and r_i is the fractional distance of the coronal slice between the anterior and posterior ends of the hippocampus.

Voxel-based morphometry

We complemented the volumetry analysis by investigating voxel-wise changes in gray matter volume relative to behavioral scores using voxel-based morphometry (VBM). Unlike the volumetry analysis, VBM is unbiased such that (1) it requires no a priori hypothesis about the location of possible differences in the gray matter, and (2) it is not operator-dependent but follows an optimized VBM protocol carried out with FSL tools (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM, Good et al., 2001; Smith et al., 2004; Douaud et al., 2007). First, structural images for the 13 participants were brain-extracted and gray matter-segmented before being registered to the MNI 152 standard space using nonlinear registration (Andersson et al., 2007). The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific gray matter template. Second, all native gray matter images were nonlinearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the nonlinear component of the spatial transformation. The modulated gray matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 4 mm. Finally, voxel-wise general linear model (GLM) was applied using
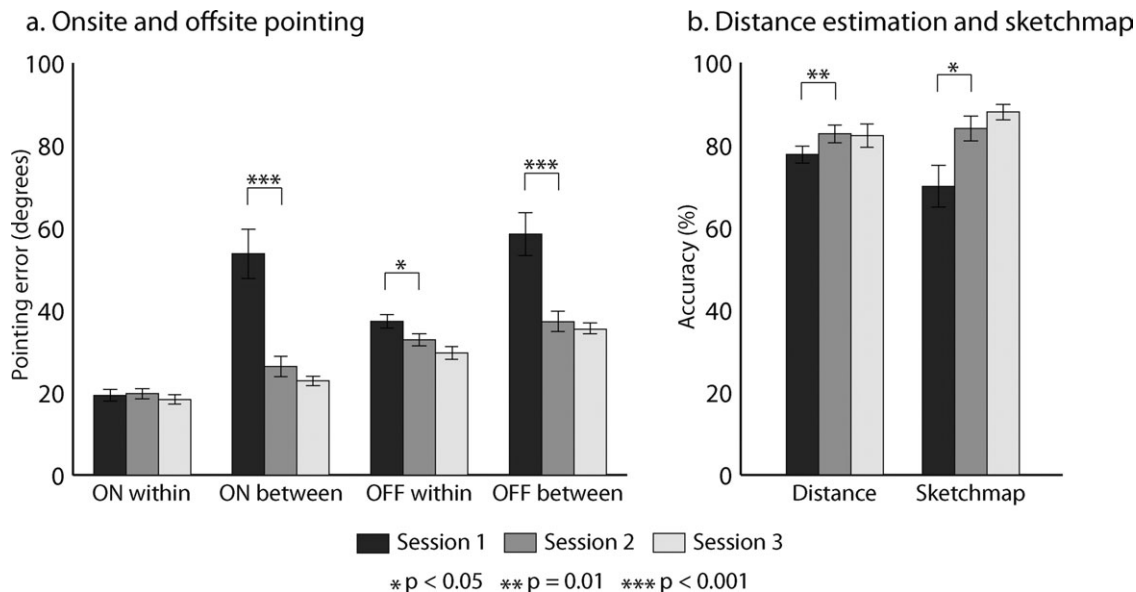
FIGURE 2. Behavioral results for the 4 spatial tasks across the three sessions. (a) Mean pointing error (and SEM) for the onsite and offsite pointing tasks. (b) Mean accuracy (and SEM) for the distance (% correct) and sketchmap ($r^2 * 100$) tasks. Performance on all tasks improved in the second session after participants learned one of the two connection routes with the exception of the onsite within pointing task where landmarks were simultaneously visible to participants. No further improvement was observed in session three after learning a second connecting route.

permutation-based (TCFE - Threshold-Free Cluster Enhancement) nonparametric testing, correcting for multiple comparisons across space.

Psychometric tests

Participants also completed a battery of psychometric tests aimed at measuring different aspects of their spatial knowledge. The tests were presented after the MRI scan in the following order: (1) The Santa Barbara Sense of Direction Scale (SBSOD; Hegarty et al., 2002). This is a self-report questionnaire consisting of 15 items and used to measure environmental spatial ability; (2) Questionnaire on Spatial Representation (Pazzaglia et al., 2000; Pazzaglia and De Beni, 2001). This questionnaire is used to differentiate between preference for landmark, route and survey-based representation during navigation; (3) Perspective taking test (Kozhevnikov and Hegarty, 2001; revised by Hegarty and Waller, 2004) where subjects are presented with a two dimensional array of objects and are asked to determine the egocentric bearing of a target object given an imagined location and facing direction; (4) Mental Rotation test (Vandenberg and Kuse, 1978; adapted by Peters et al., 1995) where participants must choose the correct test image after it is rotated; (5) Philadelphia Spatial Ability Scale (Hegarty et al., 2010) designed to measure how well a participant can perform small-scale spatial tasks such as visualizing and transforming small or medium-sized objects; (6) Paper folding test (Ekstrom et al., 1976) which requires participants to mentally perform complex spatial maneuvers to solve how a folded and hole-punched paper would look like when fully opened.

RESULTS

Behavioral Assessments of Spatial Learning

We first report the results from the behavioral segment of the experiment before examining relationships between behavioral performance and brain anatomy. As subjects learned the layout of the campus over three learning sessions, the critical question is whether there was improvement from session to session. In particular, because participants did not learn a connecting path between the two separate routes until Session 2, improvement from Sessions 1 to 2 can be attributed in part to the ability to combine the two parts of campus into an integrated map. Further improvement from Sessions 2 to 3 indicates refinement of that map. Results for behavioral tests are summarized in Figure 2.

Onsite direction estimation

In this task, participants stood in front of one of the eight campus buildings and pointed to the other seven buildings. To assess participants ability to quickly develop a cognitive map of the campus, we compared performance between Sessions 1 and 2 using a 2 x 2 x 2 mixed factor ANOVA with Session (1 vs. 2) and target location (within route vs. between route) as within-subject factors and the order in which connection routes were learned (short connection first vs. long connection first) as a between-subject factor. To assess whether there was further improvement of the map over time, we compared performance between Sessions 2 and 3 using an analogous 2 x 2 x 2 mixed factor ANOVA.

Results of these analyses indicated that accuracy improved between Sessions 1 and 2 ($F_{(1,15)} = 23.43$, $P = 0.0002$) and was greater for within-route compared with between-route judgments for these sessions ($F_{(1,15)} = 36.83$, $P < 0.0001$). There was also a significant session x target location interaction ($F_{(1,15)} = 26.35$, $P = 0.0001$) indicating greater improvement for between-route than for within-route judgments, which is to be expected given that subjects learned the within-route relationships in session one, but did not learn the between-route relationships until Session 2. Performance did not improve further between Sessions 2 and 3 ($F_{(1,15)} = 3.18$, $P = 0.10$, n.s.) although performance remained higher for within-route than for between-route judgments ($F_{(1,15)} = 7.63$, $P = 0.0002$) with no session x target location interaction in this case ($F_{(1,15)} = 0.97$, $P = 0.34$, n.s.). The order in which the connecting routes were learned had no effect on accuracy and did not interact with any other factor (all Ps > 0.5, n.s.).

These results indicate that learning occurred in the second session when participants walked one of the two connection routes, but no further learning occurred in the third session. Furthermore, the improvement between Sessions 1 and 2 was primarily for between-route judgments, which is what we would expect if subjects rapidly integrated the two parts of campus into a single map. These observations were confirmed by planned t-tests, which indicated that between-route pointing improved between Sessions 1 and 2 ($t_{15} = 5.05$, $P = 0.0001$) but within-route pointing did not ($t_{15} = -0.45$, $P = 0.66$, n.s.); neither kind of pointing showed improvement between Sessions 2 and 3 (between: $t_{15} = 1.5$, $P = 0.15$; within: $t_{15} = 1.6$, $P = 0.14$; both n.s.).

Offsite direction estimation

In this task, participants were blindfolded, disoriented, and brought to a testing room where they performed judgments of relative direction, which required them to imagine their position, and facing orientation before pointing. Results were similar to those observed with onsite pointing. Accuracy improved between Sessions 1 and 2 ($F_{(1,15)} = 22.85$, $P = 0.0002$) and was greater for within-route compared to between-route judgments for these sessions ($F_{(1,15)} = 22.81$, $P = 0.0002$) with a significant session x target location interaction ($F_{(1,15)} = 12.09$, $P = 0.003$) indicating greater improvement for between-route than for within-route judgments. Accuracy did not improve between Sessions 2 and 3 ($F_{(1,15)} = 1.97$, $P = 0.18$, n.s.) although performance remained higher for within-route than for between-route judgments ($F_{(1,15)} = 11.19$, $P = 0.004$) with no session x target location interaction ($F_{(1,15)} = 0.20$, $P = 0.66$, n.s.). Planned t-tests indicated that accuracy improved after the learning of a connecting route in Session 2 for both within-route and between-route judgments (within $t_{15} = 2.40$, $P = 0.03$, between $t_{15} = 4.47$, $P = 0.0001$) but did not improve further between Sessions 2 and 3 for either (within $t_{15} = 1.5$, $P = 0.15$; between $t_{15} = 0.71$, $P = 0.49$, both n.s.). Here again, the order in which the connecting routes were learned had no effect on accuracy nor did it interact with any

other factor (all Ps > 0.5, n.s.). These results further support the idea that subjects rapidly integrated the two parts of campus after learning a single connecting path.

Distance estimation

In this task, subjects judged distances between buildings using the method of triadic comparison. Consistent with the preceding findings with pointing judgments, performance improved on this task between Sessions 1 and 2, but did not further improve between Sessions 2 and 3. This was confirmed by planned t-tests, which revealed a significant increase in accuracy between the first and second session ($t_{14} = 3.27$, $P = 0.006$) but no further increase between the second and third session ($t_{14} = -0.24$, $P = 0.82$, n.s.). Note that because this task involves comparison between triads rather than between pairs of locations, there were not enough trials to reliably distinguish between-route from within-route effects.

Further inspection of the data revealed an interesting effect of connection route order. Specifically, participants who learned the long connection route in the second session and the short connecting route in the third session were more accurate in Session 3 than in Session 2 (Session 2 = 82%; Session 3 = 86%) whereas subjects who learned the short connecting route first showed the opposite pattern (Session 2 = 83%; Session 3 = 79%). To further assess the relationship between learning and connection route, we recoded the data from Sessions 2 and 3 based on the type (short vs. long) of connection route learned in each session. Participants were more accurate in their distance estimation after walking the short connection route than after walking the long connecting route ($t_{14} = 3.13$, $P = 0.007$). Thus, it seems that walking time, path complexity and the fact that the long connection route was situated in the exterior portion of the campus (see Fig. 1) may be mediating factors when estimating distance (Thorndyke, 1981). In particular, the circuitous nature of the long connection route may have led to spatio-temporal distortions when judging straight-line distances between locations. Furthermore, the fact that subjects who learned the short route first and the long route second showed decreased performance in Session 3 suggests that they relied in part on session-specific information when performing the task.

Sketch mapping

The final behavioral assessment was free drawing of a sketch map indicating the position of the eight buildings. These maps were analyzed using bidimensional regression, which allowed us to estimate the degree of association (r^2) between two configurations (real vs. sketched map) of related coordinate data. We then used the r^2 values to compare performance on the three different sessions. Planned t-tests further revealed a significant improvement in performance between the first and second session ($t_{15} = 2.35$, $P = 0.03$) and a nonsignificant trend towards improvement between the second and third session ($t_{15} = 1.9$, $P = 0.07$, n.s.).

Factor Analysis Showing the Relationship Between the Four Spatial Tasks

Variable	Factor 1	Factor 2
Sketch map	0.96	0.03
Distance estimation	0.95	−0.07
Offsite pointing	0.02	0.79
Onsite pointing	−0.05	0.78
Percentage of variance	45.69	31.1

Two components with eigenvalues greater than 1.0 were extracted. The first factor includes the sketch map and the distance estimation tasks while the second factor includes the onsite and offsite pointing tasks. These results support the notion that the sketch map and distance estimation tasks recruit fundamentally different cognitive mechanisms than the pointing tasks.

Relationship between tasks

To better understand the mechanisms underlying the four tasks, we investigated the relationship in performance between them. Because the preceding analyses indicated that there were no significant differences in accuracy between Sessions 2 and 3 for any of the four spatial tasks, we pooled the data from these two sessions for this and subsequent analyses, taking this averaged data to be a measure of the spatial knowledge obtained for each individual. We then examined pairwise correlations between tasks to see if participants who were good on one task would be good on the other.

There was a significant correlation between performance on the distance estimation and sketch mapping tasks ($r_{(13)} = 0.83$, $P = 0.0001$). In contrast, there were no significant correlations between the pointing tasks and distance estimation (onsite $r_{(13)} = -0.09$, $P = 0.74$; offsite $r_{(13)} = -0.05$, $P = 0.87$, both n.s.) or between the pointing tasks and sketch mapping (onsite $r_{(14)} = -0.04$, $P = 0.89$; offsite $r_{(14)} = -0.02$, $P = 0.93$, both n.s.). The correlation between the two pointing tasks (onsite vs. offsite) was also nonsignificant ($r_{(14)} = 0.29$, $P = 0.27$, n.s.). These results suggest that the distance estimation and map drawing tasks may be measuring a specific feature of spatial knowledge that is different from that measured by the pointing tasks. They also suggest that differences exist between the two types of pointing tasks, which might relate to the primary reference frame used for each (egocentric for onsite vs. allocentric for offsite), or the fact that the offsite task required subjects to imagine a wide variety of viewpoints whereas the onsite task did not.

To further assess the relationship between the four tasks, a principal components factor analysis with varimax rotation was conducted. Two components with eigenvalues greater than 1.0 were extracted. Table 1 presents the factor structure and the percentage of variance accounted for each of the orthogonally rotated factors. The first factor includes the sketch map and the distance estimation tasks while the second factor includes the onsite and offsite pointing tasks. Thus the results of the factor analysis support the idea that the sketch map and dis-

tance task recruit different cognitive mechanisms than the pointing tasks.

Psychometric tests

To better understand the relationship between spatial ability and navigation, we examined the relationship between the five psychometric tests and performance with the four spatial tasks (combined performance for Sessions 2 and 3). We did not observe any significant correlations for the onsite pointing task (all Ps > 0.28, all n.s.). Significant correlations were found between offsite pointing task and the Santa Barbara Sense of Direction Scale ($r_{(14)} = -0.51$, $P = 0.04$; where better SBSOD scores correspond to less error) and between offsite pointing task and the perspective taking test ($r_{(11)} = 0.73$, $P = 0.005$; where less error on one task corresponds to less error on the other). There were no other significant correlations for the offsite pointing task (all Ps > 0.12, all n.s.). We also did no observe any significant correlations between the distance estimation task and the psychometric tests (all Ps > 0.11, all, n.s.) or between the sketchmap task and the psychometric tests (all Ps > 0.18, all, n.s.).

Summary of behavioral results

The behavioral assessments indicate that subjects were able to obtain an understanding of the spatial relationship between different parts of campus after learning only a single connecting route. This was evidenced by improved performance between Sessions 1 and 2 on all four tasks, with no further improvement between Sessions 2 and 3. These data indicate that subjects can acquire integrative cognitive maps very rapidly. However, an important caveat is that performance was not highly correlated across tasks. This suggests that the four tasks may index different aspects of spatial learning. Notably, only the offsite pointing task correlated with the psychometric measures used to test environmental spatial ability including the SBSOD and the perspective taking test.

Neuroanatomical Correlates of Spatial Learning

MRI volumetry

Next we turned to the primary concern of the study: understanding the relationship between behavioral and anatomical variability. To assess this, we performed volumetric analysis of the size of the hippocampus and caudate in each subject. A series of planned correlations were conducted to examine the relationship between gray matter volume in these regions and performance (i.e., combined performance for Sessions 2 and 3) in each of the four spatial tasks. Note that because of the absence of correlation of performance between tasks observed in the previous section it made sense to examine each task separately rather than combining performance across tasks into a single measure. Results for the volumetry analysis are presented in Figure 3.

Of all the tasks, offsite pointing most clearly requires subjects to make straight-line inferences about the allocentric posi-

a. Right hippocampus volume vs. offsite pointing

b. Right hippocampus center of mass vs. offsite pointing

c. Right caudate volume vs. offsite pointing (within route)
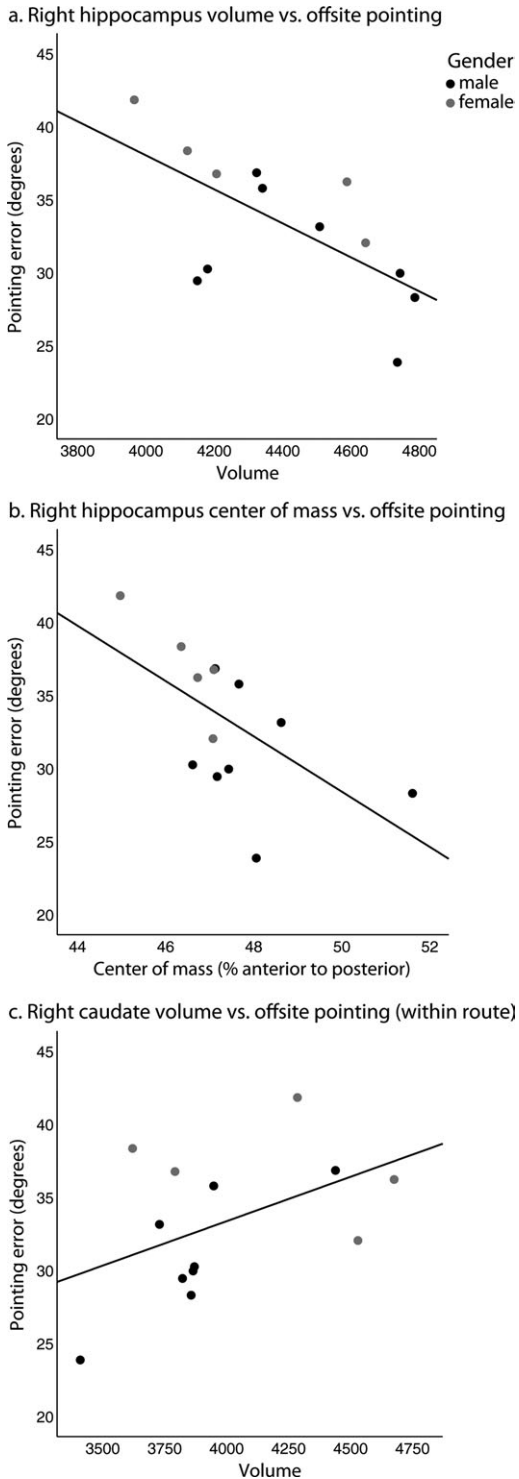
FIGURE 3.   Volumetry results. (a) The right hippocampus was larger in subjects who were more accurate in the offsite pointing task. (b) The center-of-mass of the right hippocampus was located more posteriorly in these subjects. (c) The right caudate was larger in subjects who were less accurate when pointing to buildings within the same route in the offsite pointing task.

tion of different buildings around campus—a process that can be considered analogous to shortcutting and thus revealing of an essential characteristic of cognitive maps. Consistent with

this observation, the offsite pointing task was the only spatial task for which individual differences in performance were related to individual differences in hippocampal volume. The right hippocampus was larger in subjects who made fewer errors in the offsite pointing judgments ($r_{(11)} = -0.65$, p = 0.02). Although there was a similar trend in the left hippocampus, this trend was not significant ($r_{(11)} = -0.40$, p = 0.17, n.s.). The correlation between performance and right hippocampal volume was most striking for between-route pointing judgments ($r_{(11)} = -0.61$, p = 0.03) with a similar but marginal trend for within-route pointing judgments ($r_{(11)} = -0.52$, p = 0.07, n.s.). There was no significant relationship between hippocampal volume and performance for onsite pointing (left $r_{(11)} = 0.37$, $P = 0.21$; right $r_{(11)} = 0.02$, $P = 0.95$, both n.s.), distance estimation (left $r_{(11)} = -0.21$, $P = 0.49$; right $r_{(11)} = 0.05$, $P = 0.88$, both n.s.) or sketch map drawing (left $r_{(11)} = 0.03$, $P = 0.93$; right $r_{(11)} = 0.12$, $P = 0.69$; both n.s.).

As previous research has suggested differential functional involvement of the anterior and posterior hippocampus in navigational tasks, we also investigated individual differences in gray matter separately for hippocampal subregions. We divided the hippocampus into two (anterior and posterior) equal parts based on the number of slices for each participant. The right anterior and right posterior hippocampus were larger in subjects who were more accurate in the offsite pointing task, but the relationship was more salient in the posterior subregion (anterior $r_{(11)} = -0.62$, p = 0.02; posterior $r_{(11)} = -0.75$, p = 0.003). To quantify the apparent trend of larger posterior vs. anterior hippocampus in subjects who performed well on this task, we calculated the location of the hippocampal center of mass based on the distribution of slice cross-sections along the longitudinal extent of the structure. The center-of-mass of the right hippocampus was located more posteriorly in subjects who performed better on the offsite pointing task ($r_{(11)} = -0.59$, p = 0.03). We did not observe any significant relationship between performance on the onsite pointing, distance estimation, or sketch mapping tasks and the size of the anterior (Ps > 0.78, all n.s) or posterior (Ps > 0.64, all n.s.) right hippocampus; nor was performance on these tasks correlated with right hippocampal center of mass (all Ps > 0.40, all n.s.). For all the above analyses, correlations in the left hippocampus were nonsignificant.

Our results are consistent with previous research suggesting that the hippocampus may be critical for the coding of an allocentric spatial map. However, in order to successfully complete the offsite pointing task participants must do more than simply retrieve allocentric information: they must also imagine a scene from a particular point of view and determine the resulting egocentric position of the target. This raises the question whether the effect of hippocampal size on offsite pointing accuracy is mediated by variability in egocentric perspective taking ability. To investigate this question we conducted a mediation analysis (Baron and Kenny, 1986) that took into account the effect of perspective taking ability as measured by the task developed by Hegarty and Waller (2004), which was adminis-
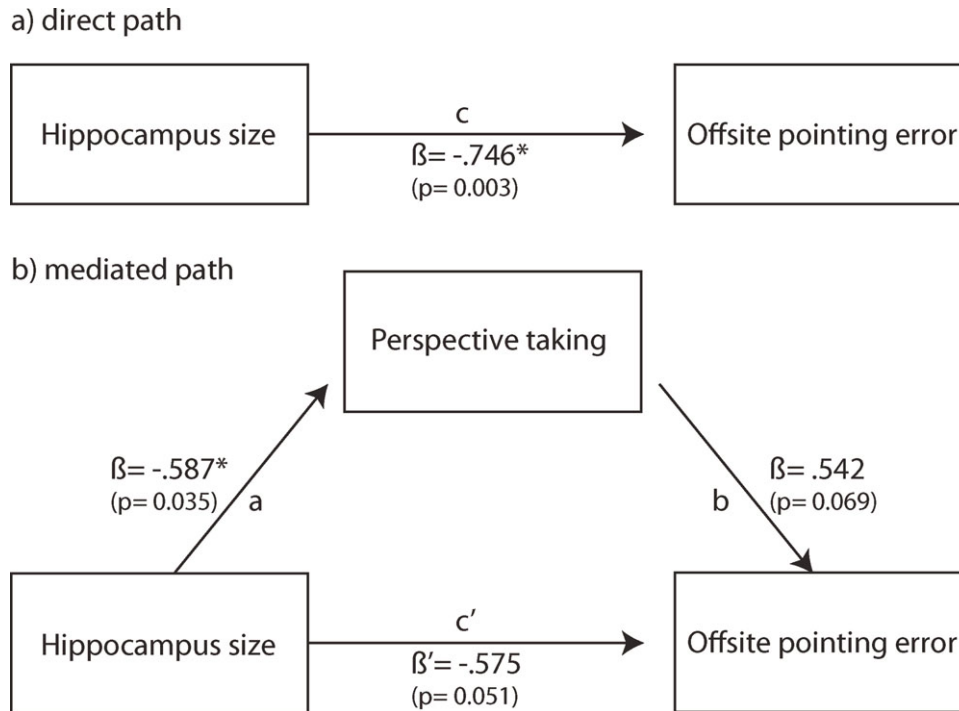
FIGURE 4. Mediation results. Mediation analysis that takes into account the effect of perspective taking ability on the relationship between hippocampal size and offsite pointing error. The total effect of right posterior hippocampal size on offsite pointing error that was mediated by perspective taking ability was 35%. These findings indicate that perspective-taking ability partially (but incompletely) mediates the effect of hippocampal size on offsite pointing performance.

tered as part of a battery of psychometric tests during the MRI session. In this task subjects are presented with a two dimensional array of objects and are asked to determine the egocentric bearing of a target object given an imagined location and facing direction. As such, this task requires subjects to impose an egocentric position and orientation; however, because all objects are simultaneously visible, subjects do not have to recover object locations from memory.

Results for the mediation analysis are presented in Figure 4. The analysis proceeded in four steps. Step 1 was to examine the effect of the independent variable (right posterior hippocampal size) on the dependent variable (offsite pointing error) without taking the mediating variable (perspective taking ability) into account. (We focused on the right posterior hippocampus because this is the region where the structure-performance relationship was the strongest.) Consistent with our previous results, this effect was significant ($\beta = -0.746$, $P = 0.003$). Step 2 was to examine the effect of the independent variable (right posterior hippocampal size) on the mediator variable (perspective taking ability). This effect (path a) was significant ($\beta = -0.587$, $P = 0.035$). Step 3 was to examine the effect of the mediator (perspective taking ability) on the dependent variable (offsite pointing error). This effect (path b) showed a trend that fell short of significant ($\beta = 0.542$, $P = 0.069$). Step 4 was to examine the effect of the independent variable (right posterior hippocampal size) on the dependent variable (offsite pointing error) while controlling for the media-

ting variable (perspective taking ability). When calculated this way, the direct relationship between right posterior hippocampal size and offsite pointing error (path c') falls just short of significance ($\beta = -0.575$, $P = 0.051$), while the indirect effect of hippocampal size on pointing error mediated through perspective taking (bootstrap estimated) is -0.006 and is statistically significant ($P = 0.044$). Further calculation revealed that the percentage of the total effect of right posterior hippocampal size on offsite pointing that was mediated by perspective taking ability was 35%. These findings indicate that perspective-taking ability partially (but incompletely) mediates the effect of hippocampal size on pointing error. Thus, hippocampal size may affect both the ability to form a cognitive map and also the ability to form an egocentric scene from that map.

We also examined the relationship between behavioral performance and gray matter volume in the caudate. Although none of our tasks were designed to measure route-based spatial knowledge, previous work has suggested a competitive interaction between the hippocampus and the caudate during spatial learning (Bohbot et al., 2007), which might be evidenced by an inverse relationship between caudate size and cognitive mapping ability. We did not observe any relationship between caudate size and behavioral performance for the onsite pointing (left $r_{(11)} = 0.26$, $P = 0.39$; right $r_{(11)} = 0.31$, $P = 0.30$, both n.s.), distance estimation (left $r_{(11)} = -0.001$, $P = 0.998$; right $r_{(11)} = -0.14$, $P = 0.64$, both n.s.), or map drawing tasks (left $r_{(11)} = 0.06$, $P = 0.85$; right $r_{(11)} = 0.15$,

$P = 0.63$, both n.s.). Nor did we observe a significant relationship between caudate size and performance on the offsite pointing task, although there was a trend in the expected direction (left $r_{(11)} = 0.39$, $P = 0.18$; right $r_{(11)} = 0.47$, $P = 0.11$). Notably, when within-route and between-route judgments were considered separately, we did observe the expected pattern whereby subjects with larger right caudates made more errors for within-route pointing judgments (left $r_{(11)} = 0.52$, $P = 0.07$, n.s.; right $r_{(11)} = 0.63$, $P = 0.02$) but not for between-route pointing judgments (left $r_{(11)} = 0.23$, $P = 0.45$; right $r_{(11)} = 0.27$, $P = 0.37$ both n.s.). These findings are intriguing, because within-route offsite pointing judgments are most likely, of all the tasks presented to the subjects, to elicit simultaneous retrieval of route-based and map-based memory structures. We did not observe any relationship between the size of the left or right hippocampus and the size of the left or right caudate (all Ps < 0.3, n.s.).

Relationship with age and gender

We also examined whether the correlations between gray matter volume (for the hippocampus and caudate) and offsite pointing error were modulated as a function of age and gender. There was no significant correlation between age and offsite pointing error ($r_{(10)} = -0.36$, $P = 0.26$, n.s.); nor was there a relationship between age and right hippocampal volume ($r_{(10)} = 0.16$, $P = 0.63$, n.s.) or right posterior hippocampal volume ($r_{(10)} = 0.28$, $P = 0.37$, n.s.). There was a marginal trend for older subjects to have smaller right caudates ($r_{(10)} = -0.52$, $P = 0.08$). Some of the nonsignificant results here may reflect the fact that our subjects were drawn from a very narrow age range (20–27), giving us little power to see variation as a function of age. With regards to gender, males performed better on the offsite pointing task than females ($t_{(14)} = 3.43$, $P = 0.004$). Although the size of the right hippocampus as a whole did not differ between genders ($t_{(11)} = 1.01$, $P = 0.31$, n.s.), males had larger right posterior hippocampii ($t_{(11)} = 2.70$, $P = 0.01$) and a marginal trend towards more posterior center of mass ($t_{(11)} = 2.06$, $P = 0.06$, n.s.). There was no difference between the genders in the size of the right caudate ($t_{(11)} = -1.54$, $P = 0.15$, n.s.).

The fact that males had larger right posterior hippocampi than females, and also a trend towards more posterior center of mass, raises the question of whether the previously observed relationships between performance and hippocampal structure could be explained by a categorical difference between the genders. To examine this, we calculated the partial correlation of offsite pointing performance on the hippocampal anatomy measures with gender controlled. Although the partial correlation between offsite pointing and right hippocampal volume remained significant ($r_{(10)} = -0.62$, $P = 0.03$), the partial correlation between offsite pointing and right posterior hippocampus was reduced to marginal significance ($r_{(10)} = -0.56$, $P = 0.06$), and the partial correlation between offsite pointing and right hippocampal center of mass was no longer significant ($r_{(10)} = -0.393$, $P = 0.21$, n.s.). Thus, it is possible that

some of these differences in the structure-performance relationship might reflect differences between the genders rather than variability within the genders. That said, we cannot draw any firm conclusions about the null results because the sample of each gender is very small (8 males, 5 females).

Voxel-based morphometry

To supplement our volumetry analyses, which focused on the hippocampus and caudate, we used voxel-based morphometry (VBM) to examine the relationship between structure and performance across the entire brain. For each of the four behavioral tasks, we implemented a separate GLM that examined the correlation (two-tailed) between gray matter volume and the demeaned behavioral score.

When correcting for multiple comparisons across the whole brain, we found no significant correlations between gray matter volume and performance on the onsite pointing, distance estimation and sketch map tasks. We did, however, observe a significant negative correlation between offsite pointing accuracy and gray matter volume in the right superior parietal lobe ($P < 0.05$, corrected; Fig. 5a). That is, subjects with more gray matter in this region made more errors on the offsite pointing task. This finding is consistent with results of a previous neuroimaging study that found that activity in the right superior parietal lobule was negatively correlated with performance on a virtual maze task and the use of allocentric strategies (e.g., reference to metric distances and cardinal directions) as assessed by a sense of direction questionnaire (SDQ-S) (Ohnishi et al., 2006).

Given our primary hypothesis regarding the role of the hippocampus and caudate, we also considered the relationship between gray matter volume and offsite pointing with a more liberal threshold ($P < 0.05$, uncorrected) in these regions. Consistent with the results of the volumetry analysis, VBM indicated a positive correlation between offsite pointing accuracy and gray matter volume in the right posterior hippocampus (Fig. 5b), and a negative correlation between offsite pointing accuracy and gray matter volume in both the left and right caudate (Fig. 5c). The negative correlation in the caudate was found for within-route but not between-route trials. At these reduced thresholds, we also observed a positive relationship between gray matter volume and offsite pointing performance in the retrosplenial cortex (BA 29/30) and a negative relationship in the precuneus. Thus, the results of the VBM analysis were consistent with those obtained through volumetry, and point to the possibility of a wider tradeoff between regions supporting allocentric and egocentric processing.

DISCUSSION

In this study participants learned the layout of a real-world campus over a period of 3 weeks. They were familiarized with two separate routes in the first learning session, a connecting
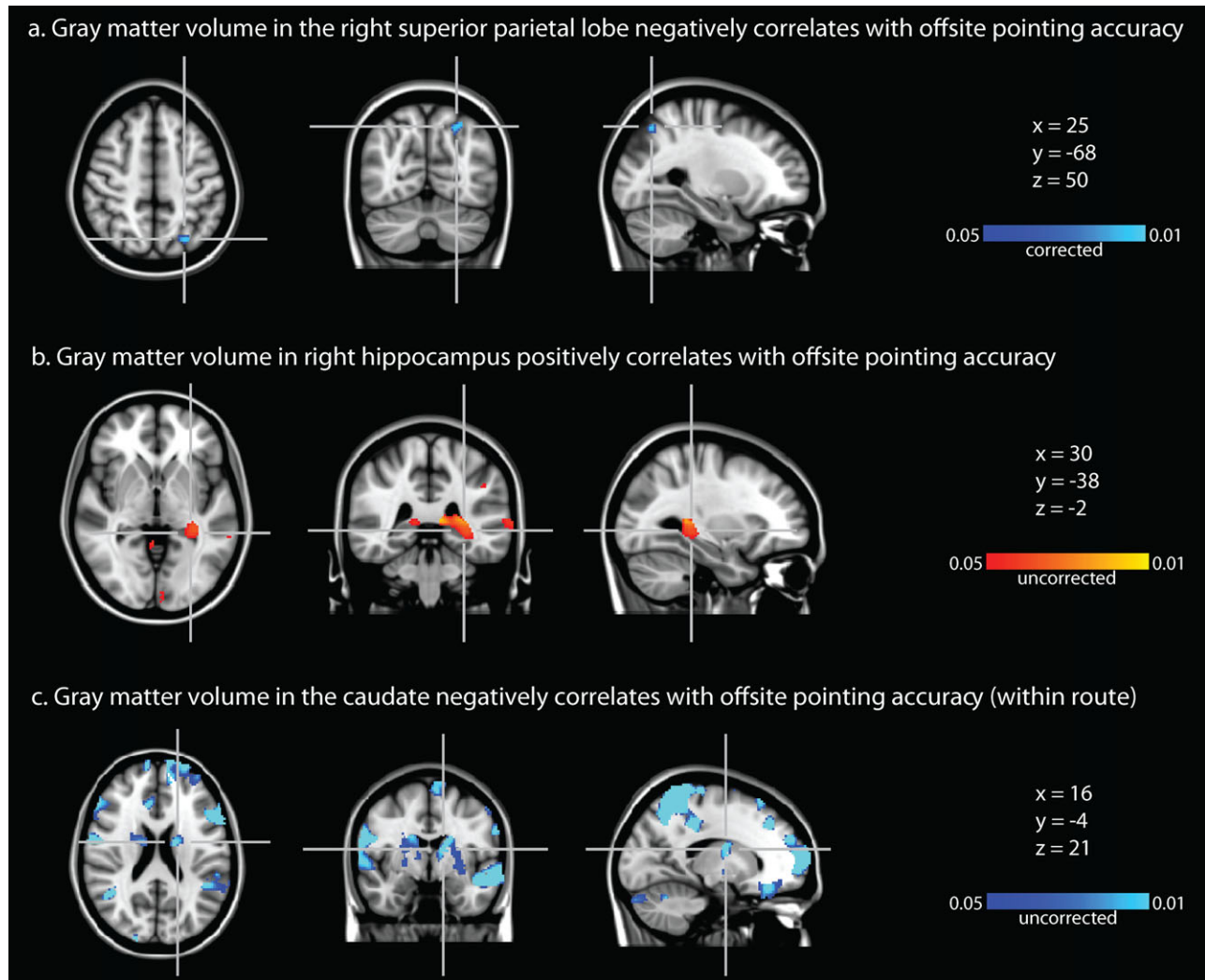
FIGURE 5. Voxel-Based Morphometry (VBM) results. (a) Negative correlation between gray matter volume in the right superior parietal lobe and offsite pointing accuracy. (b) Positive correlation between gray matter volume in the right hippocampus and offsite pointing accuracy. Note that the increase in gray matter is located in the tail of the right hippocampus. (c) Negative correlation between gray matter volume in the caudate (bilateral) and offsite pointing accuracy. Threshold in (a) is $P < 0.05$ corrected for multiple comparisons across the entire brain; thresholds in (b) and (c) are $P < 0.05$ uncorrected.

path in the second session, and a second connecting path in the third session. Their knowledge of the spatial layout of the campus was assessed through a variety of behavioral tasks after each session. They also participated in an MRI experiment in which structural data for a volumetric analysis was acquired. We report two main findings. First, behavioral data indicated that participants were able to rapidly acquire accurate cognitive maps of the environment, integrating the two parts of campus after learning a single connecting path in the second session. Second, volumetry and voxel-based morphometry data indicated that participants with larger right hippocampi performed better on a behavioral task (offsite pointing judgments) that required them to assess the allocentric locations of campus buildings. This effect was especially strong when participants were required to point to buildings that were not located along the same route.

These findings suggest that individual differences in hippocampal anatomy might provide the neuroanatomical substrate for individual differences in cognitive mapping ability.

A key behavioral indicator of a cognitive map is the ability to make straight-line shortcuts between different locations (Bennett, 1996). The offsite pointing task emulates this short-cutting skill because it requires subjects to make judgments of relative direction between different locations even when there is no direct route between them. Like shortcutting, judgments of relative direction require that inferences be made based on the Euclidean coordinates of different elements in the environment—a task that can be difficult (if not impossible) to solve without relying on an allocentric spatial map. Thus, the finding that right posterior hippocampal volume predicts performance on this task in a newly-learned environment suggests that it is

crucially involved in the initial acquisition of survey knowledge, consistent with claims from previous neuroimaging work (Wolbers and Buchel, 2005). Interestingly, the relationship between offsite pointing performance and hippocampal volume was partially (but incompletely) mediated by perspective taking ability, suggesting that part of the advantage of a larger right hippocampus is an enhanced ability to construct an egocentric scene from an arbitrary vantage point (Hassabis et al., 2007).

Complementary to these hippocampal results, performance on the offsite pointing task correlated negatively with the size of the right caudate, but only for locations along the same route. We hypothesize that this negative relationship might reflect competition between route-based representations supported by the caudate and map-based representations supported by the hippocampus: offsite pointing performance may be impaired in subjects for whom the route-based representations dominate. That is, the propensity to use route-based representation may have retarded the development of an accurate cognitive map in some subjects. Results from the VBM analysis offered additional evidence for a possible trade-off between different kinds of spatial coding by showing a negative correlation between pointing accuracy and gray matter volume in the superior parietal lobule. Previous studies have shown the parietal lobe is involved in egocentric spatial coding (Ohnishi et al., 2006; Burgess, 2008). Thus our results suggest that the propensity to use egocentric spatial mechanisms may in some cases impair performance on allocentric tasks.

We did not observe a relationship between hippocampal or caudate volume and performance on the onsite pointing, distance judgment, or sketch mapping tasks. Notably, behavioral performance on these tasks was uncorrelated with behavioral performance on the offsite pointing task, suggesting that they might rely on more transient or more egocentric spatial representations. In the case of the onsite pointing task, subjects might have relied primarily on egocentric scene-based representations to infer the location of the pointing target relative to their current position. In the case of the distance and sketch mapping tasks, the failure to find a relationship between performance and hippocampal volume is more surprising, especially given that sketch maps are commonly used in research in geography and psychology as a measure of integrated survey knowledge (Kitchin and Blades, 2002). Our results, on the other hand, suggest that subjects can use either nonspatial or egocentric spatial strategies to solve these tasks. For example, subjects might have solved the distance task by estimating the amount of time it takes to walk between different locations but these estimations may have been distorted by the complexity of the path, which meant that walking times did not match the Euclidean distances used to score the questionnaire. In the case of the sketch-mapping task, anecdotal observations indicated the majority of participants drew the buildings in the same order they learned when navigating the route, suggesting that their performance reflected route-based rather than map-based memory.

These results are generally consistent with previous research that has implicated the hippocampus in spatial learning and navigation, but provide an important advance over these earlier data. The existence of hippocampal neurons with location-specific firing fields is well established in rats (O'Keefe and Nadel, 1978); recently, hippocampal place cells have also been observed in humans (Ekstrom et al., 2003). Neuroimaging studies have shown that the hippocampus activates during encoding and retrieval of spatial information (Ghaem et al., 1997; Maguire et al., 1998; Wolbers et al., 2007) and neuropsychological studies indicate that lesions to this structure especially impact memory for allocentric locations (Abrahams et al., 1997; Holdstock et al., 2000; Feigenbaum and Morris, 2004). Larger hippocampal volumes have been linked to better memory for the locations of hidden cache sites in birds and to wider foraging ranges in mammals, whereas lack of spatial experience has been shown to induce cell loss and reduction in volume in the hippocampus (Clayton and Krebs, 1994; Lee et al., 1998). Furthermore, as mentioned earlier, larger hippocampal size predicts use of a spatial rather than a response strategy in a virtual maze (Bohbot et al., 2007), and spatial knowledge and hippocampal structure have been indirectly linked through the observation that London taxi drivers have larger posterior hippocampi compared to nontaxi driver control subjects (Maguire et al., 2000) with the size of the posterior hippocampus correlating with the number of years on the job (Maguire et al., 2006). Although all these findings suggest a link between the hippocampus and spatial coding, ours is the first study to directly show that hippocampal size relates to the quality of a cognitive map in a newly-learned real-world environment. As such, our data provide an important missing link that allows us to directly connect individual differences in cognitive map learning to their putative neuroanatomical substrate. Further, our results represent an advance over previous studies that examined navigational performance in a virtual environment but failed to find a relationship between wayfinding accuracy and hippocampal size (Maguire et al., 2003). Differences between the real and virtual environment, or between the task used to assess spatial knowledge (within-site wayfinding vs. offsite pointing) might partially explain the different results obtained in the two studies.

Whether the individual differences observed here are the result of ontogenetic variation in the hippocampus and caudate or microgenetic changes remains to be addressed. A recent study with London taxi drivers demonstrated that changes in hippocampal structure are possible by showing that the size of the posterior hippocampus increased after an extensive navigational training regime extending over a period of years (Woollett and Maguire, 2011). In contrast, the relatively short length our study (3 weeks instead of the 2–4 years for trained taxi drivers) suggests that participants came to us predisposed to encode either map-based or route-based representations. This predisposition may have been the result of a history of implementing spatial or response-based navigation strategies that might have favored the development of the caudate or the hippocampus. Alternatively, it is possible that "early life" individ-

ual differences in hippocampus and caudate size might have favored the adoption of spatial or route strategies during navigation. In any case, the current findings are more plausibly explained by an ontogenetic rather than a microgenetic origin for structural variation in hippocampal anatomy.

Consistent with previous reports (Maguire et al., 2000, 2006; Woollett and Maguire, 2011) we also found evidence that the posterior region of the hippocampus may be particularly involved in spatial learning. Although performance on the offsite pointing task correlated positively with the overall size of the right hippocampus (with a similar, albeit nonsignificant trend in the left), the relationship was stronger for the posterior portion of the structure; furthermore, the hippocampal center of mass was located more posteriorly in better performers. In rats, recruitment of the dorsal hippocampus (equivalent to the posterior hippocampus in humans) has been shown in a variety of maze learning tasks (Fanselow and Dong, 2010)—indeed, almost all place cell recordings are made from the dorsal region—and spatial ability has been shown to correlate with the amount of dorsal tissue in lesion studies (Moser et al., 1993, 1995). Place fields in the dorsal hippocampus are smaller than place fields in the ventral region, suggesting that the dorsal place cells might support more precise encoding of spatial information (Kjelstrup et al., 2008). In humans, the right posterior hippocampus activates during neuroimaging studies of navigation (Maguire et al., 1997; Shelton and Gabrieli, 2002; Suthana et al., 2009) although results from these studies are ambiguous because activity in the left hippocampus and the anterior region are also frequently observed (Spiers and Maguire, 2006; Morgan et al., 2011). Taken as a whole, these data suggest that the right posterior hippocampus supports allocentric spatial coding, although other parts of the hippocampus may play an important role in navigation by processing or evaluating this spatial information (Morgan et al., 2011).

More broadly, our results are consistent with the view that spatial behavior is mediated by a number of different representational structures that support different navigational strategies (Wiener et al., 2004). The quality of these representations and the facility with which they are employed might vary substantially across the population. Our data suggest a neuroanatomical basis for one important source of variability in navigational performance: whereas subjects with larger hippocampi may encode more accurate cognitive maps, and thus might exhibit concomitant navigational strategies such as shortcutting, subjects with smaller hippocampi may encode less accurate cognitive maps, and thus might be more inclined to use response-based strategies. By establishing a relationship between neuroanatomical and behavioral variability, these results offer a novel explanation for individual differences in navigational ability and help to clarify the enduring controversy about the existence of the cognitive map.

Acknowledgments

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