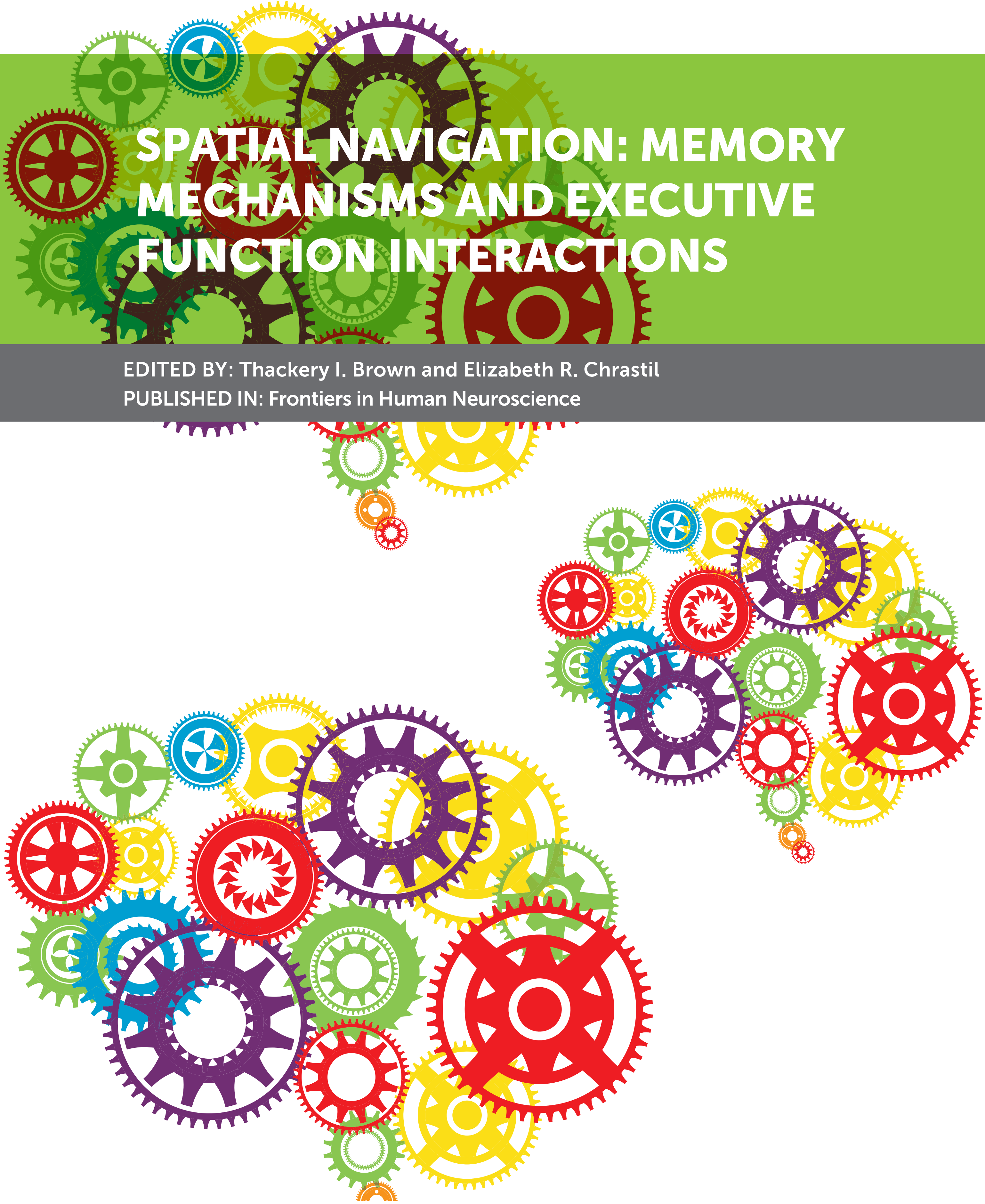

SPATIAL NAVIGATION: MEMORY MECHANISMS AND EXECUTIVE FUNCTION INTERACTIONS

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frontiers Research Topics

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SPATIAL NAVIGATION: MEMORY MECHANISMS AND EXECUTIVE FUNCTION INTERACTIONS

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EDITORIAL
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Editorial: Spatial Navigation: Memory Mechanisms and Executive Function Interactions

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Editorial on the Research Topic

Spatial Navigation: Memory Mechanisms and Executive Function Interactions

Decades of research have emphasized the importance of the medial temporal lobes for spatial navigation and long-term memory. Recent evidence suggests that structures outside of the medial temporal lobes contribute to spatial navigation by providing additional spatial coding and computations relevant for long-term memory, decision-making, and executive function. Together, multiple neural systems may dynamically interact to provide neural architecture that (1) supports dynamic encoding, maintenance, and updating of spatial information and (2) translates convergent spatial and non-spatial information into navigational memories and goal-directed behavior. It is essential that the field pursue mechanistic accounts of how such spatial codes emerge and interact across the brain, bridging theories of spatial navigation, episodic memory, and executive functions.

Recent empirical and theoretical work on these fronts has begun to tackle that very challenge. For example, one way to advance our understanding of the established role of the hippocampus in spatial memory is to explicitly interrogate its position as a node within broader network dynamics. Arnold et al. demonstrated that not only does the hippocampus serve as a network hub, but this functional position changes across encoding and retrieval. Hippocampal network centrality decreased as encoding demands lessened, both as a connector between modules and within the hippocampal neighborhood. Notably, they observed increased hippocampal network connections during mental simulations based on retrieval. Their results indicate a shift in the network dynamics surrounding the hippocampus as encoding demands change, reconfiguring from global integration to localized processing based on the degree of integration of environmental information. These findings connect with recent explorations of the interaction between "semanticized" spatial knowledge (schemas) and episodic navigational memories (van Kesteren et al.). This line of investigation demonstrates that the role of the hippocampus in spatial memory is quite dynamic, such that modulation after one-shot learning depends on the fidelity of prior spatial knowledge of the environment. Such data suggest that spatial schemas can accelerate new learning, while also reducing the computational demands on the hippocampus for subsequent simulations about the environment.

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In light of these insights into the dynamics of navigational memory, an important question to ask is how such hippocampal-extrahippocampal interactions relate to memory performance. Sulpizio et al. combined fMRI with stimuli assessing larger-scale vista space knowledge in a real-world environment. They found that hippocampal activity showed neural adaptation for repeated facing directions, suggesting a spatial heading signal. Conversely, scene-responsive cortical areas showed adaptation to distances, but the hippocampus did not. Critically, the strength of spatial position coding in retrosplenial cortex tracked individuals' ratings of their spatial abilities—suggesting that the locus of individual navigation abilities may extend beyond the hippocampus. This observation complements evidence from Burte et al. that directional sense is tied to an extended hippocampal-cortical network. Here, they observed that gray matter volumes in the hippocampus predicted individual sense of direction, whereas functional brain activity spanning frontoparietal regions—including retrosplenial cortex—were involved in comparing heading directions. Izen et al. examined individual abilities in a path integration task using resting state functional connectivity. They found that functional connections between medial temporal areas and both the right frontoparietal executive network and the default mode network were increased in better navigators. Together, these findings highlight the importance of interactions between the hippocampus and extra-hippocampal regions in defining individual navigational abilities.

The role of retrosplenial cortex in human navigation is a fascinating target for continued research, as evidenced by the studies on individual abilities in this special topic. Not only does this region provide clear direction-related signals in navigating rodents that are distinct from hippocampal spatial codes, but there is considerable variability in the anatomical loci and functional associations of retrosplenial activity across human studies. Burles et al. demonstrate that functional heterogeneity in medial parietal cortex, spanning classically-defined retrosplenial cortex and posterior cingulate, is non-trivial for navigation research. Indeed, there appears to be a dorsal-ventral functional gradient surrounding the posterior cingulate. Regions which are commonly labeled as "retrosplenial cortex" in fMRI studies may therefore be more appropriately referred to as distinct subregions that differentially subserve spatial recall (dorsal) and encoding (ventral).

This special topic also drew important attention to prefrontal circuitry and its relationship to navigational performance. For example, Burte et al. observed relationships between orbitofrontal cortex volume and task accuracy in their study; Izen et al. demonstrated that resting state functional connectivity between the medial temporal areas and networks with prominent prefrontal components predict better path integration ability. This work underlines the importance of future research generating a greater understanding of prefrontal-related executive function in spatial cognition.

What are the ramifications of such observations? One answer is they can provide insight into cognitive development across the lifespan. For example, Sneider et al. examined hippocampal and prefrontal brain activity in adolescents during a virtual Morris water maze task. They observed that during adolescence, worse performance during spatial retrieval was associated with greater BOLD activation of angular gyrus and supramarginal gyrus, whereas worse performance during visible platform navigation was associated with less activation of anterior prefrontal cortex. They suggest that in adolescents, less BOLD activation of the frontal pole in worse navigators could be a sign of less effective navigational path planning. Such questions can also be asked in aging populations, where spatial abilities and strategies may regress in the other direction. In particular, Zhong and Moffat's careful survey of the literature indicates that changes in prefrontal function may play a major role in both strategy switching and spatial association learning as we age.

The mechanistic basis for spatial strategy shifts and associative memory are ripe for continued research, even in the canonical sample of healthy college age adults. As reviewed by Goodroe et al., the classic dichotomy of attributing allocentric spatial memory to the hippocampus and egocentric route-based memories to the striatum is not comprehensive enough to include all of the mechanisms needed for many navigation scenarios. For example, some route-based memories may draw on episodic-memory mechanisms and prefrontal control processes, even after much practice. One alternative to describing navigational scenarios based on modularized brain function or spatial reference frame is to adopt a model-based vs. model-free reinforcement learning perspective of task demands. Starrett and Ekstrom offer a complementary examination of such issues, focusing specifically on challenges for distinguishing egocentric and allocentric spatial representations, while introducing a new task—the relative vector discrimination task. This new paradigm may better target the allocentric dimension of spatial representations than established virtual navigation tasks. Such advances in paradigm structure may help researchers resolve how we flexibly acquire, integrate, and draw on different reference frames of our environments. Understanding reference frames and how they relate to other theoretical perspectives such as reinforcement learning is critical for the field. As He and McNamara show, initial headings when experiencing an environment define a reference frame for the space that can influence subsequent learning and spatial updating. Together, these articles are pushing the boundaries of how we understand reference frames.

How "non-spatial" cognitive differences are associated with different behavioral strategies is also a particularly important direction for continued research. For example, although spatial ability is a clear driving factor, predispositions to anxiety, risk aversion, and enjoyment from the act of exploration, can manifest in profound differences in how we choose to traverse our environment. In fact, as Pazzaglia et al. show, latent spatial abilities better predicted route-tracing performance, whereas measures of anxiety, efficacy, and pleasure in exploring (among other personality traits) were more likely to predict shortcut-finding performance. It is intriguing to think about how such relationships interact with the dynamic nature of real world environments. For example, in this special topic, Piccardi et al. examined spatial memory in L'Aquila earthquake-exposed survivors, and suggest that continuous and extreme environmental changes could mean that people need to attend more to navigational space, leading to improvements in topographical learning. The ability to adjust learning and attentional strategies in a dynamic world may be a critical trait related to whether and how effectively people balance exploration and exploitation to maximize learning and navigational efficiency.

One exciting aspect of bringing such a diverse range of scholars together for a special topic such as this is its power to generate new ideas. Convergent and divergent findings in the empirical work, as well as in the literature reviews, compile and underscore key future directions for the field. For example, as highlighted in the extensive review by Herweg and Kahana, behavioral work in humans does not unequivocally support the use of a metric Euclidean map for navigation. Formal models of navigational behavior, which account for environmental scale and complementary learning mechanisms, may help to better understand different navigational strategies. One approach to refining such models could be to study how place- (and concept-) responsive single-cell activity relates to ongoing theta oscillations during both the encoding and retrieval of spatial and non-spatial associations. These temporally-extended and recurring oscillatory signals could complement fMRI work in the grand objective of unifying theories of medial temporal lobe function under the umbrella of mechanisms that relate or discriminate experiences across multiple temporal and spatial scales.

Other opportunities for continued research into extra-hippocampal mechanisms exist in causal/interventionist approaches. As highlighted in Brunye's review (Brunyé), recent advances in functional connectivity analyses have revealed stable functional networks that include both deep subcortical structures and regions on the cortical surface. This finding suggests that the modulation of superficial brain regions such as the inferior parietal lobule and lateral prefrontal cortex may carry powerful downstream consequences for deeper brain systems involved in spatial processing and real-world navigation. Transcranial electrical stimulation has gained popularity as a tool for modulating several aspects of perception and cognition. As we come to understand the parameters underlying effective excitation and disruption protocols with this tool, we may be able to gain causal understanding of the relationships between, for example, neocortical oscillations and spatial computations. Moreover, our growing understanding of functional network profiles within the navigation system may enable the use of such tools to indirectly target subcortical brain regions by altering neuronal activity in distant—yet functionally connected—cortical areas.

Collectively, the articles in this special topic highlight new and exciting directions for the field of spatial navigation. The studies all look beyond the traditional boundaries of spatial navigation research, either by examining functional brain networks, new techniques, individual differences, or establishing connections with personality traits and executive functions. The innovative ideas generated in this special topic provide a wealth of avenues for future research.

AUTHOR CONTRIBUTIONS

TB and EC co-wrote all aspects of the manuscript.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Learned Spatial Schemas and Prospective Hippocampal Activity Support Navigation After One-Shot Learning

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Prior knowledge structures (or schemas) confer multiple behavioral benefits. First, when we encounter information that fits with prior knowledge structures, this information is generally better learned and remembered. Second, prior knowledge can support prospective planning. In humans, memory enhancements related to prior knowledge have been suggested to be supported, in part, by computations in prefrontal and medial temporal lobe (MTL) cortex. Moreover, animal studies further implicate a role for the hippocampus in schema-based facilitation and in the emergence of prospective planning signals following new learning. To date, convergence across the schema-enhanced learning and memory literature may be constrained by the predominant use of hippocampally dependent spatial navigation paradigms in rodents, and non-spatial list-based learning paradigms in humans. Here, we targeted this missing link by examining the effects of prior knowledge on human navigational learning in a hippocampally dependent virtual navigation paradigm that closely relates to foundational studies in rodents. Outside the scanner, participants overlearned Old Paired Associates (OPA— item-location associations) in multiple spatial environments, and they subsequently learned New Paired Associates (NPA—new item-location associations) in the environments while undergoing fMRI. We hypothesized that greater OPA knowledge precision would positively affect NPA learning, and that the hippocampus would be instrumental in translating this new learning into prospective planning of navigational paths to NPA locations. Behavioral results revealed that OPA knowledge predicted one-shot learning of NPA locations, and neural results indicated that one-shot learning was predicted by the rapid emergence of performance-predictive prospective planning signals in hippocampus. Prospective memory relationships were not significant in parahippocampal cortex and were marginally dissociable from the primary hippocampal effect. Collectively, these results extend understanding of how schemas impact learning and performance, showing that the precision of prior spatial knowledge is important for future learning in humans, and that the hippocampus is involved in translating this knowledge into new goal-directed behaviors.

Keywords: memory, schema, prior knowledge, spatial learning, hippocampus, medial temporal lobe, navigation, prospective planning

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INTRODUCTION

Prior knowledge strongly affects new learning (Bartlett, 1932; van Kesteren et al., 2012). New information that is stored in relation to prior knowledge structures (or schemas) is generally better remembered (McVee et al., 2005). The updating of knowledge networks is suggested to be mediated, in part, by retrieval of associative knowledge during learning (Preston and Eichenbaum, 2013), through an interplay between the medial temporal lobe (MTL) and medial prefrontal cortex (mPFC; van Kesteren et al., 2012; Gilboa and Marlatte, 2017). In rodents, where memory tasks are frequently spatial in nature, the facilitative effects of prior knowledge have often been attributed to computations within the hippocampus (Burgess et al., 2002; Hartley et al., 2003; Squire et al., 2004; Eichenbaum et al., 2007) in concert with representations in the mPFC (Tse et al., 2007, 2011; McKenzie et al., 2013, 2014; Richards et al., 2014). By contrast, human neuroimaging studies, which use predominantly non-spatial paradigms (though see van Buuren et al., 2014; Liu et al., 2017; Sommer, 2017), have often failed to observe hippocampal activity during the encoding of new schema-related knowledge (van Kesteren et al., 2010b, 2013; Brod et al., 2015). To bring the animal and human literatures closer together, it is of interest to examine the effect of existing spatial knowledge (Burgess et al., 2002; Hartley et al., 2003; McNamara et al., 2003) on new spatial learning in humans, and how this relates specifically to neural processing in the hippocampus and surrounding MTL cortices.

In the human spatial navigation literature, the role of the hippocampus in spatial processing has often been juxtaposed with functions attributed to other memory systems in the brain (Hartley et al., 2003; Iaria et al., 2003; Voermans et al., 2004; Doeller et al., 2008; Brown and Stern, 2014) and, of particular relevance to the present study, adjoining MTL cortex (Weniger and Irle, 2006; Ekstrom and Bookheimer, 2007; Weniger et al., 2010; Howard et al., 2011, 2014; Ekstrom et al., 2014). Across studies, the updating of spatial knowledge of an environment has been alternately associated with the hippocampus or parahippocampal cortex (Wolbers and Büchel, 2005; Weniger et al., 2010), with the divergence putatively being due to differences in allocentric vs. egocentric reference frames. Converging with foundational work on cortical declarative memory consolidation (McClelland et al., 1995), functional and neuropsychological data from studies of spatial navigation and remote spatial memory (Stefanacci et al., 2000; Rosenbaum et al., 2004; Moscovitch et al., 2006) suggest that long-term storage of learned spatial knowledge may rely on posterior parahippocampal cortex and a network of connected cortical regions, rather than the hippocampus. However, current perspectives from functional studies emphasize that, especially for new or recently formed memories, it is difficult to identify clean or natural dissociations between: (a) the navigational functions of the hippocampus and parahippocampal cortex; and (b) allocentric and egocentric reference frames (Ekstrom et al., 2014; Wolbers and Wiener, 2014). Reciprocal processing in the hippocampal-MTL cortex circuitry can give rise to both memory for navigational routes as "episodes" and spatial map knowledge which may ultimately and more gradually become "semanticized," and it has been proposed that the mechanisms that give rise to these two forms of spatial memory may overlap with those underlying episodic memory and semantic knowledge in non-navigation settings (Buzsáki, 2005; Buzsáki and Moser, 2013). Consistent with these views, it may be the case that the combined, rather than selective, functions of the hippocampus and parahippocampal cortex may support recently learned spatial environment knowledge and enable new navigational experiences to update that knowledge.

Critically, both the hippocampus and parahippocampal cortex represent spatial goals from knowledge of overlearned virtual environments (Brown et al., 2016). Activity in both regions during navigational decision-making is also sensitive to the introduction of new routes/goal locations in a familiar environment (Brown and Stern, 2014; Brown et al., 2014). Such findings, along with evidence that new learning updates spatial goal representations in the rodent hippocampus (McKenzie et al., 2014), suggest that, although findings to date in humans mainly implicate extrahippocampal regions in the interaction between existing knowledge structures and new learning, the hippocampus and parahippocampal cortex may together be important for updating and accessing spatial knowledge structures in service of goal-directed behavior. As such, an important question is whether and how hippocampal and parahippocampal-dependent spatial retrieval mechanisms relate to prospective planning and goal-directed navigation for newly learned information that can be integrated into existing spatial knowledge structures.

Here, we targeted this question in humans, using a spatial navigation paradigm and fMRI to test whether: (1) as in prior rodent studies, existing spatial knowledge benefits new learning; and (2) whether the hippocampus and parahippocampal cortex, known to mediate spatial memory, support prospective planning of navigation based on new memories that relate to existing spatial knowledge. We designed a virtual navigation experiment, conceptually inspired by the event arena used in rodent research (Tse et al., 2007), to test whether the precision of prior spatial knowledge Old Paired Associate (OPA) predicts new, one-shot learning of a New object-location Paired Associate (NPA). Furthermore, we sought to examine the relationship between prospective hippocampal retrieval effects and one-shot NPA-learning facilitated by OPA knowledge. In the experiment, participants first learned the locations of faces (OPAs) through free navigational exploration of multiple, similar environments. After extensive OPA learning, they learned a new location (NPA) in each of the environments while undergoing fMRI. We hypothesized that greater OPA-knowledge precision would predict one-shot NPA-learning. Furthermore, we expected this behavioral effect to be facilitated by prospective retrieval effects in the hippocampus and parahippocampal cortex during navigational planning, supporting a role for the MTL system in incorporating rapidly integrated spatial experiences into planning and spatial goal localization.

MATERIALS AND METHODS

Participants

Twenty-two neurologically healthy, right-handed participants with normal color perception between 18 years and 35 years old were recruited through Stanford's University's Sona-systems for subject recruitment, through flyers and through posting to a postdoctoral email list. Four participants did not complete the experiment due to virtual reality-induced motion sickness on the first day (Day 1), and two additional participants did not perform well enough to progress to the second day (Day 2)/scanning part of the experiment (see below for details). Accordingly, 16 participants (eight males; mean age 23.13 years, SD 4.60 years, range 18–35; 10 Caucasian, 2 American Indian/Native Alaskan, 2 Asian, 1 African American and 1 Hispanic) were scanned and entered in the analyses. Participants self-reported to have started to learn English on average at age 2.75 (SD 3.99) years and had 17.44 (SD 3.63) years of education. On average, participants self-reported to have slept 7.13 (SD 1.20) h between Day 1 and Day 2. This study was carried out in accordance with procedures approved by the institutional review board at Stanford University. All subjects gave written informed consent in accordance with the Declaration of Helsinki on both days and received monetary compensation for their time (maximum $90).

Procedure

OPA Training (Behavioral)

Participants were instructed to learn the spatial locations of 36 unique faces embedded in 36 unique rooms (see **Figure 1**) using a 2D virtual-reality navigation approach (Vizard VR, WorldViz). Rooms were square, sized at 40 (w) × 40 (l) × 10 (h) arbitrary units (a.u.); faces appeared on small, 3 × 3 × 3 a.u. cubes. The rooms only differed with respect to the wallpaper that was printed on one of the walls in full (40 × 10 a.u.) and on the other three walls as a smaller painting (12 × 3 a.u.). Wallpapers consisted of distinctive colored fractal patterns (collected from the internet); faces were colorized images of distinct Caucasian individuals (18 males, 18 females), and appeared on all four sides of a cube positioned at a pseudo-random location in each environment (see below under "Stimuli" section for specifics). On Day 1, participants learned the 36 room-face-location associations (Old Paired-Associates; OPA) across eight self-paced training blocks (OPA blocks 1–8); on Day 2, participants performed "top-off" learning across another four self-paced training blocks (OPA blocks 9–12).

To illustrate the procedure and learn how to navigate in the virtual rooms, participants first received practice on Day 1, which consisted of three trials in rooms with gray walls and white boxes at fixed positions. They used the "up," "left" and "right" arrow buttons on the keyboard to navigate; they were not allowed to back up. Across the training trials on Days 1 and 2, participants were instructed to come up with their own strategy to learn the associations and to incorporate all three components (room/wallpaper, face and location) in memory. Furthermore, they were instructed to take the most direct route to the face when they knew its location, which allowed us to compare their traversed path length to the optimal path length Euclidian Distance (ED) from the starting position to the face's location.

Within each training block, room order was randomized. At the beginning of each training trial within a training block, participants were cued with one of the 36 faces that was associated with that specific room (randomly assigned for each participant); the face was presented on a gray background for 1 s. They were then positioned in one of the corners of the corresponding room, oriented towards the room's center. Participants were instructed to find the face, which was printed on the sides of a white cube positioned at a specific location in the room. In training OPA block 1, the face/cube was made visible throughout and participants only had to move to it to continue to the next trial. We adopted this design because it was discovered through behavioral piloting that participants would otherwise struggle to learn the 36 OPA locations in a reasonable training time. Although this renders block 1 of OPA and NPA learning (described below) incomparable, this effectively serves to boost OPA block 2+ beyond what was observed without this manipulation during piloting. In all subsequent training blocks (i.e., OPA blocks 2–12), the face/cube was hidden from sight and only appeared when participants arrived at its location ("arrival" was coded as appearing within a circle of 7 a.u. diameter). This meant that during the last 11 training blocks (OPA blocks 2–12), participants could find the face through memory or by exploring the room. A trial ended after the face was found and the participant walked into it (within a circle of <2 a.u.), after which the viewpoint rotated to the floor and was held in place with the ground texture and face stimulus centered in their field of view for 2 s, accompanied by the text "You found it, well done!." After each training block of 36 trials, participants were allowed to take a short break; participants initiated the start of the next training block by making a button press.

Across each set of four Day 1 training trials for a room, all four starting positions were used once (order determined randomly without replacement) to discourage a strictly egocentric spatial learning strategy. For each room, the associated face, path length, optimal path length and search time were logged, as well as the total trajectory in x- and y-coordinates. After OPA block 4 and after OPA block 8, participants received an association test that directly probed their memory for the wallpaper-face associations (see "Memory Tests" section below for more details). These tests were designed to further encourage participants to form room/wallpaper-face-location associations (rather than simply face-location associations). The total procedure on Day 1 took on average about 2.5 h (range 2–3 h).

Day 1 performance was assessed by computing path efficiency (PE = traversed path length/optimal path length). Based on behavioral pilot experiments, we required participants to demonstrate strong knowledge of the faces' locations at the end of Day 1. Specifically, the average PE across the final three Day 1 training blocks (i.e., OPA blocks 6–8) had to be <2 (using a weighted average of PE: OPA block 6*0.15, block 7*0.25, block 8*0.6); all but two participants reached this

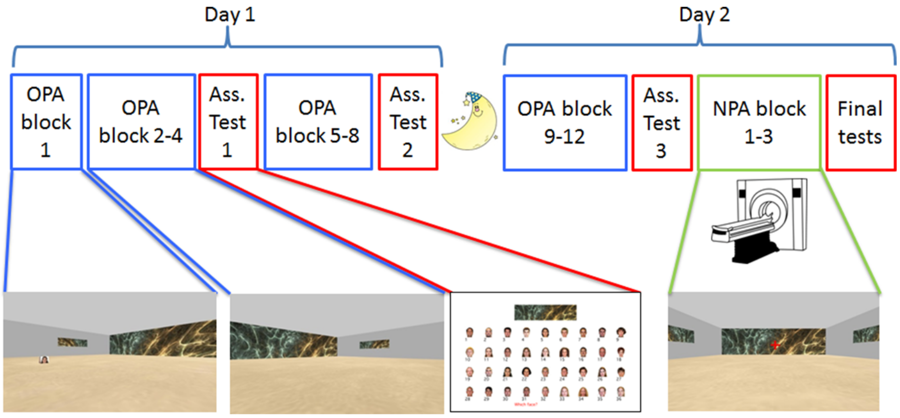

FIGURE 1 | Experimental design. Participants were tested on two consecutive days, approximately 24 h apart. The paradigm was a 2D navigational paradigm in which participants were instructed to learn face-cue locations (Old Paired Associates, OPA; in blue) in 36 rooms with differential wallpapers. On Day 1 and the beginning of Day 2, participants learned OPA-locations on a laptop computer. During OPA block 1 they saw the OPA-location and just had to move to it, but for OPA blocks 2–12 they had to search for the hidden OPA-location. After OPA blocks 4, 8 and 12, participants received an associative memory task in which they were asked to pair the right face with the correct environmental/room wallpaper (in red). After finishing OPA training, participants underwent fMRI while they learned a new (New Paired Associates, NPA; in green) location for each room, this time without a face.

level of learning and were invited to come back for Day 2 ~24 h later (mean lag of 23.97, SD 0.39 h). These criteria were set *a priori* and were calculated to differentially weight the latest block, under the assumption that it provides the most up-to-date measure of learning, while not solely depending on performance in the latest blocks due to concerns about variability due to nuisance factors (e.g., possible effects of fatigue; transient fluctuations in motivation/attention; etc). On Day 2, participants performed the four "top-off" OPA training blocks (OPA blocks 9–12), which were identical to OPA blocks 2–8 in structure, but were randomized (such that the order of, e.g., block 2 on Day 1 was the order of block 3 on Day 2), starting again once from all four starting positions. Following training, participants performed another test of the wallpaper-face associations before they proceeded to the critical fMRI scanning session. Note that all Day 1 and the Day 2 training blocks and wallpaper-face associative memory tests were administered in a behavioral testing room, four floors above the MR scanning suite.

NPA Learning (fMRI)

On Day 2 and following OPA learning, participants underwent fMRI scanning while they learned a NPA for each of the 36 rooms. All general task variables related to navigating the rooms (i.e., the size of the rooms, the fractal wallpapers, navigation speed, et cetera) were held constant between the OPA training and NPA learning. During NPA learning, participants were instructed that they would be navigating all rooms again three times, but that the hidden faces were no longer in the rooms. Instead, there would be a new location at which a hidden white box was placed and they were instructed to find and learn the location of the box. Critically, this time the white box was not visible during the first NPA block, and thus they had to search for it from the start. Moreover, to equate visual input at the start of each trial, participants did not start at the corners of the room as during OPA training, but instead always started positioned against the middle of the wall opposite to the wall covered in full with wallpaper. At the beginning of each trial, participants were placed in the room facing the opposite wall and were informed that they had to wait 8 s before they could start searching for/navigating to the NPA; this 8-s period thus provided an opportunity for participants to plan their navigation (*planning period*). The planning period was further signaled by a red fixation cross in the middle of the screen that disappeared after 8 s; the response buttons were locked during this period, ensuring the participants did not move in the environments. At the end of each trial, corresponding to when the participant arrived at the NPA's location, a white square was presented in the middle of the screen for 2 s (*goal-arrival period*). A 7-s inter-trial interval (ITI), consisting of a white fixation in the middle of the screen, separated each trial; following the ITI, the fixation cross turned green, indicating that a new trial was about to start; onset of the next trial was aligned with the onset of the next TR. For each room, in addition to the associated OPA face, path length to the NPA, optimal path length to the NPA and NPA search time, onset times were logged for both the planning period and the goal-arrival period.

Participants lay supine in the scanner and viewed the screen through a mirror on top of the coil. Head movement was minimized using padding around the head and, when participants did not object, masking tape was placed on the forehead and attached to the sides of the coil. This tape provided movement feedback to the participant. To navigate the environments, participants used a 4-key button box (fORP 932, Current Designs) under their right hand. During practice (three trials) in the scanner, a structural scan was run. As during OPA training, participants were shown the locations of the white boxes within novel rooms, enabling them to practice using the navigation buttons (the first three buttons of the button box: left (forefinger), forward (middle finger), right (ring finger)).

Subsequently, each NPA block consisted of one trial in each of the 36 rooms; these trials were randomly divided into two sets of 18 trials, which corresponded to two separate scanning runs. Thus, participants performed six runs of 18 rooms each, allowing each room to be repeated three times. After each run, participants were given the possibility for a short break of a few minutes in the scanner. When all six runs were finished, participants completed two 6-min localizer tasks (see below for more details). Then they were taken out of the scanner and were given a short break. Finally, they were taken back to the behavioral testing room to take two more memory tests and fill out some questionnaires (see below under "Memory Tests" section). In total, participants spent between 3 h and 4 h on Day 2: ∼1 h for OPA blocks 9–12, ∼2 h for the critical NPA learning phase in the scanner, and ∼0.5 h for the final memory tests and questionnaires.

Memory Tests

All memory tests were presented using PsychToolbox 3.0.10[1] in Matlab (MathWorks) on a laptop. The wallpaper-face association tests that were interleaved throughout OPA training (i.e., after OPA blocks 4, 8 and 12) probed associative memory for the face cued with the wallpaper. On each test trial, a wallpaper cue was shown on top of the computer screen (the 36 wallpaper cues were presented in random order). Below each wallpaper cue, all 36 faces were shown in random order in four rows of nine faces (see **Figure 1**), all accompanied by a number (1–36). The participants were instructed to type the number of the associated face and press "Enter" to proceed to the next trial. Trials were self-paced and reaction time was logged.

Following scanning on Day 2 (see "Procedure" section above), participants completed two final memory tests, probing final spatial memory for the NPA and OPA given the wallpaper or the OPA (face cue) outside of virtual navigation. In the first test, participants were shown a birds-eye view of the room with the wallpaper cue printed above in random order. Participants were instructed to click on the room where the NPA location was located as related to the wallpaper. After clicking, they proceeded to the next room. In the second tests, participants were shown the same view of the room, but now with a gray wallpaper and the associated OPA face cue, again in random order. They were instructed to first click where the OPA was located, after which the OPA was moved to the right location. Then, the participants were instructed to click where the associated NPA location was within the same room. After these final memory tests, participants filled out questionnaires that probed: (a) general navigating strategies Questionnaire on Spatial Representation (QSR; Pazzaglia and De Beni, 2001); and (b) strategies specific to this paradigm. Participants were also asked to report the number of hours slept between Day 1 and Day 2.

Stimuli

All rooms had gray walls, a gray ceiling and a beige textured floor. Corners were accentuated with a black line to make them more visible. Wallpaper fractals and faces were selected based on behavioral piloting that ensured each stimulus was easily identifiable and distinguishable from the others. Wallpaper-face pairings for each environment were randomized for each participant.

For each participant, the OPA locations were pseudo-randomly assigned to rooms without replacement, taken from a set of 36 predetermined locations that were calculated given a few boundary conditions: (1) locations that were too close to the walls were excluded, making sure participants could walk around the box from all sides (3 a.u.); (2) a location needed to have at least a 3-s walking distance from any corner, which ensured that participants did not immediately run into it when searching/navigating; and (3) OPA locations were calculated to be approximately evenly distributed across the environments within the aforementioned constraints (such that, across environments and participants, the floor space was approximately evenly tiled with OPA locations). For NPA locations, we calculated new location coordinates using similar boundary conditions, but the locations were positioned to have at least a 3-s walking distance from the starting position used for NPA learning. Critically, each participant's NPA locations were also constrained to be at least 7 a.u. from the same environment's assigned OPA location and at least 2 a.u. from all other OPA locations used for that participant (to prevent across-environment OPA-NPA overlap). NPA locations were not the same, for a given environment, across participants.

Localizer

Following the NPA scanning blocks, participants performed a functional localizer task (consisting of two 360 s fMRI runs) to determine subject-specific face, scene (all outdoor scenes to maximize distinction with the indoor room in our main task), and room-cue related brain activity. Because the localizer scans were performed to support the testing of hypotheses that are not the focus of the present manuscript, we refrain from reporting the details of these scans as they are not germane.

MRI Parameters

Participants were scanned at the Stanford Center for Cognitive and Neurobiological Imaging (CNI) using a 3T GE Discovery MR750 scanner and a 32-channel head coil (Nova Medical). A T2*-weighted echo planar imaging sequence (TR = 2 s; TE = 30 ms; flip angle = 77 degrees; acquisition matrix = 80 × 80; 42 oblique slices oriented along the AC-PC axis; 2.9 × 2.9 × 2.9 mm spatial resolution) was used for both the experimental and localizer scans. The number of scan volumes differed across participants and across runs because of the variable path lengths taken to the NPAs. Additionally, a 3D T1-weighted anatomical scan was acquired for normalization and activity localization (TR = 7.24 ms; TE = 2.78 ms; flip angle = 12 degrees; acquisition matrix = 256 × 256; 186 sagittal slices; 0.9 × 0.9 × 0.9 mm spatial resolution).

fMRI Preprocessing

Raw fMRI data from the spatial navigation/NPA learning task were preprocessed using SPM12[2]. First, the functional data were slice time corrected to the middle slice. Second,

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[1] http://psychtoolbox.org

[2] http://www.fil.ion.ucl.ac.uk/spm

motion correction was performed by using iterative rigid body realignment to minimize the residual sum of squares between the first and all other functional volumes. Third, rigid body co-registration to the corresponding individual T1 structural image was performed using mutual information optimization. Fourth, segmentation of the T1 structural image into gray matter, white matter and cerebrospinal fluid (CSF) was performed. Fifth, data were spatially normalized using DARTEL (Ashburner, 2007; Yassa and Stark, 2009), where a common template was calculated based on the average of all individual segmented T1 structural images (gray and white matter). Finally, data was spatially smoothed at 8 mm FWHM. To further control for the influence of artifacts, we utilized the Artifact Detection Tools (ART[3]) to identify signal intensity and combined motion-signal intensity outliers in conjunction with the movement parameters calculated in SPM. Artifacts and motion parameters were included in the single-subject first-level models (see below).

Behavioral Analyses

We first established that OPA and NPA learning rates (**Figure 2**) were significant (non-zero slopes) by averaging the normalized PEs of the 36 rooms for each block. A repeated-measures ANOVA, with 11 measurements for OPA training (the first block in which the location was visible was excluded) and three measurements for NPA learning, was used to examine learning (both PE and time to cue) of the OPA and NPA locations over blocks using IBM SPSS Statistics 24. Pearson correlations were used to examine the relationship between PE and time to get to cue.

To test for a "schema" learning benefit of OPA knowledge on subsequent NPA learning, two analyses were conducted:

1. First, as an initial coarse test of the hypothesis, a repeated-measures ANOVA examined whether performance on NPA blocks 2–3 was significantly greater than on OPA blocks 2–3. While superior NPA vs. OPA performance could reflect the benefits of prior knowledge of the OPA's location within a room during NPA learning, other accounts are also viable (e.g., learning to learn within the task). A room-level test (analysis #2) is needed to directly examine the hypothesis.
2. Second, we conducted a room-level test, analyzing whether room-by-room OPA performance during training predicted one-shot encoding success for a new spatial association (i.e., NPA learning) in the same environments (**Figure 3A**). Given that memory retrieval has been linked with mnemonic malleability (Schlichting and Preston, 2015; van Kesteren et al., 2016; Lee et al., 2017), we first examined the relationship between one-shot NPA learning and prior knowledge as a function of the precision (PE) of the most recent OPA retrieval experience in an environment (OPA block 12; hereafter "$\text{OPA}_{\text{recent}}$"). Second, we explored in a separate model how trial-invariant spatial memory performance for each environment, weighted over the last four blocks (rather than the most recent experience; within-room average PE for OPA blocks 9–12 — "$\text{OPA}_{\text{average}}$"; see below for details), relates to one-shot NPA learning.

The second set of analyses leveraged Linear Mixed Effects (LME) modeling in R Core Team (2012) to test the predicted behavioral relationships as fixed effects, while accounting for random effects and mediating factors. One powerful aspect of LME for group-level inference of this type is that we can better characterize predicted fixed effects (e.g., group-level OPA-NPA performance relationships) by accounting for a range of random effects—specifically, not only random intercepts for participants, but random slopes for participants in the tested relationship, as well as "item effects" (random, undesired systematic effects of room). When these effects are not accounted for, such random effects can color interpretation of the fixed effects. Specifically, examination of the data revealed a complex relationship between "luck" when searching the environments during the first block of NPA learning (i.e., NPA block 1) and NPA performance during the second block (i.e., NPA block 2; see **Figure 3B**). Because such instances of "luck" have dramatic biasing effects on our measure of NPA one-shot learning (i.e., NPA block 2 PE), they complicate a test of the relationship between OPA memory and NPA learning. Accordingly, we divided NPA block 1 PE data into two distinct components and included them as additional predictors in our LME models: (1) "lucky shots," defined as trajectories within 15% of the optimal path length, at which point paths began to approximate direct routes to the goal. This cutoff was derived from an initial computation of Frechet distance, as implemented in the Similarity Measures R package (Alt and Godau, 1995), which provides a measure of how far a trajectory (participant's true path) deviates from a reference trajectory (optimal path). In the context of our open field experiment, where trajectories can vary considerably in their shape, this is an ideal measure for characterizing when a true path was a spatially close match to the optimal trajectory. A Frechet Lucky Shot cutoff of 3.5 units was set based on the radius in which the hidden goal locations would become visible, which effectively meant that the participant searched for the NPA on a path that deviated from the optimal direct trajectory so little that they could not miss the target. In the standard PE metric used in the literature, this cutoff equated to $\leq$ 15% PE (with one exception, a case in which a participant accrued 31% PE by zigzagging across the optimal path. Using this participant's PE as cutoff, however, would be quite liberal, resulting in many indirect paths being classified as lucky shots); and (2) residual block 1 PEs. These block 1 PE residual data exhibited a linear relationship with NPA block 2 performance.

Respectively, "lucky shots" composed 12.0% of trials and were associated with worse NPA one-shot learning and longer block 1 residual PEs were associated with worse one-shot learning (evident in the overall one-shot learning*encoding PE relationship in **Figure 3B**). Although Lucky Shots were defined by a PE threshold, it is worth noting that they did not exhibit any relationship to the proximity of the hidden NPA location (Lucky Shot optimal path length: 12.0–36.5 [mean 20.7 a.u.] vs. 12.1–37.6 [mean 24.2 a.u.]). This may be because participants tended to employ distinctive search strategies in NPA block 1 (e.g., spiraling) that could give rise to a lucky, fairly direct trajectory towards the target. Controlling for these

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[3] http://www.nitrc.org/projects/artifact_detect/

two dimensions of NPA block 1 variability when examining the relationships between $\text{OPA}_{\text{recent}}$ and $\text{OPA}_{\text{average}}$ and NPA one-shot learning allowed us to more directly test whether OPA memory (i.e., prior knowledge of a relevant location within a room) predicts successful one-shot NPA learning (i.e., learning the newly relevant location within a room). The $\text{OPA}_{\text{recent}}$ and $\text{OPA}_{\text{average}}$ LME analyses both treated participant and environment/room (i.e., item effects) as random intercepts, and models were estimated using a restricted maximum likelihood (REML) approach. Maximal random effects (intercepts and slopes) allowed by the data were included in each model (Barr et al., 2013); if the maximal model could not be fit due to a lack of observations, or would not converge (after changing optimizers and increasing the number of iterations), the model was pruned by iteratively removing random slopes (starting with interaction terms). The package lmerTest (version 2.0-33) was used for estimating *p*-values with Satterthwaite approximations for degrees of freedom for one-sample *t*-tests from mixed effects models.

In the $\text{OPA}_{\text{recent}}$ model, the $\text{OPA}_{\text{recent}}$ predictor of NPA learning reflected PE for each room on the final trial of OPA training (i.e., OPA block 12) on Day 2, prior to NPA learning in the scanner. As noted above, we also considered the possibility that NPA learning may differentially relate to $\text{OPA}_{\text{recent}}$ and a *trial-invariant* index of OPA spatial knowledge; in contrast to $\text{OPA}_{\text{recent}}$, an average estimate of trial-invariant knowledge on Day 2 may better reflect the amount of stable, consolidated spatial knowledge for each environment prior to engaging in NPA learning (i.e., the learned "schema"). This distinction was theoretically significant to us because the schema learning literature posits that the hippocampus is less important for retrieval of learned schemas, being instead more important for event-related learning (van Kesteren et al., 2012). Although we cannot quantify consolidation in the present data, our $\text{OPA}_{\text{average}}$ measure emphasizes trial-invariant (stable) OPA performance after a night's consolidation. The prior schema learning literature would therefore predict $\text{OPA}_{\text{average}}$ performance would reduce hippocampal dependence for retrieval of even newly-integrated knowledge of the environment—which our data provide evidence for (see "Results" section below). By contrast, $\text{OPA}_{\text{recent}}$ encompasses this knowledge but also reflects vagaries of recent episodic experience (e.g., fatigue; cross-environment mnemonic interference; continued learning; and relearning driven by preceding errors that occurs on Day 2 leading up to this event) that could contribute to mnemonic malleability associated with this retrieval attempt (Schlichting and Preston, 2015; van Kesteren et al., 2016; Lee et al., 2017) and thus further mediate NPA learning.

This $\text{OPA}_{\text{average}}$ predictor was defined as the weighted mean of the four OPA training trials for each room on Day 2 (i.e., OPA blocks 9–12), prior to NPA learning in the scanner (linear weighting towards end of practice). We reasoned that the weighted mean should downweight initial trials, because on those trials participants had to reorient to the environments learned the day before and they were more prone to errors. Thus, we weighted away from the "refresher" state in the beginning and towards the maximally learned schema (we note, however, that the effect of weighting the average was ultimately minimal, with the correlations within-subjects between weighted and non-weighted room-by-room metrics being ∼0.96). We removed single outlier events (if any) from each room's mean, using Dixon's Q to identify spikes in PE with a 95% confidence interval (note: with four trials per room, two or more spikes in performance could not be considered outliers). Although the $\text{OPA}_{\text{recent}}$ and $\text{OPA}_{\text{average}}$ measures are inherently correlated, and although participants demonstrated strong OPA knowledge through high performance on these Day 2 training blocks, on average over 35% of the within-subject $\text{OPA}_{\text{recent}}$ variance across rooms was not explained by $\text{OPA}_{\text{average}}$ performance. This substantial variability in performance across rooms on the final OPA training trial could, in theory, influence subsequent NPA learning above and beyond trial-invariant $\text{OPA}_{\text{average}}$ knowledge on Day 2, and our data (below) suggest this is the case.

fMRI Analyses

Functional data from the third and fourth NPA runs (which correspond to NPA block 2) were combined into one model that modeled each trial onset (planning period) as separate regressors using a delta function. The present study's functional analyses (detailed below) focus on data from Block 2, because (1) prospective retrieval signals for NPA locations would not exist in Block 1; and (2) the relationship between Block 1 activity and subsequent performance cannot be clearly interpreted due to the fact that subsequent navigation in Block 1 was characterized by wandering behavior in search of the unlearned goal location. In our GLM, we also added a regressor for the goal-arrival in each room, modeled as a 2-s boxcar function and the navigation onset time, modeled with a delta function. Nuisance regressors included: the movement and artifact regressors, a regressor modeling scan run, and a regressor to account for global variance.

In order to directly address our question of whether and how prospective memory signals manifest in hippocampus and parahippocampal cortex as a function of schema-related learning, we extracted single-trial parameter estimates derived from our first-level models from bilateral hippocampal and parahippocampal cortex regions of interest (ROIs) for the NPA block 2 planning period. Additionally, given evidence that posterior hippocampus [and the corresponding putative "posterior medial" system (Ranganath and Ritchey, 2012)] may be preferentially recruited during episodic retrieval of detailed scene/relational information (Ranganath and Ritchey, 2012; Poppenk et al., 2013), we further segmented the hippocampus into head, body and tail regions. Anatomical ROIs were manually traced in MNI space on the group averaged DARTEL template-normalized brain using the ITK-SNAP software package[4] (Yushkevich et al., 2006) using established procedures (Insausti et al., 1998; Pruessner et al., 2000, 2002; Duvernoy, 2005; Preston et al., 2010; Brown et al., 2014). Given recent interest in the interplay between the MTL and mPFC in updating of knowledge networks (van Kesteren et al., 2012; Gilboa and Marlatte, 2017), we also conducted an exploratory analysis of mPFC recruitment

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[4] http://www.itksnap.org

during NPA block 2 planning. Due to variability in functional loci across prior studies, we defined a bilateral mPFC ROI that encompasses prior observations in the literature (van Kesteren et al., 2012) by implementing the more ventral of two medial prefrontal nodes (in yellow; 17-network) associated with the default mode network, explicitly masked to the medial wall of the PFC (Yeo et al., 2011).

The single-trial parameter estimates were entered into separate LME models for each MTL ROI (hippocampal head, body and tail, and parahippocampal cortex), to predict NPA performance in the second block (i.e., a measure of one-shot learning; see above). We employed LME modeling to render our statistical approach involving fMRI data comparable to the primary behavioral "schema learning benefit" analysis using LME. This enabled our fMRI analyses to examine activity as a key predictor while controlling for other factors (e.g., hippocampal activity predicting one-shot NPA learning while accounting for lucky shots and NPA block 1 naïve search performance). In these analyses, parameter estimates replaced $\text{OPA}_{\text{recent}}$ and $\text{OPA}_{\text{average}}$ measures in the LME models described above, to test for the predicted relationships between prospective (planning period) MTL activity and subsequent performance after one-shot learning, holding "luck" during the one-shot learning event constant. We also entered both OPA performance and parameter estimates into omnibus models, aimed at testing whether activity and OPA performance independently predict NPA performance when the other metric is accounted for.

Lastly, because we observed that OPA performance and prospective hippocampal activity both predict NPA performance after one-shot learning (see below), it was of interest to examine the relationship between OPA performance and prospective hippocampal activity during NPA block 2. To address this question, we modified the two LME models used to predict NPA performance from OPA (holding NPA luck constant) to test whether OPA performance predicts prospective MTL activity after one-shot learning.

RESULTS

Behavioral Results

Repeated-measures analysis revealed that both OPA learning (blocks 2–12 PE; Greenhouse-Geisser: $F_{(1.54,23.01)} = 54.88$, $p < 0.001$) and NPA learning (blocks 1–3 PE) were significant over blocks (Greenhouse-Geisser: $F_{(1.16,17.39)} = 63.51$, $p < 0.001$). Also time taken to find the OPA (Greenhouse-Geisser $F_{(1.91,28.63)} = 71.33$, $p < 0.001$) and NPA (Greenhouse-Geisser $F_{(1.05,15.75)} = 43.23$, $p < 0.001$) locations decreased significantly. PE and time correlated strongly (OPA $r_{(14)} = 0.91$, $p < 0.001$; NPA $r_{(14)} = 0.99$, $p < 0.001$). Associative memory for the wallpaper-face associations also significantly increased across OPA training: (Greenhouse-Geisser: $F_{(1.46,21.88)} = 42.74$, $p < 0.001$). Importantly, NPA learning (indexed by block 2 and 3 PE) was significantly faster than OPA learning (main effect of condition (OPA vs. NPA): $F_{(1,15)} = 17.40$, $p = 0.001$; see **Figure 2**). There was a significant interaction between condition and block ($F_{(1,15)} = 7.39$, $p = 0.02$), indicating that the difference between OPA and NPA performance became smaller as NPA performance approached ceiling (see **Supplementary Table S1** for full behavioral summary split by gender).

The finding of superior NPA vs. OPA learning is noteworthy because OPA training benefitted from the OPA object/location being visible in the initial encoding block (i.e., OPA block 1); by contrast, the new goal location was not visible during NPA block 1. This design difference meant that: (a) both OPA and NPA block 2 involved an attempt to retrieve a location participant had navigated to in the immediately preceding block (the presence/precision of a one-shot memory trace); but (b) OPA block 2 benefited from participants having been able to encode the OPA location in block 1 from the trial outset relative to any reference point in the environment. Despite this, NPA learning was substantially accelerated after the same number of repetitions. That said, it is worth noting that this benefit of prior OPA training on NPA learning may be accounted for, at least in part, by: (a) a general learning-to learn benefit; and (b) the fact that NPA trials began from the same start position across rooms and across blocks. Without knowing the relative impact of these respective benefits to OPA and NPA learning, this initial coarse comparison of learning rates should be interpreted with some caution. A room-level test is needed to control for these alternatives and directly examine the hypothesis that prior knowledge benefits new learning in a continuous manner, and analyses based on this approach (reported below) offer our primary evidence for schema-benefitted learning.

Post-scan Memory Tests

Average performance measures for the post-scan tests were evaluated by calculating the average ED from the correct location. In the test where NPA-location memory was probed by cueing the wallpaper, mean ED was 7.48 (SD 2.38). When cueing with the OPA face, performance was significantly poorer (mean ED 8.55 (SD 3.28); $t_{(15)} = -3.11$, $p < 0.01$). OPA performance was better than both these values [mean ED 6.32 (SD 1.79)] and correlated positively with both (vs. NPA-location cued memory $t_{(15)} = 2.58$, $p < 0.05$, $r_{(14)} = 0.66$, $p < 0.01$; vs. OPA-face cued memory $t_{(15)} = 3.96$, $p = 0.001$, $r_{(14)} = 0.76$, $p = 0.001$). OPA memory thus did not interfere with NPA learning.

Critically, holding "luck" during initial NPA object search constant [**Figure 3B**, note attenuated NPA learning in relation to NPA block 1 quartile 1 as well as extended search events (quartile 3–4)], analyses revealed that the precision of knowledge of the previously learned goal locations ($\text{OPA}_{\text{recent}}$) predicted the degree of success of one-shot learning of new goal locations ($t_{(21.27)} = 2.36$, $p = 0.03$; **Figure 3A**). By contrast, in the model using $\text{OPA}_{\text{average}}$ instead of $\text{OPA}_{\text{recent}}$, $\text{OPA}_{\text{average}}$ did not significantly predict one-shot NPA learning ($t_{(13.83)} = 1.69$, $p = 0.11$), suggesting one-shot NPA learning success is more strongly tied to the mnemonic and cognitive state of the most recent OPA retrieval experience.

fMRI Results

We next investigated the relationship between MTL activity during NPA planning after one-shot learning (i.e., planning

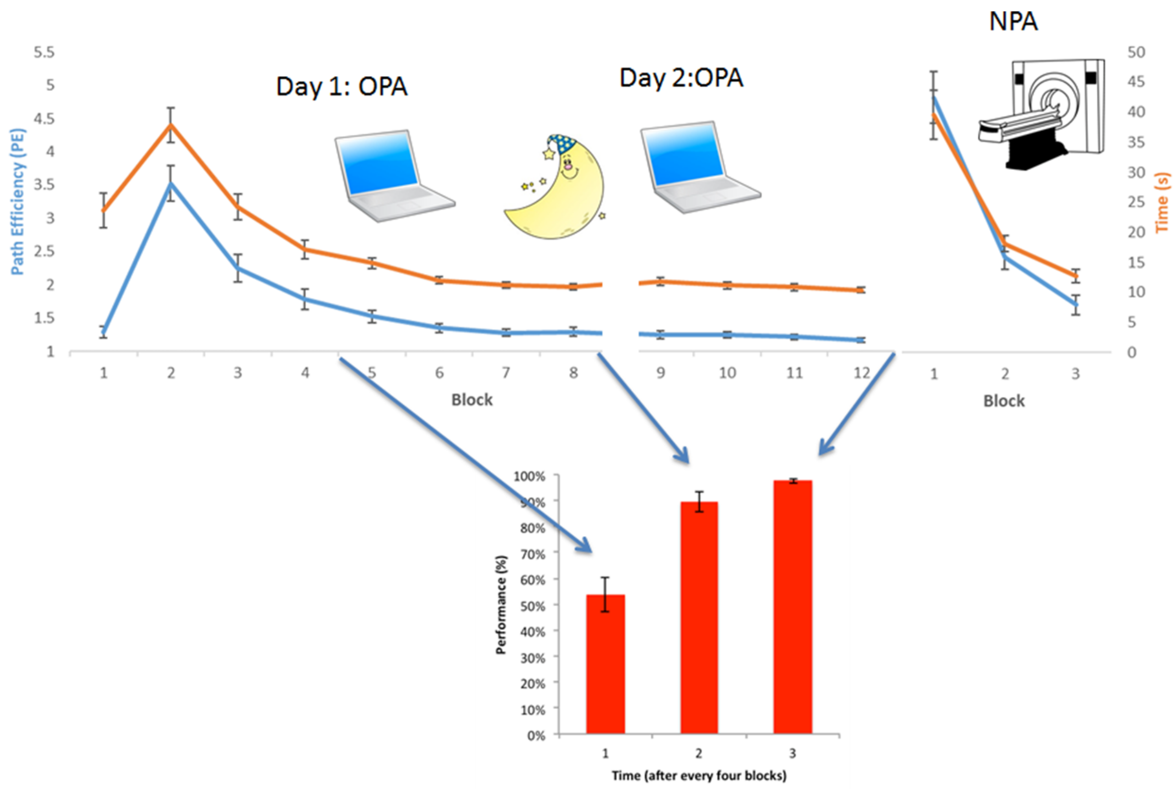

FIGURE 2 | Behavioral results OPA-training and NPA-learning. Average group-level behavioral results. (Upper) Normalized path length (or Path efficiency, PE, in blue) and time needed to find the cue (in orange) for each block, both during OPA and NPA learning blocks. (Lower) Associative wallpaper-face memory was tested after every fourth OPA block. OPA, NPA and associative performance significantly improved over blocks, revealing robust learning. Importantly, NPA learning (NPA blocks 2 and 3) was significantly faster than OPA learning (OPA blocks 2 and 3), as supported by a significant condition × block interaction.

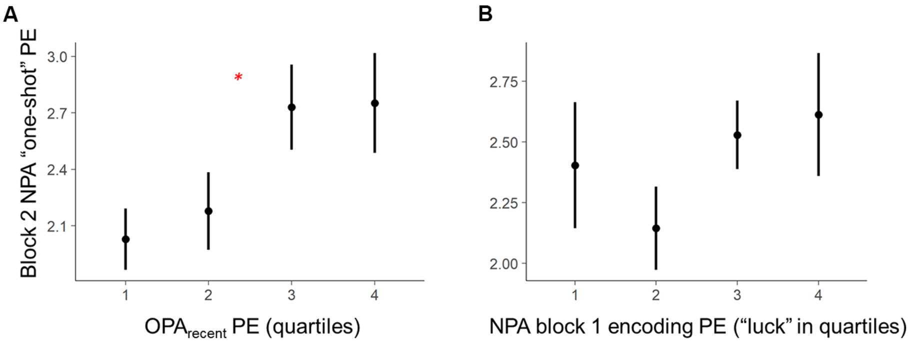

FIGURE 3 | Within-subject trial-level behavioral predictors of one-shot NPA learning. Quartiles reflect within-subject binning of environment-by-environment measures into quartiles for visualization purposes only (Linear Mixed Effects, LME analyses used continuous performance differences across each environment). **(A)** Performance on the most recent retrieval-practice experience with OPA items (i.e., OPA block 12) predicted NPA PE after one-shot learning (i.e., NPA block 2 performance). **(B)** There was a complex, curvilinear relationship between "luck" in NPA location search in NPA block 1 and one-shot learning success (controlled for in our statistical analyses). *$p < 0.05$.

period during NPA block 2) and subsequent NPA memory performance (**Figure 4**). After one-shot NPA learning, prospective planning activity across the hippocampus marginally predicted subsequent NPA spatial memory accuracy ($t_{(12.52)} = 2.01$, $p = 0.07$; **Figure 4A**). Within hippocampal subdivisions, activity in the hippocampal body significantly predicted NPA performance ($t_{(17.59)} = 2.41$, $p = 0.03$); this relationship was marginal in the hippocampal tail ($t_{(9.42)} = 2.03$, $p = 0.07$), and nonsignificant in the hippocampal head ($t_{(10.30)} = 1.26$, $p = 0.24$; **Figure 4C**). It is important to

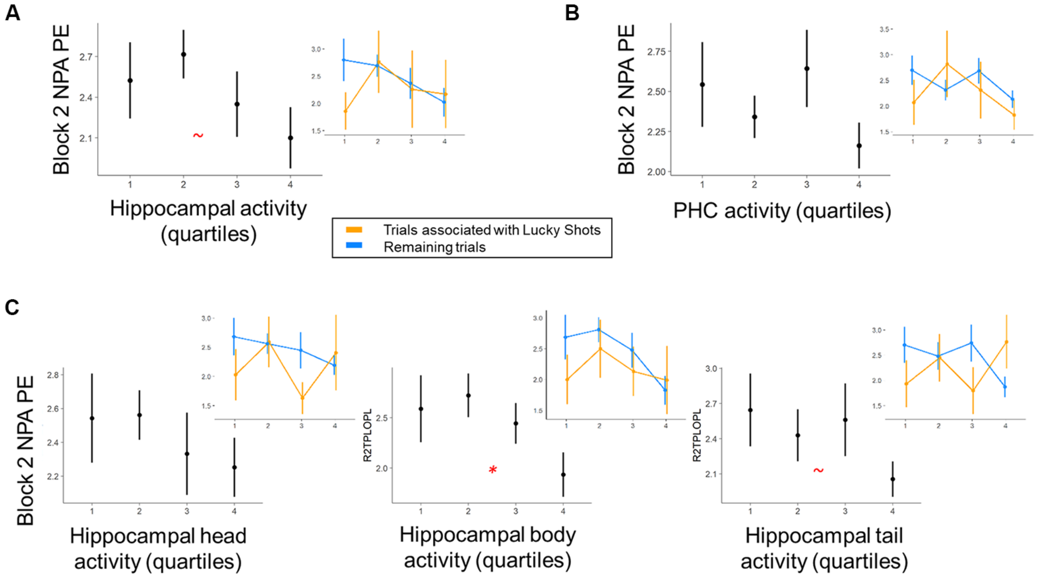

FIGURE 4 | Within-subject trial-level relationship between region of interest (ROI) activity and NPA performance after one-shot learning. Quartiles reflect within-subject binning of environment-by-environment measures into quartiles for visualization purposes only (Linear Mixed Effects, LME analyses used continuous performance differences across each environment). **(A)** During NPA block 2 prospective planning (i.e., after one-shot learning), there was a marginal relationship between hippocampal activity and navigation performance. **(B)** This relationship was non-significant in parahippocampal cortex. **(C)** Within hippocampal subdivisions, prospective planning activity in the hippocampal body significantly predicted NPA block 2 navigation performance. Inset graphs: paralleling exploration of our behavioral data, "Lucky Shots" (orange; controlled for in our analyses) altered the relationship between activity and one-shot NPA performance. $^{*}p < 0.05$, $^{\sim}p < 0.1$.

acknowledge, however, that this finding in the hippocampal body would not survive correction for multiple comparisons at traditional significance thresholds ($p < 0.05$), and therefore, despite *a priori* motivation for examining the hippocampus on the basis of rostro-caudal subdivisions, interpretative caution is warranted. Whereas hippocampal activity, particularly in the hippocampal body, exhibited prospective performance-related signals after one-shot NPA learning, the relationship between activity and subsequent performance in adjacent parahippocampal cortex was nonsignificant ($t_{(14.87)} = 0.88$, $p = 0.39$; (**Figure 4B**). Indeed, despite hippocampal and parahippocampal activity exhibiting the same qualitative relationship with NPA performance, when we included parahippocampal activity as a predictor in the same model, hippocampal body activity maintained a marginally significant relationship with subsequent NPA performance ($t_{(18.70)} = 1.90$, $p = 0.07$). Likewise, the hippocampal body remained a significant predictor of subsequent NPA performance, when controlling for activity in the hippocampal head ($t_{(51.61)} = 2.37$, $p = 0.02$), although this was not the case when hippocampal tail activity was held constant ($t_{(25.10)} = 1.64$, $p = 0.11$). Consistent with our examination of the tail and head as individual predictors, when the tail and head were included in the same model, neither were significant predictors of NPA performance (p's = 0.27 and 0.95, respectively). Note that we were restricted to examining interactions between our different ROIs in this pairwise manner because the models failed to converge when made more complex. In our exploratory analysis of mPFC activity, mPFC activity was significantly positively correlated (functionally coupled) with the MTL ROIs (all $ps < 0.001$). However, mPFC activity did not significantly predict performance on the upcoming trial after one-shot learning ($t_{(29.66)} = 1.68$, $p = 0.10$).

Given that OPA performance and, to a more modest degree, prospective hippocampal activity after one-shot learning predicted NPA performance after one-shot learning, it was of interest to examine the relationship between OPA performance and hippocampal activity (**Figure 5**). Interestingly, there was no evidence across MTL ROIs for a relationship with $\text{OPA}_{\text{recent}}$ performance ($ps > 0.70$). However, within the hippocampus there was a negative relationship between activity and $\text{OPA}_{\text{average}}$ performance (**Figure 5A**) that significantly interacted with search efficiency during NPA encoding (**Figure 5B**). Specifically, when participants had better trial-invariant OPA knowledge, if they encountered the NPA location more quickly during NPA search, they recruited the hippocampus significantly less when planning navigation to the NPA location on the subsequent trial (hippocampus: $t_{(568)} = 2.63$, $p = 0.01$; head $t_{(299.5)} = 2.65$, $p = 0.01$; body: $t_{(565.6)} = 2.48$, $p = 0.01$; tail: $t_{(568)} = 2.39$, $p = 0.02$; PHC: $t_{(567.9)} = 1.55$, $p = 0.12$; mPFC: $t_{(5)} = 2.04$, $p = 0.10$). The main effects for this relationship did not exceed trend levels ($ps > 0.08$). This finding is noteworthy because our data demonstrate that both hippocampal activity and better $\text{OPA}_{\text{recent}}$ performance positively predicted improved NPA performance after one-shot learning.

Given the outcomes of the analysis relating OPA memory to prospective MTL activity, we hypothesized that hippocampal

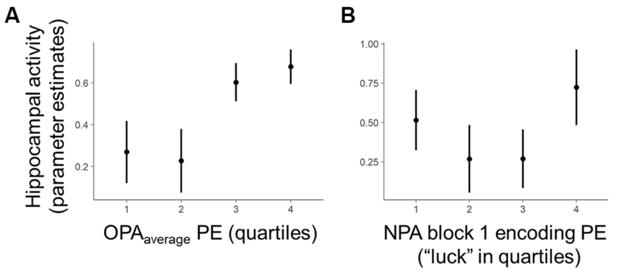

FIGURE 5 | Within-subject relationship between OPA performance and hippocampal activity. Quartiles reflect within-subject binning of environment-by-environment measures into quartiles for visualization purposes only (LME analyses used continuous performance differences across each environment). **(A)** Within the hippocampus, there was a negative relationship between planning activity and OPA$_{average}$ performance that significantly interacted with "luck" during initial NPA encoding. **(B)** Controlling for the effect of Lucky Shots, when participants had better OPA$_{average}$ performance and encountered the NPA location quickly during NPA block 1, they recruited the hippocampus and its subdivisions less on NPA block 2 when planning navigation to the NPA location.

activity and OPA$_{recent}$ performance may independently predict NPA performance when the other metric is accounted for. Due to the relatively large number of modeled parameters, the results of this exploratory follow-up analysis should be interpreted with caution, but did lend support to this idea. That is, when both MTL activity and OPA$_{recent}$ performance were entered as predictors in the same model, their independent relationships with NPA performance demonstrated above remained significant or marginally-significant. OPA$_{recent}$ and hippocampal activity both predicted NPA performance (hippocampus: $p = 0.05$, OPA$_{recent}$: $p = 0.05$). OPA$_{recent}$, but not hippocampal head activity, marginally predicted NPA performance (head: $p = 0.28$, OPA$_{recent}$: 0.051). OPA$_{recent}$ and hippocampal body activity significantly and marginally predicted NPA performance (body: $p = 0.023$, OPA$_{recent}$: 0.052). OPA$_{recent}$ and hippocampal tail marginally predicted NPA performance (tail: $p = 0.08$, OPA$_{recent}$: $p = 0.06$). OPA$_{recent}$ remained a significant predictor of NPA performance when PHC activity was held constant (PHC: 0.26, OPA$_{recent}$: $p = 0.05$). In contrast, when OPA$_{average}$ was instead entered in the model, neither MTL activity nor OPA$_{average}$ knowledge were significant predictors [holding OPA$_{average}$ constant, a marginal NPA performance relationship with activity was observed in the hippocampus and hippocampal body [$p = 0.09$ and $p = 0.06$]; all remaining *p*s for MTL activity and OPA$_{average}$ > 0.18].

DISCUSSION

Our analyses produced several key findings: (1) a continuous measure of the precision of OPA prior spatial knowledge predicts one-shot NPA learning; (2) prospective hippocampal planning activity emerges after one-shot NPA learning that predicts the precision of memory-guided navigation; and (3) hippocampal engagement during NPA retrieval after one-shot learning is reduced as a function of an interaction between greater trial-invariant OPA prior knowledge and how quickly the NPA search during encoding was achieved. These findings extend the sparse literature on how prior spatial knowledge affects new navigational learning and performance in humans. We build on this important behavioral finding to establish a link between prospective memory signals in the hippocampus and initial one-shot learning of new knowledge that is facilitated by prior knowledge.

Our paradigm, while a simplified instantiation, was designed to conceptually parallel those used in rodent studies of the influences of prior knowledge on new learning (Tse et al., 2007, 2011). We demonstrated clear evidence for a continuous behavioral effect of prior spatial knowledge on new spatial learning in humans that parallels previous rodent (Tse et al., 2007; McKenzie et al., 2013, 2014; Richards et al., 2014) and human (van Kesteren et al., 2010a,b, 2013; van Buuren et al., 2014; Wagner et al., 2015; Sommer, 2017) studies which, respectively, show memory enhancement for newly learned information built on prior spatial and non-spatial knowledge. As such, the present behavioral findings not only provide a novel link between continuous measures of spatial knowledge precision and new spatial memory learning at a trial-by-trial, environment-by-environment level in humans, but they also help bridge findings from extant rodent and human research that has been predominantly conducted in different spatial and non-spatial domains.

The ability to flexibly plan for the future is critical for achieving goals, and prominent theories posit that one must access knowledge from prior experiences to construct detailed simulations when planning for the future (Addis et al., 2007; Buckner and Carroll, 2007; Schacter and Addis, 2009). Spatial navigation is a ubiquitous real-world example in which prior knowledge informs prospection and planning of future actions, and extant data in rodents and humans support a role for the hippocampus during prospection over spatial navigation (e.g., Johnson and Redish, 2007; Wikenheiser and Redish, 2015; Brown et al., 2016). An open question is how rapidly prospective navigational retrieval activity emerges across learning, and how these signals—critical for goal-directed behavior—relate to interactions between encoding experiences and prior knowledge. The present findings demonstrate that at the neural level, prospective hippocampal signals emerge after one-shot learning and predict subsequent navigation to new spatial goals. More specifically, greater activity in the hippocampal body during prospective navigational planning to the NPA location in block 2 (i.e., after one-shot NPA-learning) predicted more precise subsequent navigation to the NPA. By contrast, although prior literature implicates MTL cortex in "schema learning" (van Kesteren et al., 2012, 2013), this relationship was not significant in the parahippocampal cortex and was marginally dissociable from the relationship that we demonstrate in the hippocampal body. Prior research has demonstrated that hippocampal computations track distance to spatial locations (Sherrill et al., 2013; Howard et al., 2014; Chrastil et al., 2015; Spiers et al., 2018), and represent information about paths taken to get there (Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Lee et al., 2006; Smith and

Mizumori, 2006; Johnson and Redish, 2007; Ito et al., 2015; Wikenheiser and Redish, 2015; Brown et al., 2016). Our findings are consistent with this literature and, critically, indicate that prospective signals can emerge rapidly, after one-shot episodic learning.

In addition to demonstrating that prior spatial knowledge facilitates new learning, the present study explored whether prior knowledge facilitates the rapid emergence of prospective signals in the hippocampus that in turn supports navigational performance after one-shot learning. Our findings revealed a complex relationship between prior knowledge, the NPA encoding experience, and prospective hippocampal signals. Specifically, our estimate of trial-invariant OPA knowledge negatively related to hippocampal activity in a manner that was mediated by how quickly NPA locations were uncovered during block 1. By contrast, the most recent OPA experience (OPA block 12), while also qualitatively negatively related, did not significantly interact with hippocampal activity; this outcome converges with our exploratory follow-up analysis which showed that when both hippocampal activity and $\text{OPA}_{\text{recent}}$ performance were entered as predictors in the model, they remained more robust independent predictors of subsequent NPA performance. These outcomes suggest that the relationship between prior knowledge and the rapid emergence of prospective signals after one-shot learning may be indirect. This process is potentially mediated not only by the complexity of the encoding experience, as indicated by our data, but also by processing in other circuitries in the brain.

One important area for future research will be to employ high-powered designs to explore the potential implications of the negative and null relationships between hippocampal activity and OPA knowledge metrics. While highly speculative, one hypothesis to explore is a facilitative relationship in which greater OPA ("schema") knowledge could facilitate more *efficient* hippocampal retrieval—enabling recovery of more focal environmental information after just one learning trial (NPA block 1). In this model, the hippocampus would be engaged to facilitate retrieval relevant for navigational planning after one-shot learning, as observed here, but increased BOLD activity may be offset by a more precise memory facilitated by an existing spatial schema. Another speculative interpretation of our results is that they fall within a "schema consolidation" perspective of memory (Morris, 2006; Tse et al., 2007; van Kesteren et al., 2012; Gilboa and Marlatte, 2017)—when participants form more robust knowledge of the OPA location during Day 1 training (reflected by trial-invariant OPA performance on Day 2), new associations may be integrated into the spatial memory structure in a manner that decreases dependence on the hippocampus for retrieval (van Kesteren et al., 2012). Given recent interest in the interplay between the MTL and mPFC in updating of knowledge networks (van Kesteren et al., 2012; Gilboa and Marlatte, 2017), it is interesting to note that mPFC appears to be functionally coupled with the hippocampus during NPA retrieval after one-shot learning. By contrast, however, mPFC was not a significant predictor of subsequent NPA performance, nor was mPFC activity significantly reduced in relation to greater prior knowledge. Here, our present design did not allow us to directly address whether mPFC activity during initial encoding provides a mechanism for accelerated cortical learning that does not depend on the hippocampus (e.g., SLIMM—van Kesteren et al., 2012). However, it is possible that mPFC may modulate hippocampal predictive signals during early learning in the presence of prior knowledge, and this will be an interesting area for continued research.

Together, our results suggest that recent OPA retrieval experiences may govern effects of prior spatial knowledge on new spatial learning, or at least significantly mediate the relationship between trial-invariant spatial knowledge and new learning. Trial-invariant spatial knowledge was less directly related to NPA one-shot learning success but interacted with the behavioral experience during initial NPA encoding to mediate hippocampal involvement in prospective navigation after one-shot learning. Although a mechanistic account bridging our prior knowledge metrics and hippocampal prospective activity after one-shot learning will require further study to address, our results suggest that the hippocampus is involved in relating old to new spatial knowledge, just as in rodent studies (Tse et al., 2007; McKenzie et al., 2013, 2014; Richards et al., 2014) and some human studies including spatial (van Buuren et al., 2014; Sommer, 2017) and, less consistently, non-spatial learning (Liu et al., 2017). Our findings are generative, motivating further research into whether these hippocampal effects are specific to schema-enhanced learning in spatial and navigational settings, or whether they generalize to other non-spatial learning contexts (as might be expected by integrative encoding accounts of hippocampal memory function; Shohamy and Wagner, 2008).

Some limitations with our design should be mentioned. Because of scanning time constraints and concerns about subject fatigue, we could not include a non-schema condition where participants learned a location in new rooms, (i.e., rooms without prior knowledge). This would be an interesting addition for future research. Also, because we wanted to equate perceptual input over NPA trials as much as possible, and because we had only three learning opportunities for NPA, we decided to have participants start at the same position on every block. For this reason, NPA learning could have been more egocentric than OPA learning, where participants started from different corners and were allowed to develop a more allocentrically focused memory. This distinction would be another useful consideration for future research.

Here, we focused on brain activity during the block 2 planning period. This is because we could not interpret activity-behavior relationships in block 1 as a memory-based search (as targeted by our study). Participants typically employed a highly distinctive search strategy (e.g., a spiral) on the first block across rooms that had no clear relationship to OPA location. As such, behavior and activity in block 1 would be dominated by implementing an environment-independent search strategy rather than any trace memory for the NPA location (which they had not encountered yet). Moreover, we could not relate behavior in block 3 to one-shot learning, because there had already been two learning possibilities prior to this block.

Interestingly, prospective NPA performance relationships were significantly related to neural activity in the body of the hippocampus. Prior literature has emphasized the potential importance of the hippocampal tail for spatial memory and successful planning towards goals (Fanselow and Dong, 2010; Sherrill et al., 2013; Miller et al., 2017), motivating our analysis of hippocampal function based on rostro-caudal subdivisions. In our data, the tail was not the locus of the most significant relationship with NPA performance, although we note that the ability of the body to predict subsequent NPA performance independently from the tail only approached marginal significance ($p = 0.11$). Interestingly, however, activity in the hippocampal body was a significant independent predictor of NPA performance from the head, suggesting functional differentiation in the anterior extent of the hippocampus. Importantly, recent work suggests prospective goal coding is distributed along the long-axis of the human hippocampus (Brown et al., 2016), rather than localizing to the tail, and although our results were somewhat unexpected they underscore the importance of evaluating hippocampal function at the level of rostro-caudal subdivisions. In turn, although the dissociation between the hippocampal body and parahippocampal cortex was only marginally significant at traditional alpha thresholds, our data suggest the hippocampal body may also make a distinguishable contribution to prospective navigation after one-shot learning from the parahippocampal cortex, in which predictive effects did not approach significance. As with the dissociation between the body and the head, this result should be interpreted with caution, but it is nevertheless interesting given that parahippocampal cortex is well-established to support spatial scene processing and is often found to support navigational performance in other contexts (Epstein, 2008; Weniger et al., 2010; Howard et al., 2011; Brown et al., 2014, 2016; Marchette et al., 2015; Epstein et al., 2017). In particular, remote and well-practiced spatial knowledge may be more reliant on parahippocampal cortex than the hippocampus (Rosenbaum et al., 2004; Moscovitch et al., 2006). One influential theory of MTL memory function juxtaposes rapid memory formation in the hippocampus with more gradual learning mechanisms that could be supported by MTL cortex (McClelland et al., 1995; Kumaran and McClelland, 2012). Therefore, one possibility is that significant parahippocampal prospective memory signals may require more repetitions to emerge than our critical one-shot NPA learning measure indicative of schema learning benefits. Another possibility is that the parahippocampal cortex's more general role in processing scene information (Epstein et al., 1999, 2017; Epstein, 2008; Marchette et al., 2015) contributes important information for performance on our task that is nevertheless less directly related to trial-wise subsequent navigation performance.

Lastly, when considering the relationship between precision of OPA knowledge and new learning, it was notable that the most recent measure (i.e., performance on OPA block 12) was more predictive of NPA learning than average performance on Day 2 retrieval blocks, which may offer a more pure representation of the level of consolidated knowledge (Dudai et al., 2015) following Day 1 training. This is an important finding, because the world is in constant flux, and the structure of our spatial memories may quantifiably evolve with continued practice in an environment (McKenzie et al., 2013). Our data suggest that the vagaries of recent retrieval-practice experience (Hulbert and Norman, 2015; Antony et al., 2017) with an individual environment influence how effectively new information about that environment is encoded and retrieved. Importantly, this $\text{OPA}_{\text{recent}}$ measure is not independent from the overall level of knowledge of a given environment (indeed, it was correlated with $\text{OPA}_{\text{average}}$, as one would expect). Consequently, $\text{OPA}_{\text{recent}}$ may relate most-closely to one-shot NPA learning due to the fact that it carries information about both the overall level of knowledge about an environment going into Day 2 and participants' current state of retrieval success, fatigue, interference between environment memories, and other factors that would be unique to the most recent trial in each environment. Therefore, our data suggest that there may be important insights to be uncovered when research into the effects of prior knowledge on new learning measures examines the influences of the most recent experience with accessing that prior knowledge. One potentially fruitful future direction will be to explore the relationship between the rapid NPA learning and retrieval effects demonstrated by our work and mechanisms of reconsolidation (Hupbach et al., 2007, 2008; Tronson and Taylor, 2007; Sederberg et al., 2011). NPA learning can be viewed as a re-experiencing of the learned environment in the context of a new navigational goal, and it may be possible to design variants of this task in which changes to a learned spatial memory engram from OPA to NPA learning experiences are quantifiable.

Alternative outcomes to what we observed might be predicted by other theories and empirical phenomena. In particular, the phenomenon of "blocking" (e.g., Hamilton and Sutherland, 1999) and, more broadly, the existence of proactive interference (e.g., Underwood, 1949) might lead to the prediction that environments in which the OPA was better learned would be the ones in which it would be harder to learn the NPA. Again, our findings demonstrated the opposite, as better OPA learning predicts better NPA learning, consistent with the schema-enhanced learning hypothesis (along with other evidence of the benefits of mnemonic integration; e.g., Shohamy and Wagner, 2008; Kuhl et al., 2010).

In conclusion, our findings revealed a relationship between the precision of prior spatial knowledge and new spatial learning in humans. Moreover, the hippocampus prospectively codes the precision of this new spatial learning after one-shot learning. Finally, prior knowledge and the complexity of encoding experiences appear to interact with prospective hippocampal signals that support one-shot learning behavior. These relationships could arise through several mechanisms, and thus our findings help frame future research in this area. The present results extend the current human schema literature, offering important insights into the behavioral manifestations of spatial knowledge that can give rise to enhanced new learning, and suggesting a potential role for the hippocampus in translating one-shot spatial learning that is facilitated by prior knowledge into prospective navigational planning.

DATA AVAILABILITY

Relevant code and data are archived on the Stanford Digital Repository: https://purl.stanford.edu/qb590gz1324

AUTHOR CONTRIBUTIONS

MvK, TB and AW designed the experiment and wrote the article. MvK collected the data. MvK and TB analyzed the data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2018.00486/full#supplementary-material

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The Neural Basis of Individual Differences in Directional Sense

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Individuals differ greatly in their ability to learn and navigate through environments. One potential source of this variation is "directional sense" or the ability to identify, maintain, and compare allocentric headings. Allocentric headings are facing directions that are fixed to the external environment, such as cardinal directions. Measures of the ability to identify and compare allocentric headings, using photographs of familiar environments, have shown significant individual and strategy differences; however, the neural basis of these differences is unclear. Forty-five college students, who were highly familiar with a campus environment and ranged in self-reported sense-of-direction, underwent fMRI scans while they completed the Relative Heading task, in which they had to indicate the direction of a series of photographs of recognizable campus buildings (i.e., "target headings") with respect to initial "orienting headings." Large individual differences were found in accuracy and correct decision latencies, with gender, self-reported sense-of-direction, and familiarity with campus buildings all predicting task performance. Using linear mixed models, the directional relationships between headings and the experiment location also impacted performance. Structural scans revealed that lateral orbitofrontal and superior parietal volume were related to task accuracy and decision latency, respectively. Bilateral hippocampus and right presubiculum volume were related to self-reported sense-of-direction. Meanwhile, functional results revealed clusters within the superior parietal lobule, supramarginal gyrus, superior frontal gyrus, lateral orbitofrontal cortex, and caudate among others in which the intensity of activation matched the linear magnitude of the difference between the orienting and target headings. While the retrosplenial cortex and hippocampus have previously been implicated in the coding of allocentric headings, this work revealed that comparing those headings additionally involved frontal and parietal regions. These results provide insights into the neural bases of the variation within human orientation abilities, and ultimately, human navigation.

Keywords: spatial cognition, navigation, allocentric headings, sense-of-direction, individual differences

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INTRODUCTION

Remaining oriented within environmental-scale spaces—environments that are too large to be viewed from one vantage point (Montello, 1993)—is essential for navigating through a city, pointing to unseen landmarks, and giving directions. While "being oriented" tends to be associated with knowing your current physical facing direction in relation to the environment (i.e., allocentric heading), we propose that knowing how imagined facing directions are related to the environment and how those imagined facing directions relate to other imagined facing directions or your current facing direction is also important for navigation tasks such as planning a route or giving directions. For instance, when giving directions, you need to know the facing direction of your addressee and imagine how that facing direction changes while traveling to ensure that their final facing direction leads them to their destination. Without being able to recall and compare imagined orientations with respect to environmental reference frames, it is impossible to provide accurate directions. We refer to this broader phenomenon of knowing your facing direction, imagining facing directions, and comparing facing directions as "directional sense." Directional sense is not a sense like vision or audition, but depends on several cues, which include visual cues and self-motion perception (Wolbers and Hegarty, 2010).

It is well known that individuals vary in their environmental-scale spatial abilities (e.g., Hegarty et al., 2006; Ishikawa and Montello, 2006; Weisberg et al., 2014), but the underlying cause of this variation is not well understood. We propose that variation in directional sense may be a major factor in variation in environmental-scale spatial abilities, because environmental-scale tasks implicitly require directional sense. For instance, pointing toward an unseen landmark requires coordinating one's facing direction with the direction to the location of the landmark. Accurate pointing cannot occur without knowing your physical (or imagined) facing direction with respect to the larger environment.

Not only are individuals variable in their environmental-scale spatial abilities, but they are also aware of their relative capacity in this regard, and are quite accurate in their self-reports of their abilities. Self-reported sense-of-direction is related to pointing toward unseen locations, distance estimation (Kozlowski and Bryant, 1977), pointing in a familiar environment, spatial updating, and learning spatial layouts (Hegarty et al., 2002). We propose that self-reported sense-of-direction maybe predictive of directional sense, due to its relationship to environmental-scale spatial abilities.

In the rest of the introduction, we describe previous work that has examined aspects of how the abilities underlying navigation are represented in the brain, alongside behavioral findings from previous studies using tasks related to the one we employ here. Although there is a substantial amount of evidence regarding different components of environmental-scale spatial abilities, no prior work has investigated individual differences in this ability at the neural level. In this paper, we investigate (1) the factors that contribute to variation in directional sense, including self-reported sense-of-direction, (2) variation in brain structure related to variation in directional sense, and (3) the neural basis of directional sense.

Animal and Human Models of Allocentric Headings

Head-direction cells, which are the neurological basis of an organism's ability to determine its facing direction (Taube, 1998), were first identified in rodents (Ranck, 1984). Originally, head-direction cells were identified in the dorsal region of a rodent's presubiculum (Ranck, 1984), but they have subsequently been identified in a set of interconnected regions (see Sharp et al., 2001 for a review). Each head-direction cell fires whenever the animal faces the cell's preferred direction (Taube et al., 1990a), which is grounded in the environment, that is, an allocentric-heading (Taube, 1998; as opposed an egocentric bearing, which is a direction relative to the axis of orientation of an organism, see Klatzky, 1998). Each cell shows a directional tuning function centered at the cell's preferred direction, such that the cell's maximal firing rate forms the peak of a Gaussian function (Taube et al., 1990a). As a collective group, head-direction cells form an attractor network of excitatory connections with cells that prefer nearby directions and inhibitory connections with cells that prefer distant directions (Sharp et al., 2001). The attractor network ensures that the head-direction system cannot code two facing directions simultaneously (Sharp et al., 2001). Familiar visual cues can reset the directional coding (Taube et al., 1990b).

In humans, the hippocampus has been conceptualized as the site of the human cognitive map (O'Keefe and Nadel, 1978), or internal representation of an environment. Support for this conceptualization has come from correlational research relating hippocampal volume to navigational experience and use of spatial strategies. Hippocampal volume was significantly correlated with time spent as a London taxi driver (Maguire et al., 2000) but not with time spent as a London bus driver (Maguire et al., 2006), suggesting that navigational experience—not route following—contributed to hippocampal size. London taxi drivers also had larger posterior hippocampi than controls, while controls had larger anterior hippocampal volume, implicating the posterior hippocampi as storing spatial representations (Maguire et al., 2000). Furthermore, number of years of navigation experience driving taxis was associated with increasing posterior and decreasing anterior hippocampal volume (Maguire et al., 2006), but navigational expertise in non-taxi drivers was not (Maguire et al., 2003). Thus, experience using one's spatial representations, rather than "innate" ability, seems to drive changes in the hippocampus (Maguire et al., 2003). Hippocampal gray matter is also related to strategy use in a virtual radial maze task in both young (Bohbot et al., 2007) and older adults (Konishi and Bohbot, 2013) such that those with more hippocampal gray matter are more likely to use navigation strategies that depend on a cognitive map. Moreover, after learning the layout of a real-world environment from direct experience, right posterior hippocampus volume was positively correlated with pointing to various locations in the environment from imagined locations and headings (Schinazi et al., 2013).

Numerous brain regions have been implicated in allocentric coding, such as the retrosplenial cortex with its surrounding areas and the hippocampus with its surrounding areas, and these areas likely interact to support spatial activities (Ekstrom et al., 2014). The retrosplenial cortex-posterior cingulate (RSC/PC) region and presubiculum have been implicated in orienting to the larger environment and might translate between the egocentric coding from the parietal lobe and the allocentric coding in the medial temporal lobes (Epstein, 2008). The RSC does this by anchoring spatial representations of location and facing direction to local topological features (Marchette et al., 2014). This can be seen in individuals with damage in the RSC as they are unable to use familiar landmarks to provide them with a sense of orientation to the larger environment (Maguire, 2001). In a repetition suppression study, headings that faced the same direction were more suppressed in the RSC/PC than headings that faced different directions (Baumann and Mattingley, 2010), demonstrating that allocentric directions are coded in the RSC. Using multivoxel pattern analysis, the RSC, along with the left presubiculum and parietal-occipital sulcus, was found to code location identity, while the right presubiculum coded facing direction relative to the cardinal directions (Vass and Epstein, 2013).

To summarize, head-direction cells code allocentric headings in rats. In humans, hippocampal volume has been associated with environmental-scale spatial learning, skills, and experience, along with strategy use; whereas, the RSC/PC region and presubiculum are likely involved in orientation and the coding of facing direction.

Heading Recall Task

While head-direction cells have yet to be identified in humans, the Heading Recall task (or what we have previously called the "Allocentric-Heading Recall task"; Burte and Hegarty, 2012, 2013, 2014) was designed as a method for investigating the functioning of a possible head-direction system in humans (Sholl et al., 2006). In the Heading Recall task, participants are placed in an initial physical facing direction (called a "default heading," **Figure 1A**). The second facing direction (called a "picture heading," **Figure 1B**) is a photograph of a building from a familiar environment. For example, a participant might be seated facing east—the "default heading"—and see a photograph of a bookstore taken while the photographer was facing south—the "picture heading." The participant should respond by turning toward the right (a turning response was used in Sholl et al., 2006; Burte and Hegarty, 2012) or pressing the right button (a button-press response was used in Burte and Hegarty, 2013), to indicate that when starting facing east one would need to turn right to face south (**Figures 1C,D**). The relationship between the default and picture headings is called "heading disparity" (**Figure 1E**). When the headings face the same direction, heading disparity equals 0°. Heading disparity is 180° when headings are facing opposite directions. Heading disparity is 90° (or 270°) when the headings are to the right (or left) of one another. It is important to note that while the Heading Recall task is most easily described in text using cardinal directions, cardinal directions are never used in the task or instructions.

Sholl et al. (2006) and colleagues hypothesized that comparing two headings that faced the same direction would be quick and accurate, because the firing of putative human head-direction cells in response to the participant's physical facing direction would prime the firing of head-direction cells in response to the picture heading. Conversely, comparing headings that faced opposite directions would be slow and inaccurate as the firing of head-direction cells from the participant's physical facing direction would inhibit the heading response from the second heading. This is due to the suppression effect of cells that code headings that are antipodal to the heading that is currently activated (Sharp et al., 2001). Consistent with these predictions, Sholl et al. (2006) found that accuracy decreased with heading disparity from 0° compared to 180°, and found a similar but marginal trend for increased correct decision latencies (i.e., response times for correct trials) with heading disparity (Experiment 1, Sholl et al., 2006). This finding provided support for their hypothesis that head-direction signals in humans function using an attractor network, similar to animal models. This alignment effect is similar to other alignment effects found relative to the body, such as the sensorimotor alignment effect (e.g., Kelly et al., 2007), and memory alignment effect (e.g., Shelton and McNamara, 1997, 2001).

In addition, Sholl et al. (2006) found that accuracy and correct decision latencies were correlated with self-assessed sense-of-direction, but were not correlated with distance to photographed location. These findings were interpreted as evidence that people's conceptualization of their own sense-of-direction is reflective of how well their head-direction cells code and compare headings, and that participants likely did not use a "mental walk" strategy to compare headings (an alternative hypothesis to their attractor network hypothesis). A study conducted in the environment used in the present study replicated these results (Burte and Hegarty, 2012) and found that familiarity ratings were related to self-assessed sense-of-direction and accuracy. Participants with a better sense-of-direction tend to be more familiar with locations in the environment and, not surprisingly, familiarity predicted accuracy in comparing headings as recognizing the pictured location is essential to the comparison. A follow-up study, in which the response mode was changed from turning in a chair to a button-press (Burte and Hegarty, 2013), revealed similar results along with a gender difference in performance: males were more accurate than females. This study also revealed that participants can accurately respond to the Heading Recall task using egocentric (e.g., right, left, front, back) or allocentric (e.g., cardinal directions, large-scale spatial referents) frames of reference, although allocentric frames of reference tend to result in higher accuracy rates (Burte and Hegarty, 2013).

Relative Heading Task

The Relative Heading task, used in the present research, was designed to investigate the nature of the alignment effect found in the Heading Recall task (Burte and Hegarty, 2014). In designing this new task, we also identified and corrected a common error made by participants[1] and created a task that could be administered in an MRI scanner.

The Relative Heading task was designed to test whether the alignment effect found in the Heading Recall task (or

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[1] In pilot studies, we attempted to use photographs for to specify the orienting heading as well as the target heading, but participants tended to misinterpret the task as a task of pointing from the location presented in the orienting heading towards the location in the target heading. (Experiment 1 in Burte and Hegarty, 2014). In order to force participants to compare the two headings, we moved to using a text description of the orienting heading, which specified a direction but not a location.

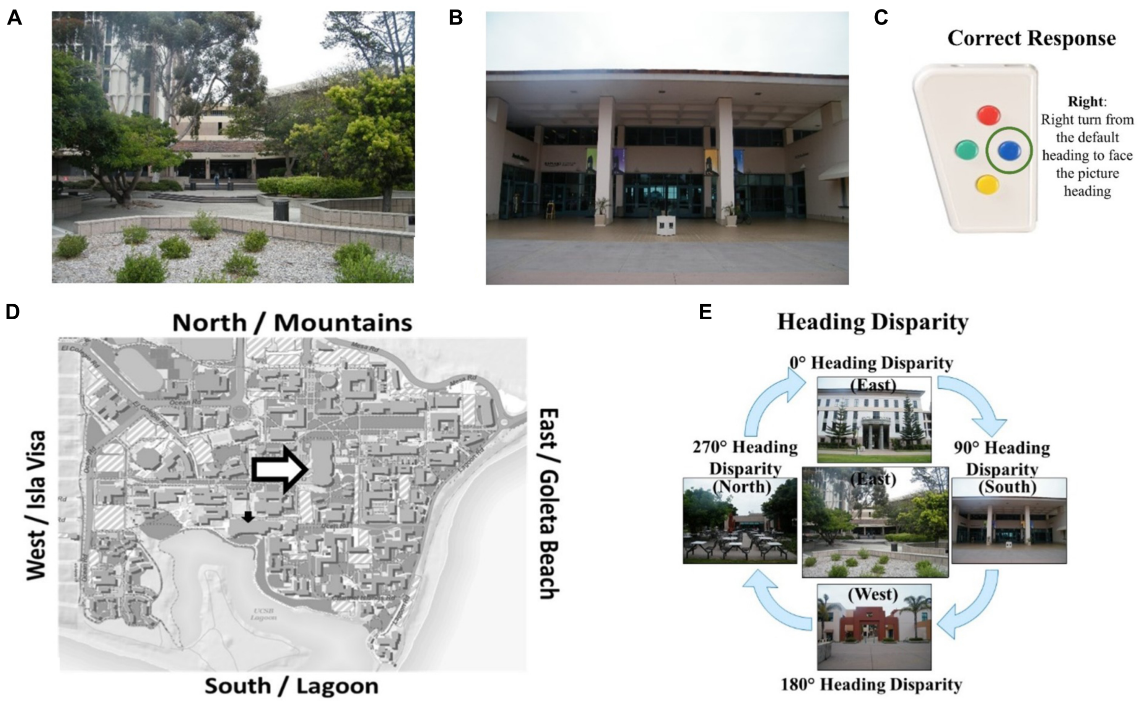

FIGURE 1 | The Heading Recall task: **(A)** the view out the window from the experiment room while the participant faces east (i.e., default heading is east), **(B)** a photograph of campus is presented (i.e., picture heading facing south), **(C)** the correct response, and **(D)** the default heading (white arrow) and picture heading (black arrow) on a campus map. Calculating heading disparity **(E)**: when facing east (center), an east-facing picture (top) will have a heading disparity of 0°, but a south-facing picture (right) will have a heading disparity of 90°.

"original alignment effect") was a sensorimotor effect caused by an attractor network such as the head-direction cells in animals or whether it could be due to other computational difficulty in comparing headings. Comparing headings that are facing the same direction would likely be computationally easier than comparing headings that are facing opposite directions. This computational difficulty would be present regardless of whether the participant's physical facing direction was priming or suppressing the firing of head direction cells in response to the picture heading, or not. The computational difficulty of comparing heading could result in an alignment effect that was similar to the one Sholl et al. (2006) found. To disentangle sensorimotor effects (due to a head direction system) from the computational difficulty of comparing headings, we designed the Relative Heading task in which the "default heading" is an imagined heading rather than the participant's physical heading. If we found an alignment effect in the Relative Heading task, then it suggests that the alignment is due to computational difficulty in comparing headings, and not just a sensorimotor effect caused by a hypothesized head direction system in humans.

The Relative Heading and Heading Recall tasks differ in how the initial "default" facing direction is presented. In the Relative Heading task (Burte and Hegarty, 2014), the initial heading is an imagined orientation presented in text (called an "orienting heading," **Figure 2A**) in contrast with the Heading Recall task, in which it is the participant's current physical facing direction. In both cases, a pictured facing direction presented by a photograph of a building from a familiar environment or the "target heading" (see, **Figure 2B**). For example, a participant is presented with an orienting heading telling them to imagine facing the mountains (the mountains are north of their location) and then is presented with a photograph of the bookstore that was taken by a photographer facing south (**Figure 2D**). The participant should respond with pressing the backward button, to indicate the difference between the two headings (**Figure 2C**). The heading disparity is the difference between the orienting and target heading (**Figure 2E**). Again, while the Relative Heading task is most easily described using cardinal directions, cardinal directions are never used in the task or instructions, so participants do not need to know the relationship between the facing directions and the cardinal directions to answer correctly, as they can use egocentric and/or allocentric frames of reference to compare the headings.

A previous study of the Relative Heading task found a partial alignment effect for correct decision latencies (180° was slower than 90°), but no alignment effect for accuracy. These results were interpreted as indicating that when the participant's physical facing direction is taken out of the task, the attractor network cannot prime or suppress the head-direction cell response to the target heading. Previous works has also found that when participants learned an environment through direct experience (as is the case in the present studies), and their physical facing direction was not part of the heading comparison, their performance did not show an alignment effect (Presson and

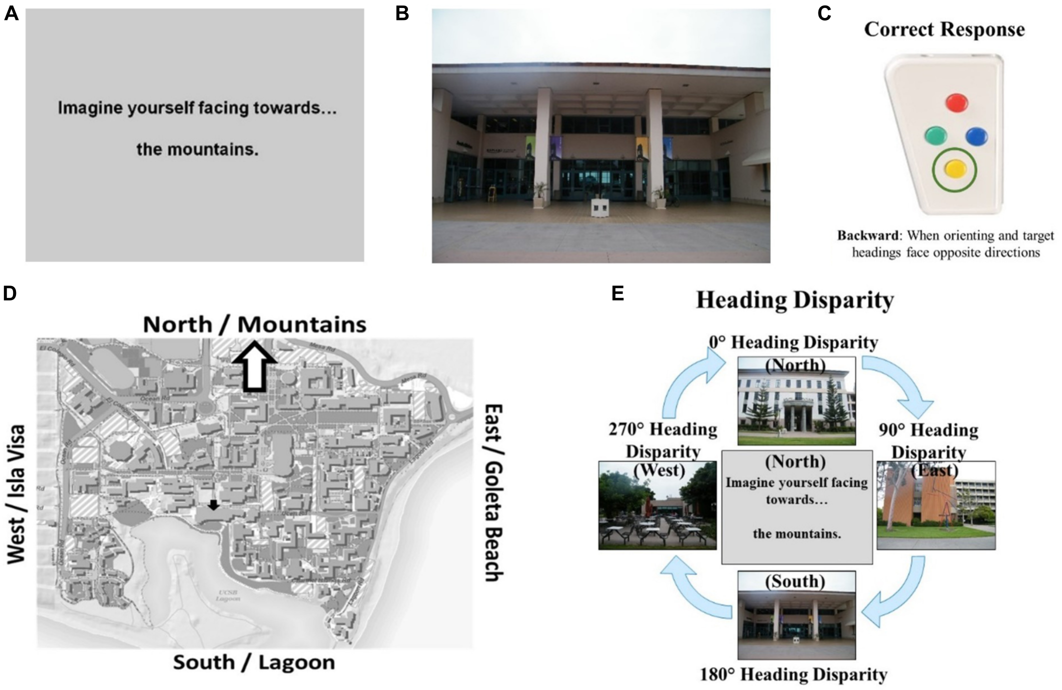

FIGURE 2 | The Relative Heading task: **(A)** an orienting heading facing the mountains (i.e., north), **(B)** a photograph of campus facing the lagoon (i.e., a target heading facing south), **(C)** the correct response, and **(D)** the orienting heading (white arrow) and target heading (black arrow) on a campus map. Calculating heading disparity **(E)**: when facing north (center), a north-facing picture (top) will have a heading disparity of 0°, but a south-facing picture (bottom) will have a heading disparity of 180°.

Hazelrigg, 1984). As in previous research on the Heading Recall task, performance in the Relative Heading varied widely across individuals, and participants with better self-assessed sense-of-direction were more accurate.

Current Study

In this paper, our first objective was to investigate the factors that contribute to variation in performance of the Relative Heading task. We investigated the effects of previously mentioned predictors of Relative Heading performance: heading disparity (0°, 90°/270°, and 180°), self-assessed sense-of-direction, distance, familiarity, and gender. Our predictions follow previous findings: at most a partial alignment effect, better performance for those with better self-assessed sense-of-direction, no relationship with distance, better performance on high-familiarity pictures, and better performance for males than females. For familiarity, we used three measures: subjective familiarity rating, correctly naming the building in a photograph, and correctly identifying the nearest neighboring building. These measures allowed us to investigate effects of objective measures of familiarity (i.e., naming and nearest building) and not just self-reported ratings. Since other environmental-scale spatial tasks, such as wayfinding, spatial orientation, and pointing tasks, are all impacted by environmental familiarity (O'Neill, 1992; Prestopnik and Roskos–Ewoldsen, 2000; Nori and Piccardi, 2011), we predict that the ability to determine the facing direction of a photograph will also depend on environmental familiarity.

We separated effects that occur on the participant-level (i.e., averaged over photographs/trials), reflecting individual differences in directional sense, and effects that occur on the trial-level (i.e., for each trial nested under each participant) in separate models. Using linear mixed models, the impact of familiarity, distance, and direction toward the photographed location on performance for each photograph could be modeled. Since participants were oriented to the testing location (during brain scanning), distance and direction from the testing location to the pictured location were included to evaluate whether the participant's physical location and orientation in the environment (which is separate from the target and picture headings) impacted their task performance. While previous work did not find a relationship between distance (from one's physical location to the location in the picture) and performance (Sholl et al., 2006; Burte and Hegarty, 2012), those analyses were completed using correlations of data aggregated across trials; we have included them in the current study so the effects of distance could be investigated on a trial-by-trial basis using linear mixed modeling. Since participants were oriented to the environment while in the scanner, we tested whether the directional relationship between their bodies and the target locations impacted performance, as this has not been previously investigated.

Structural Differences

The second objective of this study was to examine whether differences in directional sense are related to structural differences in the brains of individuals, and specifically whether variation in directional sense and self-assessed sense-of-direction were related to hippocampal volume. To accomplish this, we identified brain areas that showed a relationship between volume and both performance on the Relative Heading task and self-reported sense-of-direction. Given that hippocampal volume has been associated with environmental-scale spatial learning, skills, and experience (e.g., Maguire et al., 2000, 2003, 2006), we predict that hippocampal volume would also be related to self-reported sense-of-direction because self-reported sense-of-direction is highly predictive of environmental-scale spatial abilities (e.g., Kozlowski and Bryant, 1977; Hegarty et al., 2002; Hegarty et al., 2006). Since we have proposed that directional sense underlies human navigational abilities, we also predict that hippocampal volume will be related to Relative Heading performance.

Functional Differences

The third objective of this paper was to investigate the neural basis of directional sense and its variability. Given the steps needed to complete the Relative Heading task, we predict that brain areas involved in the following processes are likely to show task-relevant activation: (1) imagining the orienting heading (specified in text), (2) visually identifying the pictured location, (3) identifying the target heading, and (4) comparing the two allocentric headings.

Identifying allocentric headings

The first and third steps in the Relative Heading task require identifying allocentric headings from the text indicating the orienting heading and from the photograph indicating the target heading, respectively. Since the RSC/PC region and presubiculum are likely involved in orientation and the coding of facing directions (e.g., Epstein, 2008; Vass and Epstein, 2013; Ekstrom et al., 2014), these regions might show activation as participants are identifying facing directions using the imagined and visual landmarks provided by the orienting and target headings, respectively.

There is evidence that the parahippocampus, instead of the hippocampus, may be more involved in identifying the headings in the Relative Heading task. This is because the hippocampus responds to specific spatial locations, whereas the parahippocampal region responds to views of landmarks. Using intracranial electrodes while participants completed a virtual navigation task, the place-responsive cells were found in the hippocampus and location-independent view-responsive cells were found in the parahippocampus (Ekstrom et al., 2003). The parahippocampal cortex was also found to be more responsive to landmark recognition and associations with spatial locations (Ekstrom and Bookheimer, 2007). More specifically, the parahippocampus seems to be focused on processing the visual-spatial structure of scenes (Zhang et al., 2012).

In sum, the retrosplenial cortex with its surrounding areas and the hippocampus with its surrounding areas support slightly different spatial information. These differences suggest that the RSC/PC will likely be involved in the comparison of allocentric-headings in the Relative Heading task. When these areas were compared directly, the retrosplenial cortex was more involved in orientation changes and the hippocampus was more involved in self-motion changes (i.e., motion with orientation changes; Gomez et al., 2014). Since the Relative Heading Task involves solely orientation changes, we predict that the retrosplenial cortex will show greater activation as the heading disparity (or orientation change) increases.

Visually identifying the pictured locations

The second process in completing the Relative Heading task is to visually identify the pictured target heading. This process might be intertwined with the first and third processes as participants might imagine themselves in the environment facing the large-scale referent given in the orienting heading, and/or imagine themselves taking the photographer's perspective for the target heading. Imagining being in the environment (i.e., an egocentric perspective) or imagining a map or an aerial view of the environment (i.e., an allocentric perspective) might activate visual areas and areas associated with memory for locations.

Since one way of completing the Relative Heading task is by imagining taking the photographer's location and heading in the environment, areas that support taking an egocentric perspective are likely to become active. The right inferior parietal and bilateral medial parietal areas have been associated with supporting egocentric movement through a virtual town (Maguire et al., 1998), as opposed to right hippocampus and caudate that were associated with knowing where a place is located and navigating to that place quickly and accurately. Studies involving navigation have also found activation in the frontal and parietal lobes (e.g., Grön et al., 2000; Iaria et al., 2003), implicating these areas in spatial decision making and in coordinating egocentric movement through an environment.

Comparing allocentric headings

Given that the RSC/PC acts as something of a mediator between the parietal lobe and the medial temporal lobe, it has been proposed that this area translates between the egocentric coding of the parietal lobe and the allocentric coding of the medial temporal lobe (Byrne et al., 2007; Epstein, 2008). A study by Lambrey et al. (2012) supported this translational hypothesis, with the researchers finding that the RSC/PC was involved in updating imagined self-rotations. These imagined self-rotations required the updating of one's egocentric location within an allocentric reference frame, which is similar to the process of comparing allocentric headings in the Relative Heading task. This suggests that the RSC/PC might be involved not only in coding the allocentric headings of the orienting and target headings, but also in comparing allocentric headings.

MATERIALS AND METHODS

Ethics Statement

This study was carried out in accordance with the recommendations of the Human Subjects Guidelines and Procedures, from the University of California Santa Barbara's Office of Research. The protocol was approved by the Human Subjects Committee. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Participants completed consent forms before and were debriefed after both the prescreening and experiment.

Prescreening

Since familiarity with the campus was essential to completing the Relative Heading task, we used a pre-screening process to select participants who had spent at least a year on campus, and who were highly familiar with the photographed locations. Given the individual and gender differences previously found in the Relative Heading and Heading Recall tasks, we selected participants who represented a wide range of self-assessed sense-of-direction, and an equal number of males and females. We also selected participants who met the requirements for participating in an fMRI study.

Participants

Graduate and undergraduate students and staff from University of California, Santa Barbara (UCSB) completed the prescreening and were paid \$20 ($N = 104$; female $N = 59$; male $N = 45$; aged 18–20 $N = 64$; aged 21–23 $N = 33$; aged 24+ $N = 7$; maximum age = 35).

Materials and Procedure

Participants completed demographics questions (age, gender, time spent on campus), a commonly used measure of self-assessed sense-of-direction—the Santa Barbara Sense of Direction (SBSOD) scale (Hegarty et al., 2002)— three familiarity assessments, and an fMRI screening questionnaire (native language, handedness, claustrophobic, metal screening, normal or corrected-to-normal vision). For the familiarity assessments, participants rated their familiarity with campus photographs on a 7-point rating scale (1 = "Very familiar" through 7 = "Not at all familiar"), selected the name of the photographed building (4-option multiple-choice), and selected the nearest building to the photographed building (4-option multiple-choice). **Table 1** contains means and standard deviations for SBSOD scores and familiarity measures.

Selection of Experimental Participants

Participants were selected for the fMRI experiment if they met these requirements: (1) at least 1 year of experience on the UCSB campus; (2) native English speaker; (3) right-handed; (4) not claustrophobic; (5) passed metal screening for fMRI; (6) normal or corrected-to-normal vision; and (7) high familiarity with the campus photographs. High familiarity was operationalized as a mean familiarity rating of 1.0–3.0 on the 7-point familiarity scale, correctly identifying at least 85% of photographed buildings, and correctly identifying at least 65% of buildings near the photographed buildings. Based on these criteria, 76 participants (73%) were eligible to participate.

Males in the eligible group rated their sense-of-direction as better on the SBSOD than females, $t(102) = -5.48$, $p < 0.001$. While males reported higher levels of familiarity with campus photographs, $t(102) = 2.07$, $p < 0.05$, they did not differ from females in objective measures of familiarity, that is, building name accuracy, $t(102) = -1.18$, $p = 0.24$, or nearest building accuracy, $t(102) = -0.37$, $p = 0.72$ (**Table 1**). In addition to the criteria reported in the previous paragraph, participants were selected to participate in the fMRI experiment based on their sense-of-direction relative to others of the same gender (such that the distribution of sense-of-direction within the fMRI participants approximated the distribution of sense-of-direction within all the prescreening participants of each gender). We invited this group of seventy-six participants to participate; however, not all those who were invited actually participated.

Experiment

Participants

Fifty-six right-handed (female $N = 27$; male $N = 29$; aged 18–20 $N = 36$; aged 21–23 $N = 17$; aged 24+ $N = 3$; maximum age = 35) students and staff at UCSB gave informed consent as approved by the Institutional Review Board, completed the fMRI experiment, and were paid \$50. Due to excess motion or technical difficulties with the response pad, 11 participants were excluded from the analysis, leaving the remaining forty-five participants (female $N = 23$; male $N = 22$; aged 18–20 $N = 27$; aged 21–23 $N = 15$; aged 24+ $N = 3$), for inclusion in the behavioral, structural, and functional analyses.

Stimuli

Both the practice tasks and Relative Heading task used two types of stimuli: orienting and target headings. The practice tasks used four photographs from within the experiment room (which faced the cardinal directions) for orienting headings and used either four photographs from within the experiment room or four photographed buildings (different buildings from those used in the main experimental task). The practice tasks used stimuli and headings that were similar to those used in the Relative Heading task so that participants could be introduced gradually to comparing headings.

The Relative Heading task stimuli included four orienting headings specified in text using commonly used large-scale

TABLE 1 | Means, standard deviations, and *t*-tests for gender differences for prescreening participants.

	Prescreening (*N* = 104)		Females (*N* = 59)		Gender Difference	Males (*N* = 45)	
	M	*SD*	*M*	*SD*	*p*	*M*	*SD*
SBSOD 1 – poor SOD; 7 – good SOD	4.8	1.0	4.4	0.8	0.000	5.3	0.9
Familiarity Rating 1 – Very; 7 – Not familiar	1.7	0.9	1.9	1.0	0.04	1.5	0.6
Building Name Mean accuracy	94%	4%	94%	4%	0.24	95%	4%
Nearest Building Mean accuracy	85%	9%	85%	9%	0.72	86%	9%

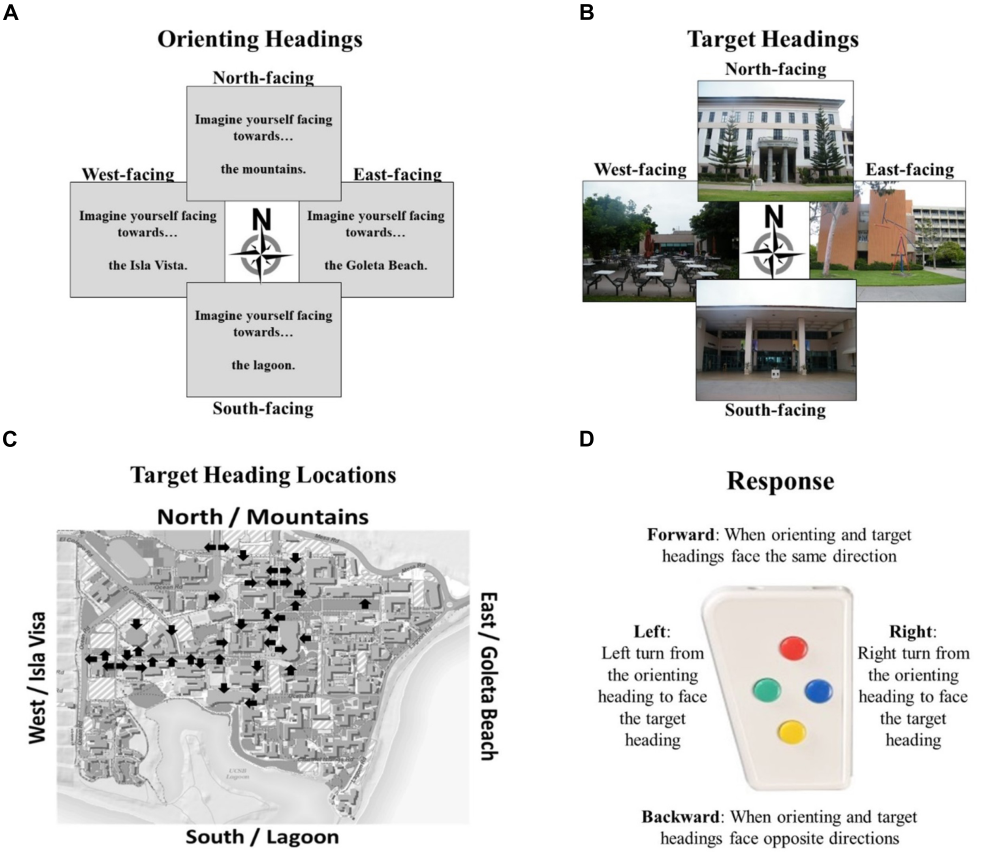

FIGURE 3 | Components of the Relative Heading Task: **(A)** orienting headings as described by large-scale spatial referents from the UCSB campus, **(B)** target headings given by photographs facing familiar UCSB buildings, **(C)** locations and facing directions of all photographed buildings, and **(D)** button box used to respond with the directional relationship starting from the orienting heading towards the target heading.

landmarks to indicate orientation (e.g., "Imagine facing toward the mountains/Goleta Beach/lagoon/Isla Vista"; **Figure 3A**), and forty target headings that consisted of photographs of prominent UCSB buildings (**Figure 3B**). The photographs of buildings were taken on a cloudy day to avoid directional cues from the sun, were cropped to exclude views of other buildings or landmarks to avoid directional cues beyond the building itself, and faced the cardinal directions (10/direction; **Figure 3C**). These photographs were sourced from the most familiar photographs used within the Relative Heading task (Burte and Hegarty, 2014), as UCSB students and staff had already demonstrated familiarity with these locations. Experiment participants (i.e., those who completed the experiment in the fMRI scanner) were all highly familiar with these photographs (mean familiarity rating of 1.7/7, mean correct building naming was 94%, and mean correct near building naming was 83%).

The orienting and target headings were aligned with the cardinal directions, the overall layout of campus, and the experiment room in which the participants completed the practice tasks, and the MRI scanner room in which the participants completed the Relative Heading task. This alignment makes the task simpler, as accuracy dramatically drops when using photographs that are misaligned to the campus layout (Experiment 3, Sholl et al., 2006). In the task instructions and orienting procedures, cardinal directions were never mentioned because they are not needed to complete the task. While participants do not need to be oriented to the environment to complete the Relative Heading task (disorientation does not impact performance compared to being oriented; Burte and Hegarty, 2014), we wanted to ensure that all participants were similarly oriented so we checked that participants knew how the experiment room and MRI scanner room were aligned with the orienting and target headings. Neither room had windows so participants did not have visual access to the environment.

Behavioral Paradigm

Practice tasks

The experiment started with three practice tasks, completed in an experiment room outside of the scanner, to illustrate what allocentric headings are and how to compare them. Participants were oriented to the campus environment, so they knew how directions in the experiment room related to the campus. The first practice task was the Heading Recall task, which used the participant's physical facing direction as the default heading and photographs taken within the experiment room as picture headings (8 trials). The second practice task was a simplified version of the Relative Heading task, in which participants were given orienting headings via text (e.g., "Imagine facing toward the mountains.") but this simplified version used photographs taken within the experiment room as target headings (8 trials). The third practice task was the Relative Heading task, in which orienting headings were given via text and target headings were given via photographs of buildings on the UCSB campus (12 trials). During this task, participants practiced responding in less than 5 s, as that was the time limit they would have for responding when in the scanner. Participants were informed that they would perform the third practice task in the scanner, except with different photographed buildings for target headings.

Relative heading task in fMRI

After the practice tasks, participants were taken to the Brain Imaging Center. Once there, they pointed toward the orienting headings to reorient them to the outside environment (to ensure that all participants had a similar level of orientation to the campus), completed three anatomical scans (localizer, T1 MP-RAGE, and GRE), and completed the Relative Heading task during functional scanning.

For the Relative Heading task, the 40 campus photographs were split into two sets, so that the first four functional runs used half of the target heading photographs, and the second four functional runs used the other half. The photographs from each heading were split randomly between the two sets (e.g., 5 east-facing in each set), but the order of the sets was not counterbalanced, to allow for similarity analyses across the sets (not reported in this manuscript).

On each trial, participants were first given an orienting heading (e.g., "Imagine facing toward the mountains"), and then were shown a campus photograph (e.g., photographer was facing east to photograph the entrance to the library). Their task was to indicate the heading of the campus photograph relative to the orienting heading. In this example, they should press the right button because facing toward the mountains (i.e., north) one would need to turn to the right to face that view of the library (i.e., east). Participants responded to the Relative Heading task using a four-directional response pad (**Figure 3D**): (1) the direction toward the participant's feet, or "forward," which indicated that the orienting and target heading faced the same direction; (2) the direction toward the participant's right, which indicated that the target heading was 90° to the right (clockwise) of the orienting heading; (3) the direction toward the participant's head, or "backward," which indicated that the orienting and target headings were 180° apart; and (4) the direction toward the participant's right, which indicated that the target heading was 90° to the left (counterclockwise) of the orienting heading. For each trial, we calculated accuracy and decision latency (i.e., time from viewing the target heading until a response was given).

Imaging

Imaging procedures

Imaging was performed in the Brain Imaging Center at UCSB using a 3T Siemens Trio MRI scanner, which was equipped with high-performance gradients. Stimulus presentation was controlled by an ASUS A55A laptop using PsychToolbox for Matlab[2]. The stimuli were presented using an LCD projector that back-projected the images onto a screen at the back of the bore, and was viewed using a mirror mounted to the head coil. Within the head coil, foam padding was used for head stabilization. Participants responded using a 4-button magnet-compatible fiber-optic button box that communicated directly with the laptop and PsychToolbox.

First, a high-resolution T1-weighted structural image was acquired (MP-RAGE: TR = 1700 ms, TE = 2.97 ms, RF flip angle = 9°, bandwidth = 240 Hz, voxel size = 1.0 mm × 1.0 mm × 1.1 mm), and then gradient-recalled echo-planar imaging was used to acquire the functional images (TR = 2000 ms, TE = 30 ms, RF flip angle = 90°, gradient-echo pulse sequence, 33 contiguous axial slices at 3.0 mm thick with a 0.5 mm slice gap, and an in-plane resolution of 64 × 64 pixels within a 192 cm field of view, producing voxels of 3mm × 3mm × 3mm). The experiment employed an event-related design and consisted of eight 7-min functional scans of the Relative Heading task. Each functional scan was preceded by five volumes to approach steady-state magnetization, which were discarded.

The functional scans consisted of mini-blocks that allowed participants to keep returning to the same orienting heading for a series of trials before switching orienting heading. This design was used because some participants experienced motion sickness when the orienting and target heading changed every trial. The mini-blocks were presented in the following manner: (1) mini-block notification slide "For the next trials, you will be imagining facing toward the [mountains/Goleta Beach/lagoon/Isla Vista]" for 4 s; (2) orienting heading for 3 s; (3) average 1 s jitter with blank screen; (4) target heading for 5 s, during which time participants responded; (5) average 1 s jitter with blank screen; and (6) repeat steps 2–5 for 4–8 target heading stimuli (**Figure 4**). Mini-blocks were arranged so that the same orienting heading was not repeated back-to-back, with runs containing 6 mini-blocks. The order of the mini-blocks, and the order of the target headings were arranged in a non-predictable quasi-random fashion. This design ensured that each unique combination (orienting heading with one of the 40 target headings) was repeated at least twice for every participant, for a total of 281 trials across all eight functional runs. Since participants had a 5 s period to respond, trials on which they did not respond within that time frame were counted as incorrect trials. Accuracy along with decision latencies on correct trials were calculated.

Structural preprocessing and analysis

Using each participant's high-resolution T1-weighted structural scan, FreeSurfer's[3] fully automated cortical surface-based pipeline (Dale et al., 1999; Fischl et al., 1999) applies a Talairach registration procedure using the MNI305 atlas, intensity normalization, skull-stripping, white matter labeling and segmentation, the intensity normalization to reveal the pial surface, pial surface labeling and segmentation, and the white and pial surfaces are overlaid on the original T1 to calculate

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[2] http://psychtoolbox.org

[3] http://freesurfer.net/

Switch in Imagined Direction

For the next set of photographs, you will be imagining yourself facing towards the mountains.

Please take a moment to imagine yourself facing this direction.

Imagine yourself facing towards...

the mountains.

FIGURE 4 | Mini-block order: **(A)** notification, **(B)** orienting heading followed by jitter, and **(C)** target heading followed by jitter. Repeat same orienting heading with different target headings for 6–8 times before switching orienting heading with a new notification.

cortical thickness. Using FreeSurfer's fully automated volume-based pipeline (Fischl et al., 2002, 2004), the T1-weighted structural scan undergoes registration to the MNI305 atlas, initial volumetric labeling, intensity normalization, volumetric alignment is completed using a high dimensional non-linear alignment to the MNI305 atlas, and volume labeling.

To know how variation in cortical volume was related to sense-of-direction and ability to compare headings, a whole-brain surface-based group analysis was performed on volumetric data (in mm^3) that was registered to FreeSurfer's surface atlas (fsaverage) using spherical cortical registration. Surface smoothing using FWHM 10 mm was run. A general linear model (GLM) tested correlations between cortical volume with Relative Heading task performance (mean accuracy and correct decision latencies over all trials) and SBSOD scores. To correct for multiple comparisons, a False Discovery Rate (FDR) of 0.05 was used.

To understand how variation in subcortical volume was related to sense-of-direction and ability to compare headings, a regional analysis was completed using the Desikan/Killiany Atlas (Desikan et al., 2006) that was registered using fsaverage so that corrections for total brain volume are not needed. A GLM tested for correlations between subcortical volume with Relative Heading task performance and SBSOD scores. FreeSurfer's structural region-of-interest analysis includes 33 subcortical areas but does not include corrections for multiple comparisons.

Given our interest in hippocampal size, we used FreeSurfer's automated segmentation of the hippocampal subfields (Iglesias et al., 2015) to calculate the volume of the four parts of the hippocampus (CA1, CA2/3, CA4, and tail) and surrounding areas (parasubiculum, presubiculum, and subiculum). Since only uncorrected volumes were produced, we corrected the volumes using total intracranial volume (eTIV). Using a multilevel linear model, we investigated the relationship between hippocampal subregions and SBSOD scores.

Functional preprocessing and analysis

FreeSurfer's FS-FAST preprocessing and analysis stream was used. Preprocessing included motion correction, slice-timing correction, B0 distortion correction, spatial normalization, and spatial smoothing (5 mm FWHM). The group analyses included registration of fMRI scans to the anatomical space, registering the anatomical to MNI305 and the surface atlas (fsaverage), registering fMRI scans to MNI305 and fsaverage, and merging subjects using fsaverage.

To investigate the neural processes that support the comparison of headings, we set up the functional analyses to focus on how heading disparity corresponds with BOLD amplitude during the target heading TRs. We focused our analyses on target heading TRs because that was the time in which participants were making the comparison (as opposed to orienting heading TRs where participants knew only the starting direction from which they would subsequently be making comparisons). Given our focus on understanding heading comparison, our analyses focused on heading disparities (i.e., the relationship between orienting and target headings). Specifically, these analyses focused on identifying brain areas in which their functional activity reflected a linear relationship as a function of heading disparity. If a functional area was involved in the comparison of headings, then activity in that area should show a positive or negative linear relationship with heading disparity. To identify these areas, we used parametric modulation analysis.

The parametric modulation analysis required selecting target heading TRs and assigning a heading disparity to each target heading TRs. Using paradigm files for each run completed by each participant, an offset and a slope were specified. It was the slope parameter that investigated whether the amplitude of the predicted hemodynamic response was modulated based on the heading disparity: (0) TRs other than target heading TRs; (1) target headings TRs with 0° heading disparity; (2) target headings TRs with 90° or 270° heading disparity; and (3) target headings TRs with 180° heading disparity.

The first-level GLM was specified with an event-related design, SPM's canonical HRF (hemodynamic response function) model with 0 derivatives[4], 2nd order polynomials for nuisance drift modeling, and motion correction parameters as nuisance regressors. The resulting group maps of the t statistics were computed using bidirectional contrasts.

In the higher-level GLMs, the offset and slope parameters were both modeled using a simple [1 0] contrast. A volume-based correction for multiple comparisons was applied, with a

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[4] http://www.fil.ion.ucl.ac.uk/spm/

voxel-wise threshold of $p < 0.001$ and a cluster-wise threshold of $p < 0.05$. Clusters were assigned labels using the MNI 305 atlas, and FreeSurfer's cortical and subcortical atlases.

RESULTS

Behavioral Results

Individual, Gender, and Familiarity Differences

First, we investigated whether previous findings of large individual differences and gender differences in heading comparison tasks (Sholl et al., 2006; Burte and Hegarty, 2012, 2013, 2014) were replicated in the current study. In line with those findings, large individual differences were found in accuracy (range = 25–89%) and decision latency for correct trials (range = 1.7–3.2 s). Males were more accurate, $t(43) = -3.63$, $p < 0.01$, left fewer trials unanswered, $t(43) = 3.34$, $p < 0.01$, took less time to respond correctly, $t(43) = 2.25$, $p < 0.05$, and reported having a better sense-of-direction than females, $t(43) = -3.69$, $p < 0.01$ (**Table 2**). There were no gender differences in familiarity. In terms of the relationship between sense-of-direction and directional sense, SBSOD scores were significantly correlated with accuracy, $r(43) = 0.41$, $p < 0.01$, and correct decision latency, $r(43) = -0.36$, $p < 0.05$.

Regression Models

To understand how participant demographics and pre-screening measures predicted variation in performance on the Relative Heading task, we used stepwise linear regression models. The following predictors were included: SBSOD score, gender, familiarity rating, building naming accuracy, and nearest building accuracy.

In a model predicting accuracy, gender ($\beta = -0.49$; $t = -3.81$, $p < 0.001$) and nearest building accuracy ($\beta = 0.28$; $t = 2.21$, $p < 0.05$) were significant predictors and explained 32% of the variance in accuracy, $F(2,42) = 9.68$, $p < 0.001$. Males out-performed females, and accuracy in the Relative Heading task increased with greater accuracy on the nearest building task (**Figure 5**). In a model predicting correct decision latency, score on the SBSOD ($\beta = -0.36$; $t = -2.49$, $p < 0.05$) was the sole significant predictor, explaining 11% of the variance in correct decision latency, $F(1,43) = 6.20$, $p < 0.05$. Correct decision latencies were shorter for those with a better sense-of-direction (**Figure 5**).

Linear Mixed Models

To identify the variables that impacted performance on each combination of orienting heading and photographed location (which included 2 trials per participant), we used the "lme4" package in R version 3.1.2 (Bates et al., 2015) to run linear mixed models. We ran a series of three models: (1) a null model that included random effects for each participant and orienting heading-photographed location combination; (2) a model that added fixed effects for familiarity rating (1–7), building naming accuracy (0,1), nearest building accuracy

TABLE 2 | Means, standard deviations, and t-tests for gender differences for fMRI participants.

	Experiment (*N* = 45)		Females (*N* = 23)		Gender Difference	Males (*N* = 22)	
	M	***SD***	***M***	***SD***	***p***	***M***	***SD***
Relative Heading Accuracy	71%	17%	63%	20%	0.001	80%	8%
Relative Heading Unanswered trials	9%	3%	11%	4%	0.002	8%	2%
Relative Heading Correct Decision Latency	2.4 s	0.4 s	2.5 s	0.5 s	0.03	2.2 s	0.3 s
SBSOD 1 – poor SOD; 7 – good SOD	4.9	1.0	4.5	0.8	0.001	5.4	0.9
Familiarity Rating 1 – Very; 7 – Not familiar	1.5	0.5	1.6	0.4	0.36	1.4	0.5
Building Name Mean accuracy	94%	4%	94%	4%	0.67	95%	5%
Nearest Building Mean accuracy	86%	9%	86%	9%	0.97	86%	9%

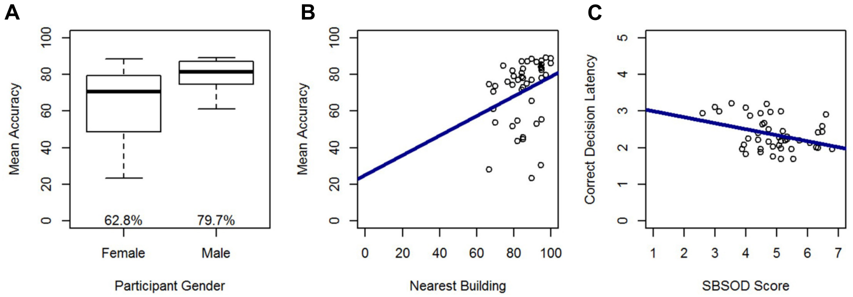

FIGURE 5 | Relative Heading accuracy as predicted by **(A)** gender and **(B)** nearest building accuracy. Relative Heading correct decision latency as predicted by **(C)** SBSOD scores. For all box plots, the box center represents the median, the box top and bottom indicate the first and third quartile, the whiskers represent a 95% confidence interval, circles represent outliers, and mean values are provided. For all scatter plots, regression lines are in blue.

TABLE 3 | Estimates and standard errors for linear mixed models.

Accuracy Model 2	*SS*	*F*	*p*	Decision latency Model 2	*SS*	*F*	*p*	Accuracy Model 3	*SS*	*F*	*p*	Decision latency Model 3	*SS*	*F*	*p*
Familiarity rating	18.7	112.9	0.000	Familiarity rating	10.9	18.3	0.000	Target heading	2.5	5.0	0.003	Orienting heading	10.1	5.7	0.001
Half * block	2.8	17.0	0.000	Half * block	72.2	121.7	0.000	Signed direction	2.1	12.6	0.001	Signed direction	5.5	9.4	0.003
Nearest building	0.7	4.3	0.04									Heading disparity	24.8	41.9	0.000
Gender (Male = 1)	2.1	12.5	0.001												

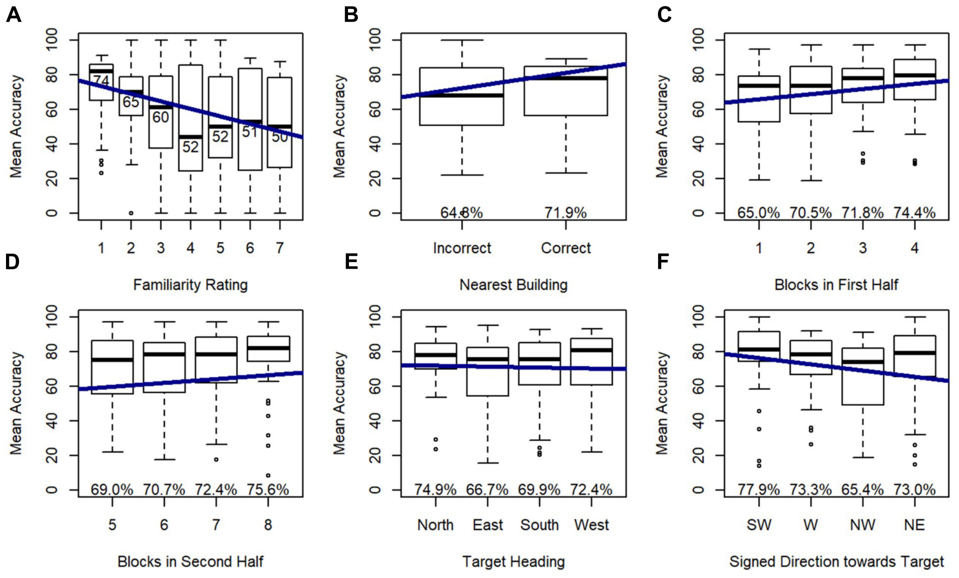

FIGURE 6 | Relative Heading accuracy as predicted by **(A)** familiarity rating, **(B)** nearest building accuracy, **(C)** blocks in first half, **(D)** blocks in second half, **(E)** target heading, and **(F)** signed direction towards target: SW = –135 to –90, W = –90 to –45, NW = –45 to 0, NE = 0 to 45.

(0,1)[5], gender (male = 1), SBSOD score (1–7), and blocks within each half of the experiment; and (3) a model that added fixed effects for orienting heading direction (N, E, S, W), target heading direction (N, E, S, W), heading disparity (0, 90, 180°), direction toward target (i.e., direction from the participant's physical orientation in the scanner to photographed location), and distance from experiment location to target. Three models were used so that the explanatory power of variables (such as familiarity) that might impact performance, but were not of primary interest in this study (i.e., variables in Model 2), were accounted for before the explanatory power of the task-level variables of interest (i.e., variables in Model 3) was investigated. The models were compared using likelihood ratio chi-squares to determine if the fixed effects added predictive power (χ^2). The estimates and standard errors for each fixed effect for each model appear in **Table 3**.

Model 2 revealed that familiarity rating, nearest building accuracy, gender, and blocks within each half of the experiment were all significant predictors of accuracy, and this model significantly outperformed the random effects model (Model 1), $\chi^2(4) = 148.29$, $p < 0.001$. As expected, accuracy increased with greater familiarity ratings (nearer to 1), when participants could accurately identify the nearest building, and males were more accurate than females. Accuracy also increased from the first to the second half, indicating improvement with exposure to the task, and accuracy increased across blocks within each half of the trials, indicating improvements with exposure to the specific photographed locations used in each half.

Model 3 indicated that target heading and signed direction toward target (i.e., direction from the participant's physical orientation toward each photographed location) were significant predictors of accuracy, and this model significantly outperformed model 2, $\chi^2(4) = 27.78$, $p < 0.001$ (**Figure 6**) indicating that these effects added explanatory power above and beyond the explanatory power of familiarity, from Model 2. *Post hoc* tests revealed that participants were more accurate on north-facing than east-facing targets ($p < 0.05$) and south-facing targets ($p < 0.001$), and were more accurate on west-facing than south-facing targets ($p < 0.05$), replicating previous research with this environment. Accuracy dropped for targets that were north

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[5] Due to an error in the prescreening, 25 participants did not respond to building naming and nearest building tasks for one east-facing photographed location. These trials were excluded from analysis (1.4% of trials).

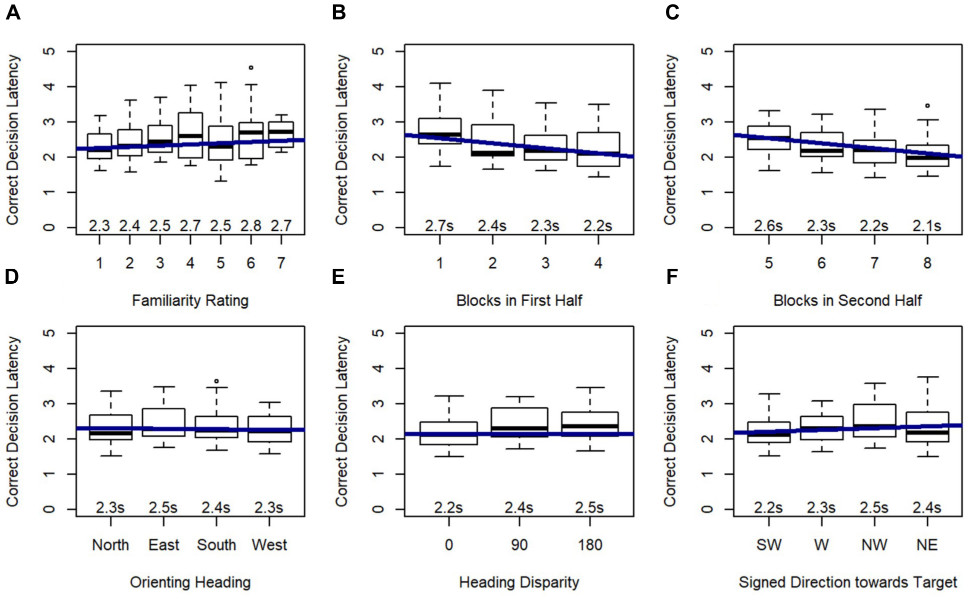

FIGURE 7 | Relative Heading correct decision latency as predicted by **(A)** familiarity rating, **(B)** blocks in first half, **(C)** blocks in second half, **(D)** orienting heading, **(E)** heading disparity, and **(F)** signed direction towards target: SW = –135 to –90, W = –90 to –45, NW = –45 to 0, NE = 0 to 45.

of the participant, which was toward the participant's head while lying down.

Correct Decision Latency

Model 2 demonstrated that familiarity rating and blocks within each half of the experiment were significant predictors of correct decision latency, and this model significantly outperformed the random effects model (Model 1), $\chi^2(2) = 140.96$, $p < 0.001$. As expected, participants were faster to respond to familiar locations, and faster in the final block of each half of the experiment.

Model 3 revealed that orienting heading, heading disparity, and signed direction toward target were significant predictors of correct decision latency, and this model significantly outperformed Model 2, $\chi^2(5) = 58.60$, $p < 0.001$ (**Figure 7**), again indicating that these effects added explanatory power beyond the explanatory power of familiarity (from Model 2). *Post hoc* tests revealed that participants responded faster on north-facing ($p < 0.01$) and west-facing ($p < 0.001$) than east-facing orienting headings, and faster on west-facing than south-facing orienting headings ($p < 0.01$). Critically, correct decision latency was faster when orienting and target heading matched (heading disparity was 0), and when the pictured location was closer to south or forward (i.e., closer to the participant's feet).

Structural Results

A whole-brain analysis was used to identify cortical volumetric variation associated with task performance and SBSOD scores (**Figure 8** and **Table 4**). Task accuracy was positively correlated with the volume of the left lateral orbitofrontal ($mm^3 = 786$, $p = 0.004$), left precuneus ($mm^3 = 1034$, $p = 0.0002$) and right middle temporal gyrus ($mm^3 = 958$, $p = 0.0006$). Correct decision latencies were positively correlated with the volume of the left superior parietal lobule ($mm^3 = 669$, $p = 0.01$). No significant correlations were found for SBSOD scores.

An ROI analysis was used to test for subcortical volumetric differences associated with task performance and SBSOD scores. The volume of the left ventral diencephalon ($p = 0.008$), left cerebellar white matter ($p = 0.02$), and right amygdala ($p = 0.006$) were significantly correlated with accuracy. No subcortical ROIs showed significant correlations with correct decision latencies. SBSOD scores were significantly correlated with both left ($p = 0.006$) and right ($p = 0.02$) hippocampal volume, such that participants with better sense-of-direction also had greater hippocampal volume. However, when we subdivided the hippocampus into its subregions (anterior, body, posterior, and tail), there was no significant relationship between hippocampal subregion volume and SBSOD scores. There was a significant relationship between volume in the right presubiculum and SBSOD scores ($p = 0.005$).

Functional Results

A whole-brain analysis was used to identify brain areas that exhibited a linear relationship between heading disparity magnitude and the hemodynamic response. This linear magnitude model found significant clusters of activation in the following areas: bilateral superior frontal gyrus (left 1: $mm^3 = 708$, $p = 0.0003$; left 2: $mm^3 = 230$, $p = 0.0009$; right 1: $mm^3 = 778$, $p = 0.0003$; right 2: $mm^3 = 306$, $p = 0.0003$), bilateral lateral occipital cortex (left 1: $mm^3 = 380$, $p = 0.0003$; left 2: $mm^3 = 285$, $p = 0.0003$; right: $mm^3 = 279$, $p = 0.0003$), bilateral pericalcarine cortex (left: $mm^3 = 305$, $p = 0.0003$; right $mm^3 = 704$, $p = 0.0003$), left superior parietal lobule ($mm^3 = 1786$, $p = 0.0003$), left fusiform gyrus ($mm^3 = 200$, $p = 0.001$), right supramarginal gyrus ($mm^3 = 1594$, $p = 0.0003$),

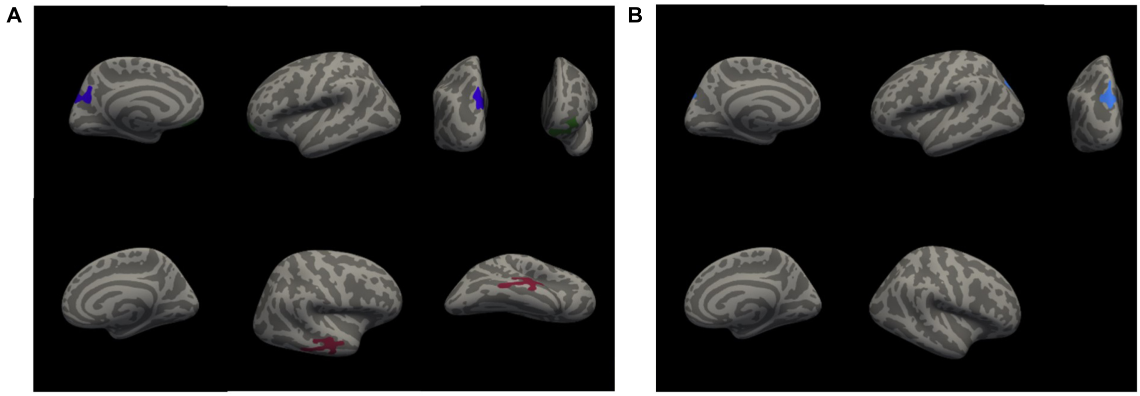

FIGURE 8 | Clusters with significant positive correlations between cortical volume and accuracy **(A)**, and between cortical volume and correct decision latency **(B)**. Colors serve only to improve the visibility/distinguishability of clusters.

TABLE 4 | Areas showing significant positive correlations between volume with accuracy and correct decision latency.

Correlate	Maxima Coordinates (MNI)			Region name	Size (mm^3)	p
	x	y	z			
Accuracy	−10.5	48.7	−21.8	Left lateral orbitofrontal	786	0.004
	−10.7	−66.4	32.0	Left precuneus	1034	0.0002
	57.9	−44.8	−13.3	Right middle temporal	958	0.0006
Correct decision latency	−18.4	−86.4	31.0	Left superior parietal	669	0.01

right precentral gyrus (mm^3 = 282, p = 0.0003), right lingual gyrus (mm^3 = 251, p = 0.0003), right lateral orbitofrontal cortex (mm^3 = 113, p = 0.04), right caudate (mm^3 = 1224, p = 0.0008) and bilateral cerebellum (left: mm^3 = 584, p = 0.04; right 1: mm^3 = 1104, p = 0.002; right 2: mm^3 = 792, p = 0.01) (**Figure 9** and **Table 5**).

DISCUSSION

Directional sense, or the ability to keep track of one's orientation with respect to an environmental reference frame, is critical to remaining oriented in known environments and is part of the multi-faceted concept of sense-of-direction. The primary goal of this work was to elucidate the neural correlates of variation in environmental-scale spatial ability, as measured by the Relative Heading task and self-reported sense-of-direction. Specifically, we examined (1) the factors that contribute to variation in performance of the relative heading task, including self-reported sense-of-direction, (2) variation in brain structure related to variation in directional sense, and (3) the neural basis of directional sense. Below, we discuss the behavioral, structural and functional results, in relation to prior research.

Behavioral Results

As in previous research on directional sense (Sholl et al., 2006; Burte and Hegarty, 2012, 2013, 2014), we found large individual differences in performance. Four predictors accounted for most of variation in direction sense: gender, self-reported sense-of-direction, familiarity, and directionality.

Gender

Males were more accurate, took less time to correctly respond, left fewer trials unanswered, and reported a better sense-of-direction than females. While gender differences are found in some but not all spatial tasks (Voyer et al., 1995; Montello et al., 1999; Coluccia and Louse, 2004) these results are consistent with results from other spatial tasks (e.g., Voyer et al., 1995; Coluccia and Louse, 2004), that likewise show gender differences in spatial tasks that involve knowledge acquired from direct experience in the environment. Critically, males and females did not differ in objective measures of familiarity, so differences in task accuracy were not likely due to familiarity differences. In both linear regression and linear mixed models, accuracy was significantly predicted by participant gender. These results are consistent with previous studies of the Heading Recall and Relative Heading task and indicate that male performance in some navigation tasks may in part be due to males' greater facility in imagining, identifying and comparing allocentric directions.

Sense-of-Direction

Self-reported sense-of-direction was significantly correlated with task performance to a significant degree as reported previously (Burte and Hegarty, 2012, 2013, 2014), and predicted correct decision latencies. These results support the notion that the Relative Heading task assesses a skill, which we called "directional

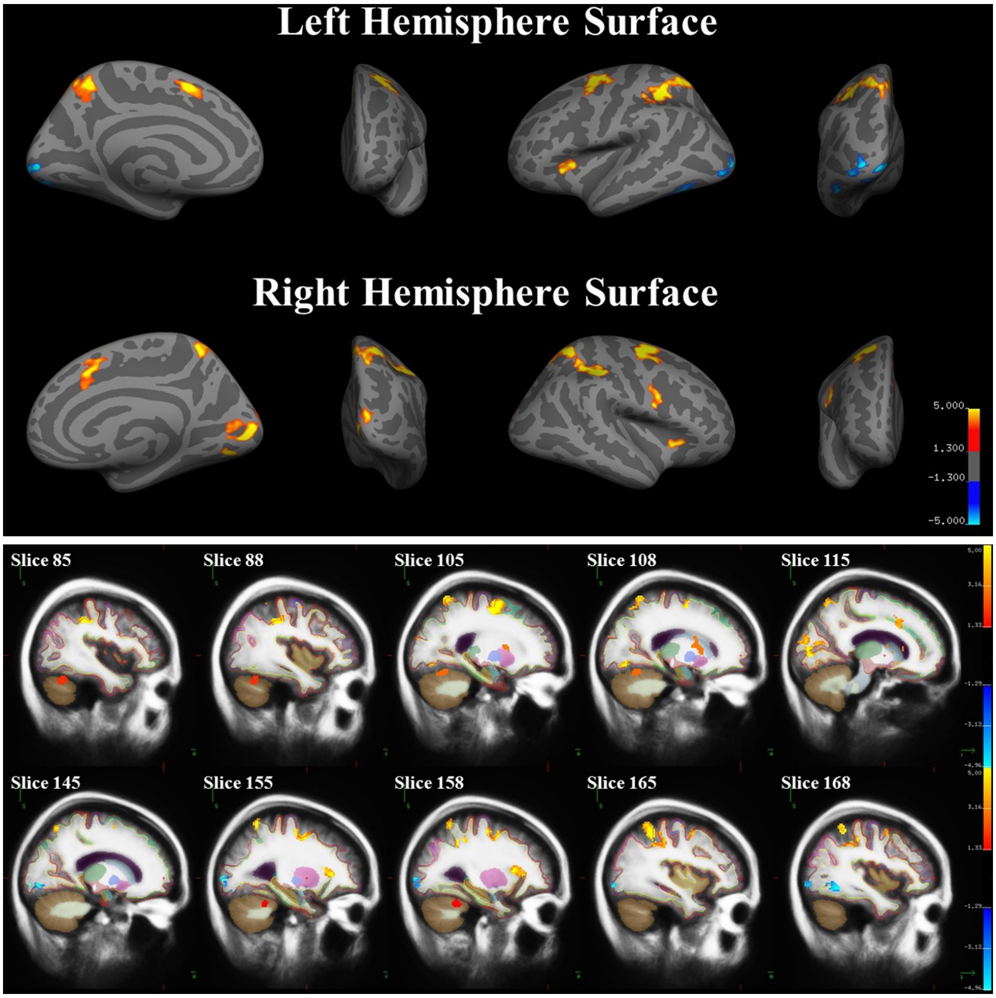

FIGURE 9 | Brain areas with significant relationships between heading disparity magnitude and the hemodynamic response. Blue areas demonstrated a negative linear relationship (i.e., decreasing activity with larger disparities) and red/yellow areas demonstrated a positive linear relationship.

sense," that underlies what individuals self-report as their sense-of-direction (Sholl et al., 2006). Following the conceptualization of sense-of-direction used to create the SBSOD scale (Hegarty et al., 2002), we propose that self-reported measures of sense-of-direction assess a set of skills that encompass how people orient themselves within known environments and with measures of spatial knowledge acquired from direct experience in the environment.

Familiarity

Even though participants were selected for high self-reported familiarity with the environment, accuracy was significantly predicted by mean near building accuracy. So even at the participant-level, one of our objective measures of familiarity was predictive of performance on the relative heading task. Previous studies (Sholl et al., 2006; Burte and Hegarty, 2012, 2013, 2014) had used self-reported ratings of familiarity to select participants and photographed locations for inclusion in their studies. While these ratings were correlated with performance in previous studies, in the current study, we found evidence that ability to identify the nearest building is more predictive than self-reported familiarity or building naming, on a participant-level. Our study points to the importance of measuring familiarity objectively, rather than relying on self-reported ratings.

At the level of individual trials, familiarity rating predicted both accuracy and correct decision latency while nearest building accuracy predicted accuracy. For the Relative Heading task, knowing where a building is located relative to other nearby buildings is more predictive than knowing its name, likely because understanding the layout of neighboring buildings is more closely related to the spatial reasoning required by the task than is knowledge of the building name, which relies on other (non-spatial) memory processes.

From these results, it seems likely that self-reported and objective measures both have their place in studies of environmental-scale spatial abilities. Self-reported familiarity might encompass more aspects of familiarity than objective

TABLE 5 | Regions that exhibited a relationship between heading disparity and the hemodynamic response.

Maxima coordinates (MNI)			Region name	Size (mm^3)	Cluster-wise p-value
x	y	z			
−21.5	−5.9	48.0	Left superior frontal	708	0.0003
−8.2	8.9	53.1	Left superior frontal	230	0.0009
22.0	−1.4	56.9	Right superior frontal	778	0.0003
9.7	16.1	43.1	Right superior frontal	306	0.0003
−32.7	−41.6	41.1	Left superior parietal	1786	0.0003
41.7	−36.2	38.6	Right supramarginal	1594	0.0006
−26.1	−96.3	−1.3	Left lateral occipital	380	0.0003
−18.8	−86.7	−8.3	Left lateral occipital	285	0.0003
14.5	−91.9	15.3	Right lateral occipital	279	0.0003
−11.4	−90.8	−2.5	Left pericalcarine	305	0.0003
10.9	−86.0	−0.9	Right pericalcarine	704	0.0003
−28.7	17.5	9.3	Left insula	624	0.02
−40.1	−55.7	−11.5	Left fusiform	200	0.001
46.0	4.7	28.2	Right precentral	282	0.003
17.7	−75.9	−9.7	Right lingual	251	0.003
29.3	26.4	2.2	Right lateral orbitofrontal	113	0.04
16.0	19.0	1.0	Right caudate	1224	0.0008
−30.0	−47.0	−29.0	Left cerebellum	584	0.04
22.0	−65.0	−19.0	Right cerebellum	1104	0.002
42.0	−61.0	−31.0	Right cerebellum	792	0.01

measures, but objective measures might better assess a particular aspect of familiarity.

Directionality

Using linear mixed models, we found that accuracy was higher for specific target headings while correct decision latency was more accurate for specific orienting headings. In both cases, performance for north and west heading tended to be better (or faster) than for east and south headings, replicating previous research with this environment (Burte and Hegarty, 2012, 2013, 2014). This pattern is likely specific to the experiment location: the mountains are to north, and the neighborhood in which most participants live is to the west. In both cases, there are clear walkways on campus that open up vistas in these directions from the center of the campus. In contrast, the landmarks signifying the South and East directions (a lagoon and a beach) are occluded by other buildings from the center of campus, so there are no clear paths or vistas leading to these locations. This pattern is consistent with findings that pointing is more accurate from perspectives aligned with salient reference systems (e.g., Shelton and McNamara, 1997, 2001). In addition, the most familiar buildings to participants are clustered toward the north and west of campus (**Figure 3C**).

A novel finding of this study is that performance was influenced by participants' physical location and orientation in the environment, even though they were instructed to imagine a different orientation, and they were lying in an MRI scanner. Specifically, we found an alignment effect such that performance was best when photographed locations were toward the participant's feet while lying in the scanner and performance degraded when photographed locations were toward the head. These alignment effects are similar to those in the Heading Recall task (Sholl et al., 2006; Burte and Hegarty, 2012, 2013) in which performance was best when photographed locations were in front of participants, and worst when performance degraded when photographed locations were behind participants. Critically, previous research has shown that these alignment effects only occur when the participant is aware of the relationship between their body and the environment (Burte and Hegarty, 2014). These alignment effects are consistent with sensorimotor alignment effects, in which pointing is more accurate from an orientation that matches the individual's physical orientation and degrades around the body (e.g., Kelly et al., 2007), or self-localization reaction times being related to angular discrepancy (Iachini and Logie, 2003).

Finally, heading disparity predicted correct decision latency, in that trials in which the orienting (imagined) and target headings were aligned were responded to the fastest. As in previous research (Burte and Hegarty, 2014), this effect was relatively weak compared to the sensorimotor alignment effect, supporting the conclusion that the original alignment effects found in the heading recall task were sensorimotor in nature. This partial alignment effect indicates that imagined headings are faster to compare when aligned, possibly because non-aligned headings need to be mentally rotated into congruence to be compared (cf. Shepard and Metzler, 1971).

Behavioral Summary

Despite the novelty and specialized nature of the Relative Heading task, performance on this task shares similarities with measures of a range of spatial skills. It shows gender differences in favor of males; sense-of-direction is predictive of performance on this task as well as other large-scale spatial tasks; and environmental familiarity impacts performance on this task. Finally, this task is subject to sensorimotor alignment effects, even when the orientation to be imagined is not one's physical orientation. So, comparing allocentric headings is impacted by individual differences and environmental features similar to many other spatial skills.

Structural Results

Sense-of-Direction

Hippocampal volume was related to self-reported sense-of-direction. Hippocampal volume has been related to path integration – a capacity that supports navigation (Chrastil et al., 2017), spatial strategy use (Bohbot et al., 2007; Konishi and Bohbot, 2013), cognitive mapping (O'Keefe and Nadel, 1978), and the ability to flexibly use spatial information acquired through route learning (Brown et al., 2014), so it follows that individuals with a better sense-of-direction might also have larger hippocampi. These results should be interpreted with caution as the subcortical analyses were not corrected for multiple comparisons, and SBSOD scores were not related to any of the hippocampal subfields. Instead, SBSOD scores were related to right presubiculum volume, a region that is involved in coding facing direction relative to the cardinal directions (Vass and Epstein, 2013). Since the knowledge and use of cardinal directions is part of what people conceptualize as a "good sense-of-direction," perhaps the use of cardinal directions is associated with greater volume in the right presubiculum.

Relative Heading Performance

Performance on the Relative Heading task was associated with the left lateral orbitofrontal cortex, left precuneus, and right superior parietal. While not originally predicted, the lateral orbitofrontal cortex has been implicated in the suppression of previously rewarded responses (Elliott et al., 2000), which is a part of the Relative Heading and Heading Recall tasks. When first teaching participants about these tasks, their first instinct is to point toward the photographed location but they learn to inhibit that response and instead compare the two headings. It might be that individuals with larger lateral orbitofrontal cortices are better able to inhibit this pointing response, which contributes to greater accuracy on the Relative Heading task. In addition, left precuneus has been associated with computation of direction toward a goal, using egocentric coordinates (Chadwick et al., 2015). Whereas, right superior parietal activity has been associated with gender differences in representing space egocentrically (Grön et al., 2000). Perhaps individuals with a larger precuneus and superior parietal lobules are more experienced at relating the location and orientation of their body to the environment, which contributed to increased task performance. However, this interpretation is tentative, as the links between structure and function are rarely straightforward to interpret.

Functional Results

We hypothesized that directional sense would be related to functional activation in areas that process task-relevant information. The Relative Heading task is composed of four processes: (1) imagining the orienting heading, (2) visually identifying the pictured location, (3) identifying the target heading, and (4) comparing the allocentric headings. However, note that not each of these processes should necessarily be expected to differ as a function of heading disparity.

Identifying Allocentric Headings

Both the orienting and target headings (processes 1 and 3) must be identified before they can be compared. The hippocampus and RSC/PC, with their surrounding areas, have been implicated in allocentric coding and likely interact (Ekstrom et al., 2014). Since the RSC/PC is more involved in orientation changes without self-motion (Gomez et al., 2014), we hypothesized that the RSC/PC might show activation related to heading disparity. However, these areas did not show a linear response with the difference between the headings. This may be because, while these areas were involved in allocentric coding, more processing was not needed as heading disparity increased. Each trial involved the same load in terms of allocentric coding as two headings needed to be identified for each trial.

Visual Processing of Pictured Locations

While the orienting heading is presented via text, the target heading must be identified from a photograph (process 2). Four areas associated with visual processing showed increased functional activation with heading disparity: lateral occipital cortex, which is involved in object perception (Grill-Spector et al., 2001), the pericalcarine cortex, which is the primary visual cortex, along with the lingual gyrus and fusiform, which are involved in visual processing and reading (Mechelli et al., 2000). It is possible that these visual processing areas showed a linear response with the difference between the headings, because the visual processing and imagery needed to compare the headings scale linearly. For example, if 0° deviations between headings are easier to determine (the behavioral data suggests that this is true because decision latencies were shorter for 0° deviations), then participants might focus less attention to the photographed target headings and orienting heading text, and/or visualize less when comparing the headings. However, if 180° deviations between headings are more difficult to determine, then participants might attend more to the photographs and text, visualize the environment or nearby buildings, and/or imagine turning or moving in the environment. So, in this task, visual processing increases with the angular deviation between the headings.

Comparing Allocentric Headings

Once the photographed location has been identified, participants need to compare the orienting and target heading. This can be done using an egocentric (i.e., imagining turning the body within the environment) and/or allocentric (i.e., east is 90° right from north) perspectives (Burte and Hegarty, 2013). Given that the RSC/PC has been implicated in translating between egocentric and allocentric coding (Byrne et al., 2007; Epstein, 2008), we predicted that the RSC/PC would be involved in not only the coding of allocentric headings (steps 1 and 3) but also in heading comparison (step 4). We observed several clusters that might be related to the comparison process: superior frontal gyrus, superior parietal lobule, supramarginal gyrus, and lateral orbitofrontal cortex. The posterior parietal and frontal structures are involved in body-centered spatial coding (for a review see Galati et al., 2010), indicating that participants might have related heading disparity to the response buttons in a body-centered manner. Similar to the structural findings, the lateral orbitofrontal cortex is involved in suppression of previously rewarded responses (Elliott et al., 2000) and this suppression effect increased with heading disparity. Contrary to our prediction, we did not observe activation in RSC/PC, possibly because parieto-frontal regions carry out the comparison by translating the allocentric coding done in the RSC/PC into ego-relative coordinates (Filimon, 2015).

Unpredicted Results

Three areas showed functional activation related to heading disparity that fell outside our focus on hippocampal and RSC/PC-connected areas: caudate, precentral gyrus, and cerebellum. The caudate tends to be active in spatial tasks that required delayed motor responses (Postle and D'Esposito, 1999). In the Relative Heading task, the button-press response must be delayed until after the picture heading is presented and the comparison of headings has occurred. Given that decision latencies increase with increasing heading disparity, it follows that activation in the caudate should also increase with heading disparity. The significant cluster in the right precentral gyrus was likely associated with the button-press response, although activity in this area might have been associated with imagined motions, as increasing heading disparities would require increased imagined turning. Furthermore, significant clusters were found in the lobes of the cerebellum, spanning Crus I and lobules IV, V, and VI. Right Crus I has been implicated in sequence-based navigation (i.e., navigation based on egocentric representations; Iglói et al., 2014), Crus I and lobules VI were associated with working memory, and lobule V with finger tapping (Stoodley et al., 2012). These nuclei have been associated with highly relevant processes, in particular, accounting for heading disparity in the context of understanding self-motion (Baumann et al., 2015) and tracking rotational self-motion (Chrastil et al., 2017). The present task may rely on the same computational machinery, but in service of computing stationary heading disparity, rather than parsing self-motion.

CONCLUSION

We have demonstrated that a shared network, featuring many regions that have previously been associated with spatial reasoning including superior frontal gyrus, superior parietal lobule, supramarginal gyrus, lateral orbitofrontal cortex, and caudate, is active in comparing headings. While the retrosplenial cortex and hippocampus have been frequently implicated in the coding of allocentric headings, this work revealed frontal and parietal regions were involved in comparing headings that the RSC/PC and hippocampus coded. Moreover, in line with previous work, we found large individual and gender differences in task performance, as well as in self-reported sense-of-direction. These individual differences may also relate to structural differences in relevant areas including superior parietal cortex. Thus, this work has helped to further our understanding of variation in directional sense.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

All authors listed contributed to designing this study. HB and BT developed the experimental stimuli and materials, oversaw data collection, and completed data analysis. HB drafted the initial version of this manuscript as part of her Ph.D. dissertation. HB and BT wrote, and MH edited this manuscript.

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Resting State Connectivity Between Medial Temporal Lobe Regions and Intrinsic Cortical Networks Predicts Performance in a Path Integration Task

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Humans differ in their individual navigational performance, in part because successful navigation relies on several diverse abilities. One such navigational capability is *path integration*, the updating of position and orientation during movement, typically in a sparse, landmark-free environment. This study examined the relationship between path integration abilities and functional connectivity to several canonical intrinsic brain networks. Intrinsic networks within the brain reflect past inputs and communication as well as structural architecture. Individual differences in intrinsic connectivity have been observed for common networks, suggesting that these networks can inform our understanding of individual spatial abilities. Here, we examined individual differences in intrinsic connectivity using resting state magnetic resonance imaging (rsMRI). We tested path integration ability using a loop closure task, in which participants viewed a single video of movement in a circle trajectory in a sparse environment, and then indicated whether the video ended in the same location in which it started. To examine intrinsic brain networks, participants underwent a resting state scan. We found that better performance in the loop task was associated with increased connectivity during rest between the central executive network (CEN) and posterior hippocampus, parahippocampal cortex (PHC) and entorhinal cortex. We also found that connectivity between PHC and the default mode network (DMN) during rest was associated with better loop closure performance. The results indicate that interactions between medial temporal lobe (MTL) regions and intrinsic networks that involve prefrontal cortex (PFC) are important for path integration and navigation.

Keywords: resting state, navigation, path integration, default mode network, central executive network, fronto-parietal, executive function, memory

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INTRODUCTION

Humans differ considerably in their individual navigational abilities, and successful navigation relies on several different skills and capabilities (Wolbers and Hegarty, 2010; Chrastil, 2013). One such navigational ability is *path integration*, the constant updating of the navigator's position and orientation during movement, particularly in sparse environments without landmarks

(Mittelstaedt and Mittelstaedt, 1980, 1982; Byrne et al., 2007). Significant individual variability has been observed in path integration abilities in human navigators (Loomis et al., 1993; Klatzky et al., 1999). Intrinsic differences between individuals in both brain structure and function could provide mechanisms that underlie these varying abilities. We previously examined structural differences, finding that better navigators in a path integration task had larger local gray matter volume in the hippocampus, retrosplenial cortex (RSC) and medial prefrontal cortex (mPFC; Chrastil et al., 2017). In the present study, we examined intrinsic functional connectivity differences using the same path integration paradigm.

The goal of this study was to examine the relationship between path integration abilities and functional connectivity to canonical intrinsic brain networks. Intrinsic networks within the brain reflect past inputs and communication (Damoiseaux et al., 2006; Fox and Raichle, 2007; Papo, 2013) as well as structural architecture (van den Heuvel et al., 2009), and have a strong relationship with task-based networks observed during functional tasks (Laird et al., 2011; Cole et al., 2014a). Individual differences in intrinsic connectivity have been observed for common networks (Mueller et al., 2013), suggesting that these networks can inform our understanding of individual spatial abilities. Here, we examined individual differences in intrinsic connectivity using resting state magnetic resonance imaging (rsMRI), in which participants were scanned at rest while maintaining fixation on a crosshair. We then tested whether functional connectivity to rsMRI networks was correlated with performance in a path integration task that they had completed earlier in the scan session.

Specifically, we were interested in intrinsic functional communication between navigation brain regions and the default mode network (DMN) and between navigation brain regions and the central executive network (CEN). The DMN and CEN were chosen *a priori* because of their involvement in and potential importance to memory and navigation. The DMN is linked to episodic memory and representations of self (Buckner and Carroll, 2007; Buckner et al., 2008; Laird et al., 2011), both of which could be important for tracking self-motion and remembering a target location. Many regions of the DMN, including the hippocampus, RSC and mPFC are also associated with activity during navigation tasks (Maguire et al., 1998; Shelton and Gabrieli, 2002; Wolbers and Büchel, 2005; Brown et al., 2010, 2016; Sherrill et al., 2013; Marchette et al., 2014; Chrastil et al., 2016). The CEN contains fronto-parietal regions, and consists of highly-connected hub regions that allow for adaptive implementation of task demands, linking this network to executive control functions (Dosenbach et al., 2006, 2007; Seeley et al., 2007; Cole et al., 2013, 2014b). Path integration requires working memory to keep track of the home location, while also updating new incoming spatial information and resisting distraction. These executive control functions could play a key role in understanding individual differences in path integration abilities.

Previous research in both animals and humans suggest that the medial temporal lobe (MTL) regions of hippocampus, parahippocampal cortex (PHC) and entorhinal cortex are likely candidates to support path integration abilities, as are RSC and mPFC. Rodent models have found several cellular fundamentals for path integration, including place cells in the hippocampus (O'Keefe and Nadel, 1978), grid cells in entorhinal cortex (Fyhn et al., 2004) and head direction cells in postsubiculum and RSC (Taube et al., 1990; Chen et al., 1994; Cho and Sharp, 2001). Functional imaging studies have demonstrated that hippocampal activity predicts accuracy in navigation in sparse environments (Wolbers et al., 2007; Sherrill et al., 2013), and PHC activity has also been observed during path integration (Sherrill et al., 2013). Lesions of the hippocampus and entorhinal cortex have been shown to cause impairments of path integration in rodents (Whishaw et al., 1997; McNaughton et al., 2006; Brun et al., 2008). BOLD activity in the hippocampus, PHC and RSC increases with Euclidean distance from the home location and with increased translation and rotation during virtual self-motion (Chrastil et al., 2015, 2016), suggesting that these regions support path integration. Together, the previous literature indicates a key role for MTL as part of a path integration network, thus, we expected functional connectivity related to MTL areas in the present study.

Path integration often involves tracking a start or home location and we previously found task-based functional imaging evidence in support of a homing signal in the human brain (Chrastil et al., 2015). We now focus on mechanisms that could underlie this homing signal. To achieve this goal, we examined individual differences in path integration performance. Understanding the relationship between path integration accuracy and network connectivity could provide insight into: (i) which brain areas contribute to path integration performance; and (ii) how those regions work in concert with other brain regions to yield accurate path integration. We predicted that better navigators would demonstrate increased functional connectivity between brain regions that support navigation, including the hippocampus, PHC, entorhinal cortex and RSC, and several canonical cortical networks. Specifically, we predicted that functional communication with the DMN (which has been linked to episodic memory and representations of self (Buckner and Carroll, 2007; Buckner et al., 2008; Laird et al., 2011)) and the CEN (linked to executive control (Dosenbach et al., 2006, 2007; Seeley et al., 2007; Cole et al., 2013, 2014b)) would be associated with path integration accuracy.

MATERIALS AND METHODS

Participants

Thirty-one participants were recruited for this study from the Boston University community as part of previous studies (Chrastil et al., 2015, 2016). This study was carried out in accordance with the recommendations of experimental protocol guidelines, Partners Human Research Committee and the Boston University Charles River Campus Institutional Review Board. The protocol was approved by both the Partners Human Research Committee and the Boston University Charles River

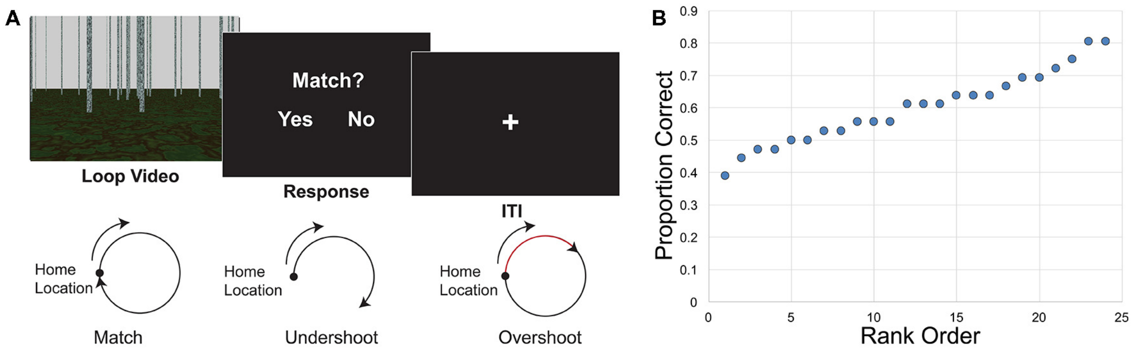

FIGURE 1 | Loop closure task. **(A)** Participants watched a video of movement in a loop trajectory in a sparse, landmark-free environment. At the end of the video they decided whether the video ended in the same place in which it started (match) or somewhere else (non-match). Bottom, illustration of match and non-match trials. Both overshoots and undershoots of the home location were considered non-matches. **(B)** Behavioral results indicate the distribution of performance. Individual proportion correct of the 24 participants ranged from 0.389 to 0.806, and are displayed here in rank order from worst to best performance.

Campus Institutional Review Board. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Because resting state analysis is particularly susceptible to movement artifacts (Van Dijk et al., 2010, 2012; Satterthwaite et al., 2013), participants with absolute movement >1 mm were eliminated from analysis to achieve the resolution necessary for network analysis. Two participants were eliminated from the final analysis due to excessive motion during resting state (rsfMRI) scanning, three participants were not scanned due to claustrophobia, one participant was found to be ineligible after screening, and one participant fell asleep during the experimental task. Twenty-four participants were included in the final data analysis (mean age 23.13 ± 4.18 (SD); 10 males, 14 females). Twenty-two of these participants were right handed, two were left handed. All participants had no history of neurological disorders.

Stimuli and Tasks

Complex path integration and self-motion processing involve tracking location, often the start or home location. This paradigm required participants to track self-motion during videos shown from a first-person perspective. Briefly, in the complex path integration task (loop closure task), participants viewed a single video of movement that traveled in a circle in a sparse environment (**Figure 1**) and then indicated whether the video ended in the same location in which it started (Chrastil et al., 2015). This study is based on additional analyses from our previous fMRI study on the neural correlates of path integration. A description of the loop closure task is presented here, and our publication introducing these paradigms (Chrastil et al., 2015) provides a longer description of the stimuli and task that is relevant to both the initial fMRI study and the current connectivity study.

Environment

The virtual environment was developed using POV-Ray v.3.6[1], a 3D ray-tracing modeling program. The environment consisted of a textured ground plane with approximately 150 textured poles, or "trees," randomly placed in the scene (**Figure 1A**). The textured ground and trees in the environment provided optic flow information during the video presentation of movement. The trees were taller than the top of the screen so that height changes could not be used as a cue to distance. The large number of trees and random placement discouraged participants from using the scene arrangement as a landmark, and each video had a different random arrangement of the trees. Movement in the videos never passed directly through a tree. Self-motion information used in this study stemmed purely from visual motion, with no vestibular or proprioceptive input, due to the constraints of fMRI scanning. Videos of movement in the environment were presented as a series of images at 30 frames per second. The videos were presented to participants using E-Prime 2.0 (Psychology Software Tools, Inc.), which also recorded the exact timing of stimulus presentation and participants' responses.

Loop Closure Task

In the loop closure task, the camera movement in the video traveled in a circular pattern. Once the video ended, participants had to indicate whether the movement in the video ended at the same location in which it started, at the home location. Half of the videos ended in the home location ("match," a full 360° traversal of the loop), and half were non-matches, ending at another point along the circle. Half of the non-matches were undershoots, such that the movement only traversed partway around the circle (225° of the loop). The other half were overshoots, such that movement went past the home location and went partway around a second loop (495° of the loop). Participants were given clear instructions that overshoots were considered non-matches, and that it was important to determine whether the end point itself was the same as the start location. Three different radii of curvature (2.0, 3.0 and 4.5 virtual units) and two different travel speeds (1.5 and 2.0 virtual units/s) were used in the loop task, crossed to yield six angular speeds (0.33,

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[1] http://www.povray.org/

0.44, 0.50, 0.67, 0.75 and 1.00 radians/s). The length of the videos for the loop task ranged between approximately 4–25 s, with an average of 11.5 s. After the video, a response screen was presented, and participants had up to 2 s to respond whether the loop returned to the home location. A 6 s intertrial interval (ITI) began as soon as the response was recorded, thus the duration of the response was based on participants' reaction time. Loops turned both to the right and to the left in equal numbers; we combined over left and right turning direction for analysis.

Resting State Task

The functional imaging of interest took place during a resting state scan that occurred after the test runs of the path integration task. During the resting state scan, participants were instructed to keep their eyes open and look at a fixation cross, but they could think about whatever they liked. One 6:12 min long resting state scan was acquired after the experimental task scan runs.

Procedure

Pre-scan Training

Participants were trained outside the scanner the day prior to scanning. Participants were given a general description of movement in the environment and shown a short example. In addition to the loop closure task, participants were trained on additional tasks not presented here (loop, distance, angle, curve and static image change; see Chrastil et al., 2016). They were then given specific instructions and several practice runs with feedback for each of the tasks in turn. Participants also completed several individual abilities questionnaires, which are discussed in detail elsewhere (Chrastil et al., 2015, 2016, 2017).

Experimental Task

While the structural scans were being acquired, participants were given a practice run with feedback using examples from the training, with eight trials per task block. Following practice, there were six functional test runs, randomized across participants, for a total of 36 trials per condition. Each of the test runs consisted of one block each of the experimental tasks (loop, distance, angle, curve and static image mentioned in the section on pre-scan training). Each block contained six trials of the task, with match and non-match trials counterbalanced across runs. The task order of each block was counterbalanced across runs. Length and direction of movement, as well as speed of travel, were counterbalanced across conditions and runs. Because the ITI began as soon as participants made their responses, the scan time for each of the six runs varied somewhat, but generally lasted just under 10 min. Total scan time for the experimental task was approximately 1 h. Following the experimental task runs, the 6:12 min resting-state scan was acquired.

MRI Image Acquisition

Images were acquired at the Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital in Charlestown, MA, USA using a 3 Tesla Siemens MAGNETOM TrioTim scanner with a 32-channel Tim Matrix head coil. High-resolution T1-weighted multi-planar rapidly acquired gradient echo (MP-RAGE) structural scans were acquired using Generalized Autocalibrating Partially Parallel Acquisitions (GRAPPA; TR = 2530 ms; TE = 3.31 ms; flip angle = 7°; slices = 176; resolution = 1 mm isotropic). T2*-weighted BOLD images were acquired for the resting state scan using an echo planar imaging (EPI) sequence (TR = 2,000 ms; TE = 30 ms; flip angle = 85°; slices = 33, resolution = 3.0 × 3.0 × 3.44 mm, interslice gap of 0.5 mm). Functional image slices were aligned parallel to the long axis of the hippocampus.

Behavioral Analysis

The primary outcome measure of path integration ability was the proportion of correct trials. Behavioral performance was assessed using MatLab (MathWorks) and SPSS20 (IBM). A one-sample *t*-test was used to assess overall performance against chance levels (0.50 proportion correct).

fMRI Preprocessing

Resting state BOLD images were reoriented in SPM8 (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London) so that the origin (coordinate x, y, z = [0, 0, 0]) was the anterior commissure. The remainder of the preprocessing was done with FSL (FMRIB, Oxford, UK; FSL version 5.0.6) using the MELODIC preprocessing stream (Jenkinson et al., 2012). We used the FSL default settings unless otherwise noted. Brain extraction was done using BET to isolate the brain from the skull and other surface features (Smith, 2002) and the first five volumes were deleted. MCFLIRT was performed for motion correction (Jenkinson et al., 2002), and participants were removed from the analysis if absolute mean displacement exceeded 1 mm. Spatial smoothing with a Gaussian kernel of full-width half-maximum (FWHM) of 6 mm was performed, along with a high-pass filter with sigma set at the default 100 s. FLIRT was used to register functional images both to their own MPRAGE image and to MNI standard space (Montreal Neurological Institute, Montreal, QC, Canada; Jenkinson and Smith, 2001; Jenkinson et al., 2002). In order to remove any signal representing noise, each participant's individual components were visually inspected and artifacts were removed using the *fsl_regfilt* command line tool.

Functional Connectivity Analysis

Functional connectivity analysis was used to uncover the relationship between performance on the loop closure task and network connectivity. The regression analysis correlated performance with the strength of network connectivity. The significant effects shown in each voxel in the results indicate connectivity with the network of interest that varied by performance at that voxel. We conducted a whole-brain analysis of this question. Thus, this analysis tests whether the strength of connectivity between any given voxel in the brain and the CEN or DMN increased with accuracy in the loop task.

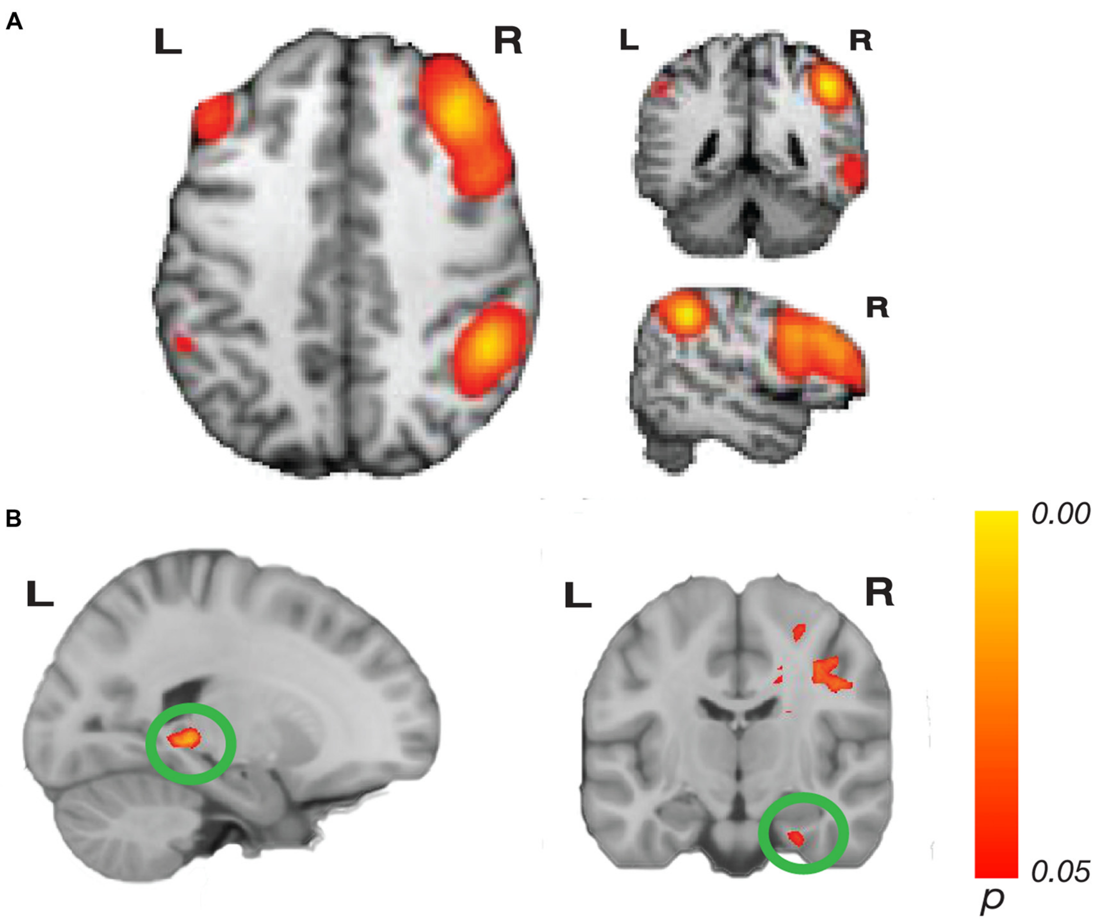

FIGURE 2 | Network connectivity results of the central executive network (CEN). **(A)** The CEN as defined by Laird et al. (2011; modified with permission). **(B)** Activations show regions where resting state connectivity to previously defined template networks was significantly associated with accuracy (Whole-brain analysis, threshold-free cluster enhancement (TFCE) with permutation testing, family-wise $p < 0.05$). Hippocampus tail (left; xyz: −20, −38, −2) and entorhinal cortex (right; xyz: 28, −14, −32) connectivity to the right CEN increased with path integration accuracy. Complete results for the right CEN are shown in **Table 1**.

Network Definitions

BrainMap 20 templates (Filippini et al., 2009; Laird et al., 2011) are pre-defined templates of 20 major intrinsic cortical networks. We used these templates to test connectivity to three networks: the CEN, containing fronto-parietal regions, and the DMN, containing the medial prefrontal and posterior cingulate/precuneus areas. The CEN is separated into two networks in the BrainMap 20 templates, with one network dedicated to the right hemisphere, and one dedicated to the left hemisphere network, yielding three total networks of interest. These networks were chosen *a priori* because of their involvement in and potential importance to memory and navigation (Seeley et al., 2007; Buckner et al., 2008; Cole et al., 2013). The loop closure task requires encoding distance and orientation during movement, while monitoring the home location. This process requires working memory to track and update the home location during movement, resistance to distraction from internal and external stimuli, rapid processing of incoming visual information and tracking of path integration errors, which could relate to the CEN. Episodic memory, and thus the DMN, could be important for performance of the loop closure task because the participant needs to create a memory of the target location and continuously update their location in space. These networks were predefined in the FSL templates (**Figures 2A**, **3A**), which included all brain regions in the network. Each complete network was the target of a whole-brain analysis to test for areas that showed significantly increasing connectivity to that network as a function of accuracy in the task.

Regression Analysis

Dual regression was performed using the pre-defined BrainMap 20 templates (Filippini et al., 2009; Laird et al., 2011) to identify regions of the brain that were functionally connected to each network. In dual-regression, first a subject-specific timeseries was generated by regressing group-level spatial maps (i.e., the BrainMap template for a given network) as spatial regressors into each individual subjects' 4D resting state dataset.

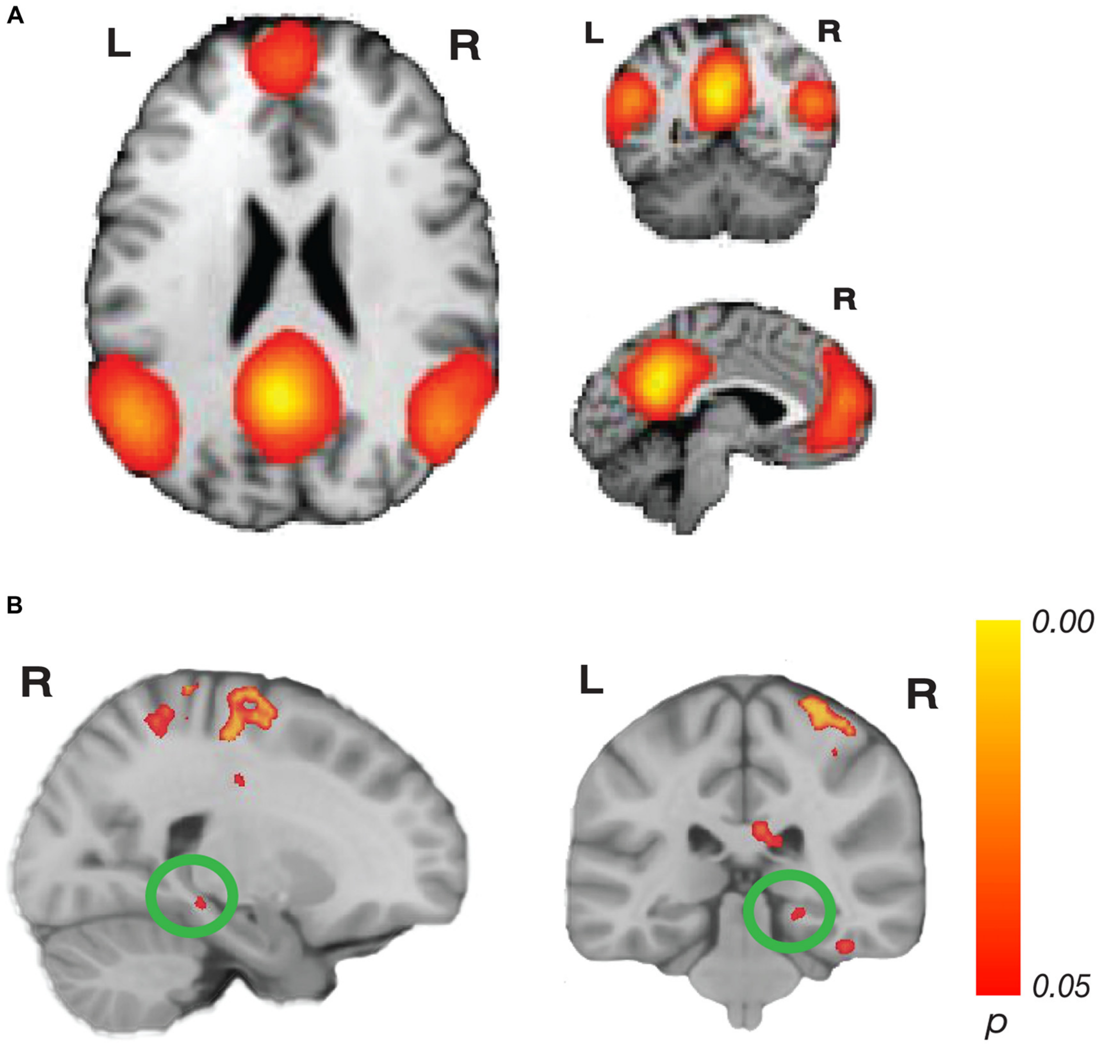

FIGURE 3 | Network connectivity results of the default mode network (DMN). **(A)** The DMN as defined by Laird et al. (2011; modified with permission). **(B)** Activations show regions where resting state connectivity to previously defined template networks was significantly associated with accuracy (Whole-brain analysis, TFCE with permutation testing, family-wise $p < 0.05$). Parahippocampal cortex (PHC; xyz: 22, −32, −10) connectivity to the DMN increased with accuracy. Complete results for the DMN are shown in **Table 2**.

Subsequently, those subject-specific timecourses were regressed into the same 4D resting-state dataset as temporal regressors to get one subject-specific spatial map of the connectivity to that network (Nickerson et al., 2017). We then tested for individual differences by including accuracy in the loop closure task as the primary regressor of interest. We included sex and age as covariates in the model to control for these potential confounding factors. We conducted a one-sample *t*-test for each regressor, examining the relationship between accuracy in each of the behavioral task and connectivity to the *a priori* networks of interest. We examined both positive (related to better performance) and negative (related to poorer performance) correlations.

We note that our results could show regions both outside of the network of interest and regions within the network that were significantly connected related to performance because our whole-brain analysis examines all voxels in the brain. For example, the RSC is part of the DMN, and a significant finding in RSC in the DMN contrast would indicate that RSC has significantly greater connectivity to other parts of the DMN in people who did better at the task. Thus, some of our results could be within-network, although they are not explicitly stated as such.

To conduct this whole-brain analysis for significant connectivity to the three complete networks that was related to accuracy in the loop closure task, we used *randomize*, a permutation testing method, to test for significance. We conducted 500 random draws of the data, and then compared our model with these random permutations. Dual regression and *randomize* were run using threshold-free cluster enhancement (TFCE), correcting for family-wise error to a level of $p < 0.05$. TFCE is a method that does not require a cluster-forming threshold and has been shown to give better sensitivity (Smith and Nichols, 2009), such that smaller but very strong clusters were permitted, rather than weaker but larger cluster extents, which can make localization difficult. Thus, the mass of significant clusters passed the permutation test threshold of corrected $p < 0.05$. In addition to this correction, we excluded clusters with five or fewer voxels from the results. We used Damasio (Damasio, 2005) and Pruessner (Pruessner et al., 2000, 2002) as references for localization in the cortex.

RESULTS

Behavioral Results

Behavioral performance has been described in depth elsewhere (Chrastil et al., 2015, 2017), but key findings that relate to this analysis are repeated here. Overall proportion correct in the loop closure task was 0.600 (SEM ± 0.023). Performance was significantly higher than chance (0.5) performance ($t_{(23)} = 4.366$, $p < 0.001$). Individual proportion correct ranged from 0.389 to 0.806, with a fairly even distribution of performance (**Figure 1B**), suggesting that the correlations with connectivity were not driven by outliers.

Network Connectivity Results

We analyzed resting state connectivity using previously defined networks, testing whether the strength of connectivity to these networks increased with accuracy in the loop task. We examined the relationship between accuracy in the loop closure task and connectivity to three *a priori* networks of interest—the right and left CENs and the DMN. A significant result in each cluster shows that the strength of connectivity between voxels in that cluster and the CEN or DMN increased with accuracy in the loop task. Importantly, variations in connection strength to these networks could occur *within* regions of the network itself as well as brain regions *outside* of the network. Here, we report MNI x, y, z coordinates of peak voxels in each cluster, as well as the *t*- and corrected *p*-values for the peak voxel, and the size of the cluster (k).

Our whole-brain analysis looked for areas that showed increasing connectivity to a network as a function of accuracy in the path integration task. This analysis revealed significant intrinsic connectivity between the right CEN and the left hippocampus tail (xyz: −20, −38, −2; $t_{(23)} = 6.78$; $p = 0.016$; $k = 87$) and right entorhinal cortex (xyz: 28, −14, −32; $t_{(23)} = 5.40$; $p = 0.04$; $k = 20$; **Figure 2**) that was related to accuracy in the loop task. In addition, a large cluster ($k = 3275$) was found in the right hemisphere, which included a large swath of white matter but also extended into PHC (xyz: 18, −30, −10; $t_{(23)} = 6.16$; $p = 0.038$) as well as thalamus, caudate and cingulate. In addition to these clusters, we found a cluster that spanned middle temporal gyrus and superior temporal sulcus, a cluster in cingulate sulcus, and two clusters in the cerebellum (one cluster spanned left and right cerebellum). **Table 1** has complete results of the right CEN results. There was no significant performance-related connectivity to the left CEN, and no significant relationship with worse performance.

For the DMN, we found a significant relationship related to accuracy with PHC (xyz: 22, −32, −10; $t_{(23)} = 6.05$; $p = 0.044$; $k = 14$; **Figure 3**). This cluster borders on the hippocampus and subiculum region. An additional cluster in the MTL region included the collateral sulcus and part of the parahippocampal gyrus (xyz: −32, −28, −24; $t_{(23)} = 5.46$; $p = 0.034$; $k = 102$). Other regions found in the DMN analysis included a cluster spanning pre-central gyrus, postcentral gyrus and superior parietal lobule, a cluster in precuneus, two clusters in the cerebellum, a cluster in cingulate sulcus, several clusters in temporo-occipital gyrus and a cluster in superior temporal sulcus. No significant results for the negative contrast were found. Complete results for the DMN can be found in **Table 2**.

DISCUSSION

In this experiment, we combined behavioral accuracy in a loop closure task, which provided a measurement of path integration ability, and resting state fMRI analysis (rsMRI). We found that better performance in the loop closure task was associated with increased functional connectivity between the right CEN and hippocampus tail, PHC and entorhinal cortex. We also found that functional connectivity between the DMN and PHC was associated with better loop closure task performance. The results suggest that interactions between MTL regions and

TABLE 1 | Brain regions where greater accuracy in the path integration task was associated with increased connectivity to the right central executive network (CEN).

Cluster size (k)	Brain region	*p*-value	Left MNI *x*, *y*, *z*	*p*-value	Right MNI *x*, *y*, *z*
3275	White matter extending into			0.036	28, −68, 6
	Thalamus			0.034	16, −28, 8
	Caudate			0.04	18, 6, 18
	Cingulate			0.02	14, −26, 32
	Parahippocampal Cortex			0.038	18, −30, −10
87	Hippocampus Tail	0.016	−20, −38, −2		
56	Middle Temporal Gyrus/Superior Temporal Sulcus	0.024	−52, −32, −8		
39	Cerebellum	0.032	−2, −56, −4	0.04	2, −56, −4
20	Entorhinal Cortex			0.04	28, −14, −32
7	Cingulate Sulcus			0.048	12, 14, 38
7	Cerebellum	0.048	−8, −48, −14		

Here, we report MNI x, y, z coordinates of peak voxels in each cluster, as well as the t- and corrected p-values for the peak voxel, and the cluster size (k).

TABLE 2 | Brain regions where greater accuracy in the path integration task was associated with increased connectivity to the default mode network (DMN).

Cluster size (k)	Brain region	*p*-value	Left MNI *x*, *y*, *z*	*p*-value	Right MNI *x*, *y*, *z*
1838	Precentral Gyrus			0.016	30, −18, 64
	Postcentral Gyrus			0.01	30, −38, 64
	Superior Parietal Lobule			0.044	30, −54, 68
123	Precuneus	0.026	−6, −54, 56		
102	Collateral Sulcus	0.034	−32, −28, −24		
88	Cingulate Sulcus	0.03	−18, −26, 38		
81	Temporo-Occipital Gyrus			0.034	40, −32, −24
72	Temporo-Occipital Gyrus	0.044	−32, −6, −44		
69	Inferior Temporal Gyrus	0.046	−48, −10, −36		
59	Cerebellum	0.044	−24, −46, −26		
32	Superior Temproal Sulcus			0.044	46, −20, −10
31	Cerebellum	0.048	−2, −58, −22		
22	Precentral Gyrus			0.046	60, −2, 34
19	Temporo-Occipital Gyrus			0.048	34, −18, −34
14	Parahippocampal Cortex			0.044	22, −32, −10
10	Temporo-Occipital Gyrus	0.048	−38, −34, −20		

Here, we report MNI x, y, z coordinates of peak voxels in each cluster, as well as the t- and corrected p-values for the peak voxel, and the cluster size (k).

both the CEN and DMN are important for navigation. In particular, both CEN and DMN have major network nodes in PFC, indicating a link between individual navigational abilities and executive function, working memory and episodic memory processes.

Our first major finding is that increased intrinsic connectivity between MTL regions and the right CEN is predictive of navigational ability. The CEN is important for adaptive implementation of shifting task demands and other executive control functions (Dosenbach et al., 2006; Seeley et al., 2007; Cole et al., 2013, 2014b). Executive control could be important for the loop closure task because performance of the task requires working memory to track and update the home location during movement, resistance to distraction from internal and external stimuli, rapid processing of incoming visual information and tracking of path integration errors. BOLD activation has previously been observed during other navigational tasks in nodes of the CEN, including dorso- and ventro-lateral PFC (dlPFC and vlPFC), posterior parietal cortex and intraparietal sulcus (IPS; Spiers and Maguire, 2006; Brown et al., 2010; Sherrill et al., 2013; Howard et al., 2014; Chrastil et al., 2016; Javadi et al., 2017). During our functional imaging of the loop closure task, we found parietal BOLD activation in regions that are part of the CEN during correct loop closure trials (Chrastil et al., 2015). Together, these findings indicate a role for this fronto-parietal network during path integration and navigation.

Surprisingly, we did not find any significant connectivity with the left CEN that was related to accuracy in the loop closure task. It is possible that the left networks connected equally well to all navigators, or that lateralization of this network plays a significant role. Although the left hemisphere has generally been more closely associated with executive functioning, the right hemisphere tends to be more associated with spatial processing (e.g., Smith and Jonides, 1999; Carpenter et al., 2000; Duncan and Owen, 2000). This divergence could underlie our finding significant connectivity for only the right lateralized CEN.

The CEN showed intrinsic connectivity with several navigational brain regions. Specifically, we found increased connectivity between regions within the right CEN and the hippocampus, entorhinal cortex and PHC in better navigators. These MTL regions are vital to path integration, and experiments in both animals and humans, as well as computational models, have demonstrated that these areas are important for the updating of spatial location. Grid cells in rodent entorhinal cortex demonstrate firing patterns that code spatial arrays, facilitating the updating of spatial location (Fyhn et al., 2004; Hafting et al., 2005). The spatial information in grid cells could then be used to update location information in hippocampal place cells (O'Keefe and Nadel, 1978; O'Keefe and Burgess, 1996; Burgess et al., 2007; Hasselmo, 2009). These grid and place cell-like firing patterns have also been observed in humans (Ekstrom et al., 2003; Doeller et al., 2010; Jacobs et al., 2013), suggesting a similar system for path integration. Entorhinal cortex also codes for direction and distance to goals in humans and has larger gray matter volume in better navigators (Howard et al., 2014; Chadwick et al., 2015; Sherrill et al., 2018), while the hippocampus has been shown to be important for path integration in a number of studies (Philbeck et al., 2004; Wolbers et al., 2007; Morgan et al., 2011; Sherrill et al., 2013; Howard et al., 2014; Yamamoto et al., 2014; Chrastil et al., 2015; but see also, Shrager et al., 2008). These functional findings, together with the results presented here, suggest that communication between brain regions important for path integration and executive function areas is important for successful navigation.

Our second major finding was that better navigators have increased intrinsic connectivity between PHC and the DMN. Although the DMN was originally viewed as a task-negative network, it has since been linked to many cognitive processes, including episodic memory and representations of oneself (Buckner and Carroll, 2007; Buckner et al., 2008; Laird et al., 2011). Episodic memory could be important for performance of the loop closure task because the participant needs to create a memory of the target location and continuously update their location in space. Self-referential processing could also be vital to tracking self-motion during loop closure and visualizing the path during movement. A recent study found cooperative interactions between the DMN, the right CEN and the mPFC during an internally-directed memory search task (Kragel and Polyn, 2015), suggesting that the networks we identified here are important for a broad variety of memory tasks, especially those related to self-processing.

Many of the regions commonly observed in navigation tasks are hubs of the DMN (Maguire et al., 1998; Shelton and Gabrieli, 2002; Wolbers and Büchel, 2005; Brown et al., 2010; Sherrill et al., 2013; Marchette et al., 2014), and in the functional version of this task we found corresponding BOLD activation in many DMN regions, including the hippocampus, RSC, PHC and angular gyrus (Chrastil et al., 2015). In the present study, we found PHC in particular to be related to DMN activity; this part of PHC borders on the hippocampus and subiculum region, an area known for grid cells, head direction cells and boundary vector cells (Taube et al., 1990; Lever et al., 2009; Boccara et al., 2010; Vass and Epstein, 2013). PHC has also been shown to be relevant to spatial context and scene processing (Bar and Aminoff, 2003; Davachi et al., 2003; Epstein, 2008; Epstein and Vass, 2013; Preston and Eichenbaum, 2013; Brown and Stern, 2014), and as well as to path integration tasks (Sherrill et al., 2013; Chrastil et al., 2015, 2016). Together, previous research on PHC suggests a strong role for processing self-motion during path integration by means of updating spatial information. The results of the present study are consistent with these findings, and suggest that better navigators have increased ability to process the incoming spatial information to update their self-localization in the environment.

Regions of the PFC are nodes in both the CEN and DMN. Dorsal mPFC, dlPFC and vlPFC are nodes in the CEN (Seeley et al., 2007; Cole et al., 2013), and ventral mPFC is a node in the DMN (Buckner et al., 2008). Previous research indicates that executive function, working memory, cognitive control and goal-directed behavior are important parts of successful navigation (Spiers, 2008). In this study, we found that good navigators have functional communication between navigation regions in the MTL and the CEN. However, it is possible that the connections with prefrontal networks observed here are driven by completely independent network associations; our correlational analysis cannot determine the direction of causality or a potential independent source. Researchers must look beyond the MTL, including potential links with prefrontal function, to fully understand the neural mechanisms underlying spatial navigation. The strong connectivity between the MTL and the CEN as well as the DMN indicate that PFC provides a potential avenue for future research on navigational abilities.

Notably, we did not observe any connectivity effects involving RSC or mPFC, regions in which we previously found structural variation corresponding to individual path integration ability on this same task (Chrastil et al., 2017). These regions are also nodes of the DMN (Buckner et al., 2008; Andrews-Hanna et al., 2010). RSC BOLD activity has been related to tracking heading direction (Baumann and Mattingley, 2010; Marchette et al., 2014; Shine et al., 2016) and path integration (Sherrill et al., 2013; Chrastil et al., 2015, 2016). Furthermore, lesions to RSC cause impairments in path integration (Save et al., 2001; Save and Poucet, 2009). mPFC BOLD activity has been observed during path integration, both while tracking locations and while encoding the basic translations and rotations of self-motion (Spiers and Maguire, 2007; Wolbers et al., 2007; Sherrill et al., 2013; Arnold et al., 2014; Chrastil et al., 2015), suggesting that mPFC could contribute to the encoding and maintenance of spatial information during path integration. However, the lack of functional connectivity findings in the present study suggests that both RSC and mPFC communicate with the CEN and other parts of the DMN similarly across all ability levels. Although the pattern of functional connectivity may not differ, the increased gray matter volume could still impart an advantage in better navigators (Chrastil et al., 2017).

We found other notable differences between our previous structural results (Chrastil et al., 2017) and the functional connectivity analyses presented here. For example, the increased hippocampal connectivity with the CEN in the present study was found within the posterior hippocampus for better navigators, whereas structurally we previously reported larger gray matter volumes in anterior hippocampus for better navigators (Chrastil et al., 2017). Our previous gray matter volume analysis also did not uncover structural differences in either PHC or entorhinal cortex, whereas the connectivity results suggest increased connectivity in both these areas for better navigators. Together, these differences highlight the importance of conducting multiple types of analyses for a complete understanding of individual differences. In addition, these results suggest that gray matter volume and functional connectivity measurements might tap into different aspects of individual abilities. Gray matter volume could be related to intrinsic neural resources, while rsMRI could be measuring the way in which neural resources interact. Taken together, the results of the two studies indicate that people who are better at path integration have larger gray matter volume in the anterior hippocampus, RSC and mPFC, and have greater functional communication between the hippocampus tail, PHC and entorhinal cortex with the CEN, and between PHC and the DMN.

Finally, we should note some limitations for our study. Although there was substantial variation in behavioral performance, the sample size was limited. The sample size could reduce our power to distinguish true effects. In addition, the resting state scan was completed after the task, which could influence resting state function (Waites et al., 2005; Barnes et al., 2009). Thus, resting state in this case could potentially be considered another measure related to the task. Because we were measuring individual performance, the influence of task could increase the size of our effects. However, participants completed other four tasks during the course of the scan (see "Materials and Methods," section), none of which were correlated with each other in behavioral performance (Chrastil et al., 2017), reducing potential task carry-over effects specific to loop closure.

In conclusion, we found evidence for functional communication between brain regions in the MTL that are vital for navigation and both the CEN and DMN, two cortical networks that are important for memory, self-referential processing and executive function. Individuals with greater communication between MTL regions and both the CEN and DMN had greater accuracy in the loop closure task. These results suggest that the strength of communication between navigation regions and primary memory and executive function networks is important for successful navigation. The results of this study suggest that in the future a broader examination into working memory and executive functions will be necessary to understand the breadth of human navigational abilities.

AUTHOR CONTRIBUTIONS

EC and SI contributed equally to this work. SI conducted the analysis and wrote the article. EC designed the research, wrote the article, collected data, and conducted analysis. CS designed the research and wrote the article.

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Continuous Environmental Changes May Enhance Topographic Memory Skills. Evidence From L'Aquila Earthquake-Exposed Survivors

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Exposure to environmental contextual changes, such as those occurring after an earthquake, requires individuals to learn novel routes around their environment, landmarks and spatial layout. In this study, we aimed to uncover whether contextual changes that occurred after the 2009 L'Aquila earthquake affected topographic memory in exposed survivors. We hypothesized that individuals exposed to environmental changes—individuals living in L'Aquila before, during and after the earthquake (hereafter called exposed participants, EPs)—improved their topographic memory skills compared with non-exposed participants (NEPs) who moved to L'Aquila after the earthquake, as only EPs had to modify their previous cognitive map of L'Aquila. We also hypothesized that memory improvement was selective for the navigational space and did not generalize across other spatial and verbal domains. To test these hypotheses, we compared the topographic and spatial memory skills of 56 EPs without post-traumatic stress disorder (PTSD) symptoms to the skills of 47 NEPs using the Walking Corsi Test (WalCT; memory test in the navigational space) and the Corsi Block-Tapping Test (CBT; visuospatial memory test in the reaching space); EPs and NEPs were matched for gender, education and general navigational skills. A sub-group of participants also underwent the Rey-Auditory Verbal Learning Test (RAVLT; verbal memory test). The results showed that only EPs had better performances on topographic learning (TL) assessed using the WalCT rather than spatial learning assessed by the CBT. This outcome suggests the possibility that EPs specifically improved topographic memory. This effect may be due to continuous exposure to environmental changes that have required individuals to learn novel paths within the city and integrate novel information, such as "new towns," into their pre-existing mental representation of the city. Implications and limitations of the study are discussed.

Keywords: post-traumatic stress, topographical learning, human navigation, spatial orientation, adaptation mechanisms, earthquakes, natural disasters, trauma-induced sequelae

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INTRODUCTION

The L'Aquila earthquake produced important environmental changes, which encompassed more than 45 towns and small villages. One year after the earthquake, the city center resembled a "ghost town" (Alexander, 2010, 2013; Díez, 2012; Contreras et al., 2014), with some areas remaining off-limits to citizens. Reconstruction and urban changes are still taking place almost 10 years later. On the one hand, isolated reconstruction initiatives have focused on individual buildings, without a holistic plan for urban recovery (Contreras et al., 2014); on the other hand, a large number of initiatives have included building new houses in settlements outside of the city center. This has forced individuals living in L'Aquila before, during and after the earthquake to acquire new spatial knowledge about the new districts (see **Figure 1**). The characteristics of such an urban plan pose important questions related to the spatial navigational skills of exposed survivors.

Boccia et al. (2016) found that post-traumatic stress disorder [PTSD: a psychological consequence of a traumatic event involving alterations in behavioral, psychological, physiological, biological and social responses (American Psychiatric Association, 2013)] has both a common network, which spans from the parietal to the frontal cortex and includes limbic structures, and specific networks that are more related to the type of stressor (e.g., the parahippocampal gyrus, the superior temporal and frontal gyri and the middle frontal gyrus, for natural disasters). Some of these structures play key roles in human navigation given that, in the presence of natural disasters, it is possible to observe functional changes in the neural networks since they relate to the perception of surrounding environments and familiar places that have been disrupted by the disaster; for example, the parahippocampal gyrus is involved in scene/place perception and environmental spatial navigation (Epstein and Morgan, 2012; Boccia et al., 2014). Meanwhile, Piccardi et al. (2016a) found that PTSD due to natural disasters modified the cerebral network, e.g., the insula, the lingual gyrus and the inferior and superior frontal gyri in the right hemisphere, involved in learning spatial sequences in the environmental space. These cerebral areas are related to different spatial abilities: the lingual gyrus and insula are involved in learning sequences in the navigational space with specific and complementary contributions (Nemmi et al., 2013). The inferior frontal gyrus is activated during the mental rotation of 3-D objects and letters (Jordan et al., 2001), while the superior frontal gyrus is involved in maintaining spatial orientation in working memory (Cornette et al., 2001).

Interestingly, Tempesta et al. (2012) found that individuals with PTSD caused by the L'Aquila earthquake showed a deficit in forming a cognitive map of a virtual environment although they had spared skills in using the map. The authors interpreted their results as a consequence of hippocampal alterations that have also been reported in patients with PTSD (e.g., Bremner et al., 1999; Bremner, 2001; Shin et al., 2004). Accordingly, Iaria et al. (2007) showed activation of the bilateral hippocampi during the formation and use of a cognitive map (Iaria et al., 2008). Finally, the results by Tempesta et al. (2012) are also consistent with sleep disturbances that participants in their study experienced, which may have led to impaired sleep-dependent spatial memory consolidation.

What about exposed-survivors who do not develop PTSD? In spite of the impact natural disasters have on communities, a large number of exposed survivors undergo a natural recovery process without experiencing any psychopathological consequences (Boscarino et al., 2005; Bonanno et al., 2010). According to the stress-habituation model (Meichenbaum and Novaco, 1985; Jaycox et al., 1998), the effects of a traumatic stressor decrease over time as people adapt to the stress exposure. Although chronic exposure to stress can lead to negative outcomes such as exhaustion, cognitive dysfunction, avoidance behavior and depression (Juster et al., 2010), low or moderate levels of acute stress can be adaptive. For example, it has been found to increase social behaviors such as mutual contact and searching for reassurance from others (Schuster et al., 2001). Traumatic events may also result in different physical and behavioral outcomes, as well as differences in the probability of developing PTSD, as a consequence of individual factors such as personality, gender, age and genetic factors (Ditlevsen and Elklit, 2012; D'Amico et al., 2013; Santiago et al., 2013; Husarewycz et al., 2014; Perrin et al., 2014; Giannini et al., 2016; Piccardi et al., 2016b). Thus, adaptation is crucial to survival, and individual differences in cognitive and emotional responses to both the stressor and context have been found to be key factors in determining outcomes, e.g., anticipation, appraisal, coping, learning and other types of information processing (Hobfoll, 1989; Lazarus, 1991; Holahan et al., 2000; Ironson et al., 2000). An allostatic response, that is, maintaining stability through change, along with adaptation to a current stressor may be considered as a two-stage process that includes central and peripheral allostatic accommodation. Allostatic accommodation encompasses not only the state of being in "homeostatic imbalance" (Sapolsky et al., 2000) but also the process of either bringing the system back to its original equilibrium or finding a new one (adaptive plasticity). The evidence stemming from the mechanisms underlying the post-traumatic growth (PTG)—namely positive psychological changes such as personal resilience, resetting life priorities and openness to new possibilities resulting from major life crises or traumatic events—seems to suggest that in the absence of PTSD, trauma exposure can lead to different responses to the stressor.

Environmental changes occurring after natural disasters such as earthquakes may foster individual skills as they force individuals to re-learn environmental information and acquire new spatial knowledge. Accordingly, spatial ability is understood to be widely affected by experience, for instance, playing video games (Dorval and Pépin, 1986; De Lisi and Wolford, 2002; Feng et al., 2007), orienteering (González et al., 2013; Schmidt et al., 2016), geo-caching (Barnikel et al., 2014; Ellbrunner et al., 2014) and other experiences or targeted training procedures (Cavallini et al., 2003; Boccia et al., 2017) seem to influence spatial ability in everyday life. De Lisi and Wolford (2002) found that girls improved two-dimensional mental rotations

FIGURE 1 | City map of L'Aquila before and after the earthquake. The figure shows the deep, urban modifications that inevitably forced citizens to re-learn the paths of their city after the earthquake. The background map shows: 1) the city center (the red circle; 2) suburbs, where the "new towns" (depicted in black on the map) were built for citizens whose houses were destroyed during the earthquake. The map was derived from the website of the Italian Civil Protection (decree n. 6, 11 May 2009. Source: http://www.protezionecivile.gov.it/jcms/it/view_dossier.wp;jsessionid=162AA553223F304BCBBADDF517785517?contentId=DOS282). On the top right panel of the figure, the map focuses on the changes of L'Aquila city center. Here, a typical route between a starting (S) and an ending (E) point is depicted as it appeared before (blue line) and after (yellow line) the earthquake. The path from S to E was quite short before the earthquake (approximately 0.6 km). However, due to the presence of blocked routes, going from S to E after the earthquake required a very long path (approximately 3.4 km). The map was created using Google Earth© 2018 and Google Maps© 2018. After the earthquake, landmarks along the route dramatically changed. Examples are provided in the a–c boxes (a the bridge "ponte Bel Vedere"; b the students' dormitory; c the "Duca degli Abruzzi" hotel). The three white stars indicate their positions on the map.

and performed at the same level as boys through practice with the popular videogame Tetris. Other studies have found that playing video games may also result in an improvement of topographic orientation in daily life (e.g., Kass et al., 1998; Rafi et al., 2005).

Until now studies have focused on spatial orientation and visuospatial memory skills in individuals suffering from PTSD, almost neglecting the possible modifications in spatial orientation skills in individuals exposed to traumatic events but who never showed signs of PTSD. Here, we aimed to fill this gap by focusing our investigation on topographic and visuospatial memory skills in young individuals who were exposed to the 2009 L'Aquila earthquake but never developed PTSD symptoms. To this end, individuals who were exposed to the L'Aquila 2009 earthquake (exposed participants, EPs) and individuals who were not exposed to the earthquake (non-exposed participants, NEPs) and moved to the city after the disaster were enrolled in the study. Our hypothesis is as follows: EPs had been exposed to continuous environmental changes soon after the earthquake and in the years following it. Due to the large number of modifications occurring in L'Aquila after the earthquake, EPs may have modified their topographic learning (TL) skills as happens for individuals exposed to other experiences such as geo-caching, orienteering and navigational training. In this light, environmental changes that occurred after the earthquake should have acted as navigational training. It is also possible that an optimal level of stress may have improved general memory skills, as predicted by PTG. In the first case, we would expect to see a specific improvement in TL skills compared with visuospatial and verbal memory skills. Otherwise, we would observe general memory improvement across different verbal and spatial domains.

PARTICIPANTS

A total of 103 college students participated in this study (37 males and 66 females; mean age = 24.48 ± 3.10 years; age range = 19–35 years). They were recruited from the Department of Life, Health and Environmental Science of the University of L'Aquila. Participants were enrolled on a voluntary basis from January 2016 to June 2018. The sample was divided in two groups according to their exposure to the April 6, 2009 earthquake that occurred in L'Aquila, Italy: 56 EPs, including 34 females and 22 males (mean age = 24.9 ± 3.52 years; SE = 0.47; range = 19–35 years), and 47 NEPs including 32 females and 15 males (mean age = 24 ± 2.46 years; SE = 0.36; range = 19–33). The EPs were either in the metropolitan area or a nearby district on April 6, 2009 (from 1.65 km to 20 km from the epicenter of the earthquake). They lived in or nearby L'Aquila before and after the earthquake. The NEPs had never experienced an earthquake, had never been to L'Aquila before the earthquake, and had started to attend the University of L'Aquila only 2–3 years after the earthquake. An initial interview indicated that none of the participants had neurological or psychiatric disorders or alcohol/drug addictions.

To evaluate the presence and nature of the traumatic events on the participants in the 6 months before testing, a trauma symptom inventory (TSI) was obtained (Briere, 1995; Italian Version: Gambetti et al., 2011); none of the participants showed PTSD symptoms. The EPs and NEPs were also compared on each clinical scale of the TSI in order to exclude any possible confounding effects. The two groups were matched for anxious arousal ($t_{(101)} = 0.06, p = 0.95$), depression ($t_{(101)} = 0.88, p = 0.38$), anger or irritability ($t_{(101)} = -0.75, p = 0.45$), intrusive experience ($t_{(101)} = 0.42$, $p = 0.67$), defensive avoidance ($t_{(101)} = 1.46$, $p = 0.15$), dissociation ($t_{(101)} = 0.94$, $p = 0.35$), sexual concerns ($t_{(101)} = -0.92, p = 0.36$), impaired self-reference ($t_{(101)} = -0.20$, $p = 0.84$), dysfunctional sexual behavior ($t_{(101)} = -2.39, p = 0.019$) and tension-reduction behavior ($t_{(101)} = -2.39$, $p = 0.019$). A significant threshold was set at $p = 0.05/10 = 0.005$ by using Bonferroni's correction for multiple comparisons.

The participants' sense of direction and familiarity were evaluated using the "Familiarity and Spatial Cognitive Style Scale" (FSCS; Piccardi et al., 2011b; Italian version: Nori and Piccardi, 2012). None of the participants reported navigational deficits or developmental topographic disorientation (Iaria et al., 2005, 2009; Bianchini et al., 2010). The two groups did not differ in their abilities to read a schematic map or to follow the path indicated on a map ($t_{(101)} = -1.04$, $p = 0.3$) as demonstrated by scores on a screening test (Semmes Test; Semmes et al., 1955).

A sub-group of participants composed of 40 EPs (24 females and 16 males, mean age = 25 ± 3.34, SE = 0.5) and 32 NEPs (24 females and 8 males, mean age = 24 ± 2.33, SE = 0.41) were also asked to perform a verbal memory test to check verbal memory functioning.

All participants signed a written consent form. The experiment was conducted in accordance with the ethical principles for human experimentation outlined in the Declaration of Helsinki. The study was approved by the Institutional Review Board of L'Aquila University.

MATERIALS AND METHODS

The following tests were administered to all participants:

Walking Corsi Test (WalCT: Piccardi et al., 2008b, 2013)

Walking Corsi Test (WalCT) is a large-scale version of the Corsi Block Tapping Test (CBT; Corsi, 1972) and has been repeatedly used in experimental and clinical practice (e.g., Piccardi et al., 2008b, 2010, 2015; Bianchini et al., 2010, 2014a,b; Nemmi et al., 2013; Palermo et al., 2014; Verde et al., 2015; Palmiero et al., 2016; Tedesco et al., 2017) to assess memory of short paths in a vista space. According Wolbers and Wiener (2014), the vista space is "the space that can be visually apprehended from a single location or with only little exploratory movements.... Typical examples for vista spaces are single rooms or town squares such as the St. Peters Square in Rome" p. 3. Nine black squares (30 × 30 cm) were placed on a floor within a layout, together with a starting point located outside the layout (see **Figure 2A**). Here, two aspects of topographic long-term memory were assessed, namely, TL and topographic delayed recall (TDR). The examiner showed a fixed 8-square sequence by walking and stopping on each square. The participant was instructed to reproduce the same sequence after the examiner has presented it. The learning criterion, indicating that learning was achieved, corresponded to three consecutive correct reproductions without additional demonstrations by the examiner. If the participant did not achieve the learning criterion, the sequence was repeated by the examiner for a maximum of 18 trials. No feedback regarding performance was provided. During each trial, the

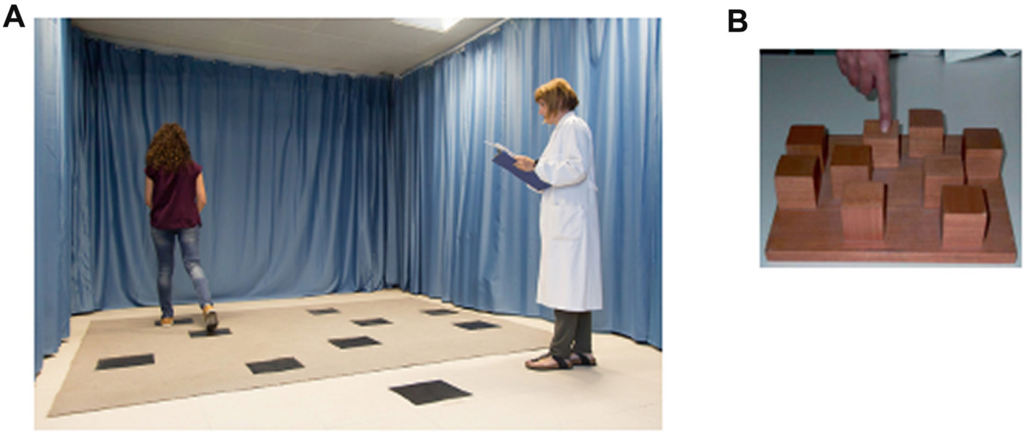

FIGURE 2 | (A) The Walking Corsi Test (WalCT): examiner and participant while performing the task. Written informed consent was obtained from the subjects represented in the figure for publication of this experiment. A copy of the written consent is available for review by the Editor-in-Chief of this journal. **(B)** The Corsi Block-Tapping Test (CBT) apparatus.

number of correct squares reproduced was registered and used for the final score. The learning score was computed by adding the number of correct squares on each of the 18 trials (maximum score: 144). After 5 min, the examiner asked participants to reproduce the 8-square sequence again in a single attempt. The number of squares correctly reproduced was computed and used as a measure of TDR (maximum score: 8).

Visuospatial and Verbal Memory

The following tests were used to control for the specificity of the TL effect and to exclude general memory impairment in the sample.

Corsi Block-Tapping Test (CBT: Corsi, 1972; Italian Version: Piccardi et al., 2013)

The CBT consists of nine blocks (4.5 × 4.5 cm) fixed on a baseboard (30 × 25 cm) in a scattered array (**Figure 2B**). Two aspects of visuospatial long-term memory in the reaching space were tested: visuo-spatial learning (VSL) and visuo-spatial delayed recall (VSDR). In the VSL, the participants had to learn an eight-block sequence presented by the examiner. The experimenter tapped the series of eight blocks at a rate of one block every 2 s, after which the participant had to tap the same block sequence in the same order it was presented. The learning criterion was reached if the participant reproduced the correct sequence three times in a row (max number of trials: 18). The learning score was calculated by attributing one point for each block correctly tapped until the criterion was reached. This was then added to the score corresponding to correct performance of the remaining trials (up to the 18th; maximum score: 144). Five minutes after the VSL was completed, the VSDR was administered. The examiner asked participants to reproduce the previously learned 8-block sequence. Scores were calculated based on the number of blocks correctly reproduced (maximum score: 8).

Rey's Auditory Verbal Learning Test (RAVLT: Rey, 1958; Italian Version: Carlesimo et al., 1996)

Two aspects of verbal memory were tested: verbal learning (VL) and verbal delayed recall (VDR). The examiner read aloud a list of 15 words at the rate of one per second. The participants were then asked to repeat all of the words from the list that they could remember. This procedure was carried out a total of five times (maximum score: 75). After a 15-min delay, the participants were asked to recall as many words as possible from the first list (maximum score: 15).

All participants were tested individually in a quiet laboratory room with artificial lighting and seated facing the examiner on a height-adjustable office chair during the article and pencil tests (i.e., CBT, RAVLT, FSCS and TSI). They were brought to an adjacent experimental room, without landmarks, where the WalCT and Semmes Test were located.

The test administration was randomized for each participant in order to avoid possible mental fatigue and learning facilitation effect during the experiment.

Statistical Analysis

All scores were transformed into percentages in order to make them comparable. Two mixed factorial ANOVAs with Group (EPs vs. NEPs) and Apparatus (CBT vs. WalCT) as the independent variables were performed for the learning and delayed recall scores. The groups' performances on the VL tasks were also compared using ANOVA 2 × 2.

A Bonferroni correction was applied using a significance threshold of $p = 0.05/2 = 0.025$, after correcting the p-level for two ANOVAs.

RESULTS

Descriptive statistics for each variable are shown in **Table 1**.

Results on Topographic Learning and Delayed Recall

The mixed factorial ANOVA for learning scores (TL vs. VSL) revealed a significant group-by-task interaction ($F_{(1,101)} = 6.693$, $p = 0.011$; partial $\eta^2 = 0.062$). *Post hoc* pairwise comparisons, performed using Bonferroni's procedure, showed that EPs were better able to learn a navigational path (WalCT-mean = 134–93%; SE = 1.7) than the visuospatial sequence (CBT–mean = 129–89.5%; SE = 1.9; $p = 0.013$). This result was also replicated in the sub-group of participants: ($F_{(1,70)} = 6.488$, $p = 0.011$; partial $\eta^2 = 0.06$; Bonferroni's correction: $p = 0.013$). The main effects of Group ($F_{(1,101)} = 0.004$, $p = 0.95$) and Task ($F_{(1,101)} = 1.33$, $p = 0.25$) were not significant.

The mixed factorial ANOVA on delayed recall (TDR vs. VSDR) revealed a significant main effect for Task ($F_{(1,101)} = 6.63$, $p = 0.011$; partial $\eta^2 = 0.011$). The delayed recall of the topographic task (WalCT—mean = 7.72–96.5%; SE = 0.1) was higher than the delayed recall of the visuospatial task (CBT—mean = 7.21–90.2%; SE = 1.8). This result was not replicated in the sub-group of participants: ($F_{(1,70)} = 1.76$, $p = 0.19$). The main effect of Group ($F_{(1,101)} = 0.401$, $p = 0.53$) and the group-by-task interaction ($F_{(1,101)} = 0.173$, $p = 0.68$) were not significant.

Verbal Memory Learning and Recall

In the sub-group of participants performing VL and VDR, the comparison between EPs and NEPs (two different ANOVAs were performed) revealed no significant effects (VL: $F_{(1,70)} = 0.0009$, $p = 0.98$; VDR:$F_{(1,70)} = 1.492$, $p = 0.23$).

DISCUSSION

Topographic memory is crucial for environmental spatial navigation. It is also used for processing and storing information about the environment, such as landmark features and specific locations, as well as spatial relations between landmarks (Berthoz, 1997; Kessels et al., 2001; Piccardi et al., 2008b; Palmiero and Piccardi, 2017). It differs from other forms of memory (i.e., verbal and visuo-spatial) as suggested by evidence from normal developmental processes (Piccardi et al., 2014a,b), neuroimaging data (Nemmi et al., 2013) and classical

TABLE 1 | Means, standard deviations and standard errors for each variable of interest in both groups.

	Exposed participants			Non-exposed participants		
	Mean	**S.D.**	**S.E.**	**Mean**	**S.D.**	**S.E.**
WalCT-TL	134	8.13	1.7	130.4	16.6	1.85
WalCT-TDR	7.7	1.04	0.14	7.74	0.9	0.13
CBT-VSL	129	15.5	1.9	132.4	12.3	2.06
CBT-VSDR	7.11	1.88	0.25	7.32	1.66	0.24
Rey-VL (*N* = 72)	51.9	9.76	1.54	51.97	9.58	1.7
Rey-VDR (*N* = 72)	11.45	3.27	0.52	12.28	2.27	0.40

Raw scores for each variable of interest; raw scores were transformed into % values to compare participants' performance on the different tests. Legend: S.D., Standard Deviation; S.E., Standard Error; WalCT-TL, Walking Corsi Test—Topographic Learning; WalCT-TDR, Walking Corsi Test—Topographic Delayed Recall; CBT-VL, Corsi Block-Tapping Test—Visuo-Spatial Learning; CBT-VDR, Corsi Block-Tapping Test—Visuo-Spatial Delayed Recall; Rey-VL, Rey's Auditory Verbal Learning Test—Verbal Learning; Rey-VDR, Rey's Auditory Verbal Learning Test—Verbal Delayed Recall.

interference paradigms (Piccardi et al., 2015; Verde et al., 2016). In patients with brain injuries (Piccardi et al., 2008a, 2011a), people with drug-resistant epilepsy (Piccardi et al., 2010) and healthy individuals affected by developmental topographic disorientation (e.g., Bianchini et al., 2010), it is possible to observe selective impairments in topographic memory but not in visuospatial memory for reaching spaces (e.g., Piccardi et al., 2010, 2011a). Because of this, tests that require moving towards and reaching locations, along with those that require remembering paths in real or virtual environments, are needed to detect the presence of impairments in topographic memory. In this study, participants were asked to learn, memorize and recall new paths (square sequences) in the WalCT with the expectation that individuals who were exposed to the L'Aquila earthquake would perform better than individuals who arrived and lived in L'Aquila in the years following the earthquake stemmed from the challenges confronted by the former group after having to continuously re-learn city paths (see **Figure 1** that maps environmental changes that happened in L'Aquila after the earthquake).

In some ways, the EPs group had been exposed to navigational training as their city map had been continuously updated over time.

After investigating the topographic memory skills in our sample, we found that EPs obtained higher scores and needed fewer repetitions to learn a new path in the navigational space than in the reaching space. This demonstrates a selective improvement of topographic memory with respect to visuospatial memory. Once a path was learnt however, it was delay-recalled equally well by both groups and, within the EPs group, there was no difference between information-delayed recall in the reaching and in navigational spaces. This result suggests that being exposed to environmental changes after a natural disaster may foster the acquisition of new topographic knowledge but not its recall.

The present results deserve consideration, especially when considered together with the findings by Tempesta et al. (2012) who observed a deficit in forming cognitive maps of the environment in PTSD individuals assessed 1 year after the earthquake. Differences between the present results and those by Tempesta et al. (2012) may be due to the extensive time (about 9 years) that had passed since the earthquake. The absence of differences between the EPs and NEPs groups in our study 9 years after the earthquake does not imply that there were no differences in the EPs closer to the adverse event. Instead, the differences may be due to the presence of PTSD in participants from the previous study. In our study, possible resilience mechanisms in individuals who never developed PTSD may have fostered memory skills. This is consistent with the PTG prediction. However, a general PTG effect should be detected in spatial, topographic and verbal memory. Finding that the EPs showed better topographic, rather than visuospatial, memory point to the hypothesis that navigational changes acted as training in the EPs. Additionally, finding dissimilarities among different types of memory tested—namely, between the WalCT and CBT—observed 9 years after the event suggests that topographic memory, contrary to other forms of memories, could have been continuously trained from the time of the earthquake.

These data are in line with remarks by Edelman (1987) who pointed out that memory could be considered an adaptive and dynamic capacity that implies context-dependent reactivation and one that provides a re-categorization of past information based on the present. As Schachtel (1947) declared, memory is the "capacity for the organization and reconstruction of past experiences and impressions in the service of present needs, fears and interests."

It is worth noting that this advantage specifically concerns topographic memory rather than visuospatial memory and is not generalizable to other navigational skills, neither as self-referred (as supported by FSCS interview) nor as tested with the Semmes Test. The enhancement of topographic memory appears to be specific and not generalizable to other forms of memory. These results are in line with the effects of navigational training in toddlers, which have resulted in improving specific aspects of navigational skills without general effects on navigation *tout court* (Boccia et al., 2017).

Turning from the evidence showing alteration of the cerebral network (i.e., the insula, the lingual gyrus, the inferior and superior frontal gyri in the right hemisphere) involved in learning spatial sequences in the environmental space in the presence of PTSD as a consequence of natural disasters (e.g., Piccardi et al., 2016a), the present results suggest that the increase in the capability to learn topographic sequences in EPs might be modulated by specific brain circuits that have not been altered, thus playing a key role in positive coping mechanisms. It may be possible that a restructured cognitive map that requires substitutions, insertions and deep changes may produce an observable effect at the behavioral and, possibly, at the neural level. Nevertheless, this issue needs further investigations.

Despite the novelty of these results, it should be recognized that there was no baseline evaluation of topographic memory in the EPs. However, it is unlikely that participants of the exposed group were accidentally recruited with higher topographic memory skills, especially as the scores on the Semmes Test and FSCS were not different between the two groups. However, a longitudinal design that involves testing participants during the aftermath and in the short, medium and long term after trauma exposure is needed to confirm the present data. Moreover, future studies should conduct longitudinal investigations to assess clinical populations with different severities of psychological distress to better understand whether topographic memory should be considered a protective factor to prevent mild cognitive impairments and/or psychological trauma-induced sequelae. The collection of salivary cortisol samples to measure psychological stress may also be useful in future studies as the absence of these physiological measures in the present study do not allow conclusions to be drawn with respect to the mechanisms underlying adaptational plasticity. To fully demonstrate our interpretation, future studies should use a spatial updating task to more directly explore the idea that environmental changes foster the acquisition and storing of new spatial knowledge, thus resulting in an improved cognitive map of the environment. We limited our investigation to TL, which is undoubtedly the process underlying the formation of the mental map, but this is just a small part of the numerous processes underlying spatial navigation.

Another limitation of the present study was the absence of measures taken before the earthquake. There is no evidence regarding the EPs' mental maps before the disaster; therefore, it was not possible to make comparisons with their new mental maps. However, by observing **Figure 1**, it is reasonable to assume that important environmental changes occurred and that these changes required individuals to update previous mental maps. The NEP group learned the new town after they moved to L'Aquila following the earthquake. The absence of differences within the NEP group between visuospatial, verbal and topographic memory seems to suggest that this kind of topographic practice did not produce an enhancement of topographic memory. Their answers to the FSCS showed that they were confident in moving around L'Aquila city without experiencing topographic disorientation episodes. Therefore, the two groups cannot be considered equivalent with respect to the degree of familiarity with the city, a factor that has importance in human navigation proficiency (e.g., Nori and Piccardi, 2011; Lopez et al., 2018).

In conclusion, these results may shed light on positive, long-term changes that occur in environmental mental representation mechanisms after exposure to a natural disaster. To our knowledge, this aspect has not been previously investigated and deserves further study to better understand cognitive map formation under post-traumatic stress in the absence of clinical disorders.

AUTHOR CONTRIBUTIONS

LP, MP, MB, AMG and SDA conceived and designed the experiment. AB, FB and PC collected data. MP and MB analyzed data and all authors contributed to the writing of the article.

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REVIEW
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Spatial Representations in the Human Brain

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While extensive research on the neurophysiology of spatial memory has been carried out in rodents, memory research in humans had traditionally focused on more abstract, language-based tasks. Recent studies have begun to address this gap using virtual navigation tasks in combination with electrophysiological recordings in humans. These studies suggest that the human medial temporal lobe (MTL) is equipped with a population of place and grid cells similar to that previously observed in the rodent brain. Furthermore, theta oscillations have been linked to spatial navigation and, more specifically, to the encoding and retrieval of spatial information. While some studies suggest a single navigational theta rhythm which is of lower frequency in humans than rodents, other studies advocate for the existence of two functionally distinct delta–theta frequency bands involved in both spatial and episodic memory. Despite the general consensus between rodent and human electrophysiology, behavioral work in humans does not unequivocally support the use of a metric Euclidean map for navigation. Formal models of navigational behavior, which specifically consider the spatial scale of the environment and complementary learning mechanisms, may help to better understand different navigational strategies and their neurophysiological mechanisms. Finally, the functional overlap of spatial and declarative memory in the MTL calls for a unified theory of MTL function. Such a theory will critically rely upon linking task-related phenomena at multiple temporal and spatial scales. Understanding how single cell responses relate to ongoing theta oscillations during both the encoding and retrieval of spatial and non-spatial associations appears to be key toward developing a more mechanistic understanding of memory processes in the MTL.

Keywords: spatial memory, navigation, cognitive map, episodic memory, MTL, theta, place cells, grid cells

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INTRODUCTION

Space is one of the most fundamental dimensions along which we organize our perceptions and memories. Kant wrote in 1781 *"Space is a necessary a priori representation that underlies all outer intuitions (Der Raum ist eine notwendige Vorstellung a priori, die allen äußeren Anschauungen zum Grunde liegt)"* (Kant, 1781). Every *outer intuition*, every object we perceive or imagine possesses a specific shape and occupies a specific location in space. Memory for spatial relations and spatial contexts associated with specific experiences thereby helps us navigate and interact with the objects we encounter. There is an extensive body of research on the neurophysiology of spatial memory in rodents, in which invasive brain recordings can be collected during navigation. Memory research in humans, in turn, had traditionally focused on verbal memory tasks without a spatial component. Here we review studies that have begun to address this gap using virtual navigation tasks in combination with electrophysiological recordings and neuroimaging in humans. These studies are the basis for our understanding of inter-species differences and similarities in spatial memory and further inform the ongoing debate on the generality or specificity of coding spatial vs. conceptual information (Eichenbaum et al., 1999; Milivojevic and Doeller, 2013; Constantinescu et al., 2016).

Spatial coordinates can be extracted from various sensory inputs including visual (Goodale and Milner, 1992; Kravitz et al., 2011), auditory (King et al., 2011; Salminen et al., 2012) and somatosensory (Badde and Heed, 2016) signals. Based on studies in humans (Silver and Kastner, 2009; Galati et al., 2010) and non-human primates (Andersen et al., 1997), there is strong consensus that these signals are integrated in the posterior parietal cortex (PPC). Here, they are combined with proprioceptive information and translated between *egocentric* reference frames centered on different body-parts (e.g., eye, head, or hand) to facilitate movement planning with different effectors (Grefkes and Fink, 2005; Medendorp et al., 2005; Moon et al., 2007; Van Der Werf et al., 2008; Filimon, 2010; Herweg et al., 2014). Egocentric coordinates can be distinguished from *allocentric* (Burgess, 2006) coordinates (sometimes referred to as world-centered or object-centered), which represent spatial information with respect to external reference frames (e.g., with respect to specific objects or along salient dimensions of an environment) and, hence, are independent of the position of the individual. Allocentric spatial coding has mainly been associated with the medial temporal lobe (MTL) and forms the basis for a *cognitive map* (Tolman, 1948) of the environment, from which information on the spatial relations of landmarks or objects can be flexibly extracted when needed. First described by Tolman (1948), the idea of a cognitive map pioneered model-based learning in general (Doll et al., 2012) and inspired research on the neural basis of an allocentric spatial map in particular.

In the following sections, we will review neurophysiological evidence for an allocentric spatial map in the human MTL, which is used to code observer-independent spatial relations during (virtual) navigation, exploration, or imagination (see section "An Allocentric Spatial Map in the Human MTL?"). We then consider interactions between this spatial map in the MTL and other brain regions involved in the encoding and retrieval of spatial information, such as the PPC and prefrontal cortex (PFC; see section "Spatial Representations in a Brain-Wide Network"). Although the idea of a spatial map is tightly linked to spatial navigation, behavioral studies on human way finding suggest complementary learning and decision processes, which we will highlight in Section "Cognitive Mapping and Complementary Learning Mechanisms in Human Spatial Navigation." Finally, we will consider the role of the MTL in declarative memory formation and retrieval more broadly (see section "Functional Overlap in the MTL: A Common Map for Physical and Conceptual Space?") and propose avenues for future research.

AN ALLOCENTRIC SPATIAL MAP IN THE HUMAN MTL?

Studies of awake behaving rodents claim to have identified the building blocks of an allocentric spatial map in the firing of individual neurons and neuronal oscillations in the MTL (Moser et al., 2008). This section reviews recent progress in translating these findings to human navigation.

Spatially Selective Single Cells – Observed via Invasive Recordings or Inferred From Population Activity

Hippocampal place cells (O'Keefe, 1976, 1979) increase their firing rate whenever an animal traverses a particular place in the environment (O'Keefe and Conway, 1978) and entorhinal grid cells preferentially fire on the vertices of a hexagonal grid (Hafting et al., 2005). These cells represent an animal's spatial location with respect to landmarks and spatial boundaries, and often independent of the animal's facing direction. We and others (Moser et al., 2008), therefore interpret these findings to be consistent with an allocentric reference frame (although alternative accounts exist: Wolbers and Wiener, 2014; Filimon, 2015). While early fMRI studies confirm a role for the human MTL in spatial navigation (Aguirre et al., 1996; Maguire et al., 1998; Bohbot et al., 2004; Wolbers et al., 2007; for a review see Maguire et al., 1999), more direct insight at the cellular level comes from intracranial recordings in patients with pharmaco-resistant epilepsy. In these patients, micro-wire bundles extending from the tip of medial temporal depth electrodes (Misra et al., 2014) can be used to record single unit spiking activity.

As human patients navigated virtual environments, place-selective cells were observed in three independent studies in the hippocampus, parahippocampal gyrus (including entorhinal cortex) and amygdala (**Figures 1A,B,E**; Ekstrom et al., 2003; Jacobs et al., 2013; Miller et al., 2013). One of these studies only considered cells whose firing rate was a function of place but not view, and found those cells to be significantly clustered in the hippocampus with an average of 1.7 non-contiguous place-fields (Ekstrom et al., 2003). Moreover, two studies found predominantly omnidirectional coding (i.e., same firing rate for different directions; Ekstrom et al., 2003; Jacobs et al., 2013) and one study found predominantly unidirectional coding (Miller et al., 2013). In rodents, omnidirectional and unidirectional place cells are associated with open field and maze-like environments, respectively (McNaughton et al., 1983; Muller et al., 1994), suggesting that traversal of an area in different directions allows for omnidirectional representations, which are independent of one particular serial order of processing (Buzsáki, 2005). The data on human place-responsive cells aligns with this idea – while Jacobs et al. (2013) used an open field environment, the environment used in Miller et al. (2013) featured constrained paths and high buildings. Although Ekstrom et al. (2003) also used a city environment, the paths were wider and the buildings smaller than in the study by Miller and colleagues, allowing for

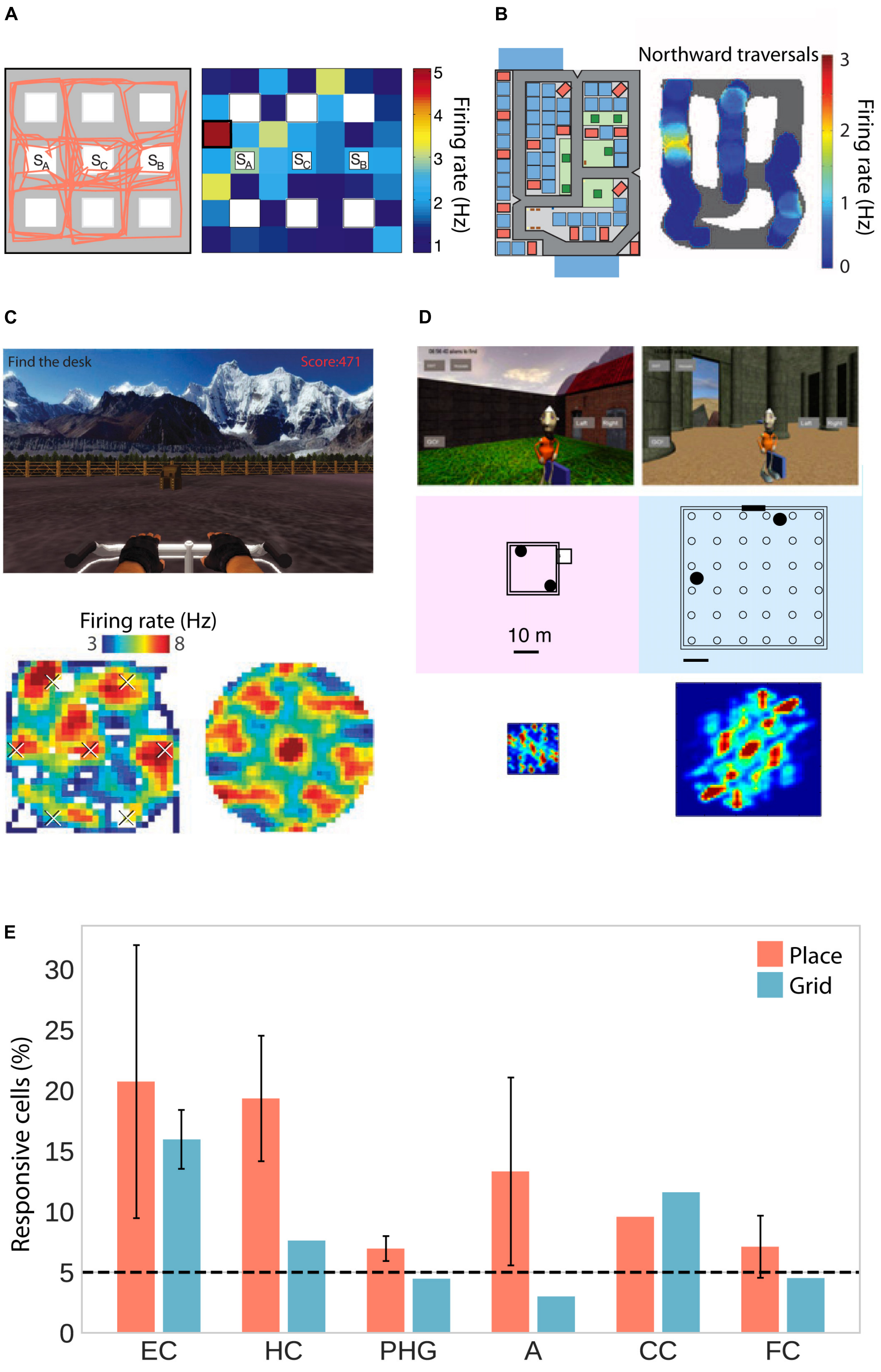

FIGURE 1 | Place and grid cell activity in humans. **(A)** Traveled path *(left)* and firing rate map of an exemplary place cell (*right*) in a city block environment. Adapted with permission (Ekstrom et al., 2003) from Springer Nature. **(B)** City environment (*left*) and firing rate map for an exemplary unidirectional place cell firing only during northward traversals (*right*). Adapted with permission (Miller et al., 2013) from Science. **(C)** Open-field environment (*top*), firing rate map (*lower left*), and spatial autocorrelation function (*lower right*) of an exemplary grid cell. Adapted with permission (Jacobs et al., 2013) from Springer Nature. **(D)** Small (*left*) and large (*right*) virtual arena with corresponding autocorrelation functions showing small and large grid spacing, respectively. Adapted with permission (Nadasdy et al., 2017) from PNAS. **(E)** Percentage of place- and grid-responsive cells in the entorhinal cortex (EC), hippocampus (HC), parahippocampal gyrus (PHG), amygdala (A), cingulate cortex (CC), and frontal cortex (FC). Data were summarized from Ekstrom et al. (2003); Jacobs et al. (2013), Miller et al. (2013), and Nadasdy et al. (2017). Standard error of the mean is shown if more than one of the studies reported data for a given brain region.

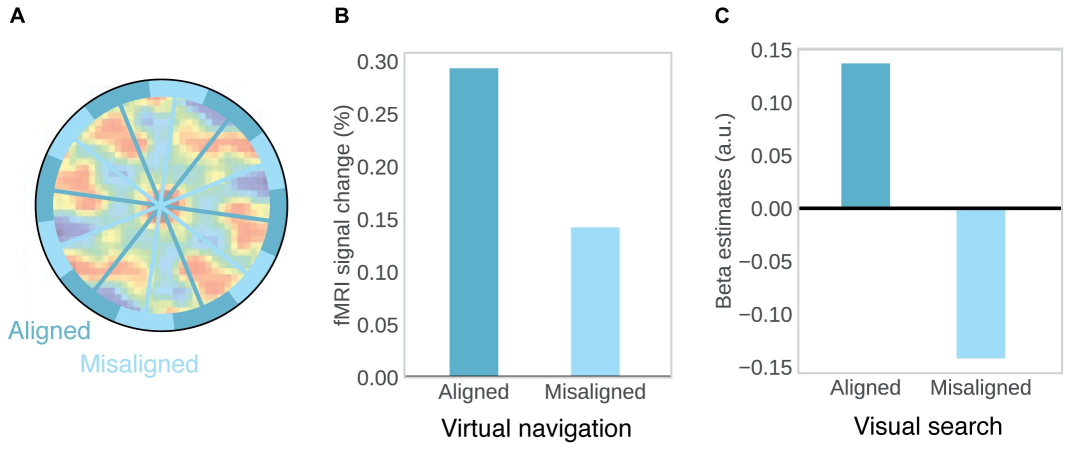

FIGURE 2 | Evidence for grid-cells in fMRI BOLD. **(A)** Rationale for observing grid-like activity in BOLD contrast. Based on the assumption that grid cells show a similar grid orientation across the population, movement in a direction aligned with the common grid direction should be associated with higher firing rates across the population and therefore higher BOLD signal than movement in a direction misaligned with the grid. Underlying autocorrelation function adapted with permission (Jacobs et al., 2013) from Springer Nature. **(B)** During virtual navigation, movement in a direction aligned with grid orientation, which was estimated from an independent subset of the data, resulted in higher BOLD in the entorhinal cortex than movement in a direction misaligned with the grid. Data from Doeller et al. (2010). **(C)** Analogously, eye movements in a direction aligned with grid orientation in a visual tracking task are associated with higher BOLD than eye movements in a direction misaligned with the grid. Data from Nau et al. (2018).

higher variability in taken paths and visibility of large portions of the environment from any one location.

In addition to these putative place cells, studies in humans have also confirmed the existence of grid cells, which fire at the vertices of a hexagonal grid spanning the environment. Two studies observed grid-like firing with sixfold rotational symmetry in the human entorhinal cortex and hippocampus in a virtual open-field environment (**Figures 1C–E**; Jacobs et al., 2013; Nadasdy et al., 2017). Moreover, navigation in a circular path environment elicited spatially periodic activity without rotational symmetry in the entorhinal cortex, which may reflect grid cell activity anchored to individual corridors or some other form of distance coding (Miller et al., 2015). One of the studies showing sixfold rotational symmetry estimated grid spacing (i.e., the distance between adjacent grid nodes) to be at least 1–6 m in the real world (Jacobs et al., 2013). The other study showed that spacing was a function of environment size, with coarser spacing in larger environments (**Figure 1D**; Nadasdy et al., 2017). Studies in rats suggest that neighboring (Hafting et al., 2005) and distant (Barry et al., 2007) grid cells share a similar orientation. In a small sample of epilepsy patients, orientation was consistent across patients and anchored to environmental geometry (i.e., square vs. rectangular shaped; Nadasdy et al., 2017).

Consistent orientation across cells is the basis for fMRI studies on grid-like activity, as movements in a direction aligned with the common grid direction should be associated with higher firing rates, and increased BOLD signal, than movements in a direction unaligned with the grid (**Figure 2A**). This effect may be further increased by conjunctive grid × head direction cells which fire at the vertices of the grid only at one particular running direction (Doeller et al., 2010). The BOLD contrast for aligned vs. misaligned trajectories can be calculated after initially estimating grid orientation on a subset of the data. Using this logic, grid-like activity in BOLD signal was observed in the entorhinal cortex (**Figure 2B**; Doeller et al., 2010; Kunz et al., 2015; Stangl et al., 2018). Separate studies observed the same effect during imagined movement (Horner et al., 2016) and stationary heading (Bellmund et al., 2016). Furthermore, grid orientation varied across subjects, ruling out that visual features of the environment were driving the effects (Doeller et al., 2010; Horner et al., 2016) and the coherence of grid orientations within each subject was correlated with spatial memory performance (Doeller et al., 2010; Kunz et al., 2015). In agreement with single-unit recordings in monkeys (Killian et al., 2012), two recent studies observed grid-like activity in entorhinal BOLD signal representing visual space in a 2D stimulus array (**Figure 2C**; Julian et al., 2018; Nau et al., 2018), suggesting that allocentric spatial coordinates are extracted from such arrays and used to code spatial positions, even in the absence of navigation and explicit memory demands (Julian et al., 2018).

Oscillatory Activity

The studies reviewed above suggest that the place- and grid-cell network is largely conserved across species. Similar convergence across species has been observed with respect to neural oscillations. Most prominently, theta oscillations (4–8 Hz) have been observed in the rodent (Vanderwolf, 1969; Buzsáki et al., 1983) and human MTL during navigation compared to stillness (**Figure 3A**). Using intracranial electroencephalography (iEEG) in humans, theta has been observed in a radial arm maze (Bohbot et al., 2017), an open-field (**Figure 3B**; Bush et al., 2017) and a city environment (Ekstrom et al., 2005), as well as during real-world ambulatory movement (Aghajan et al., 2017; Bohbot et al., 2017). In addition, magnetoencephalography (MEG) studies have source localized theta activity to the MTL (Cornwell et al., 2008;

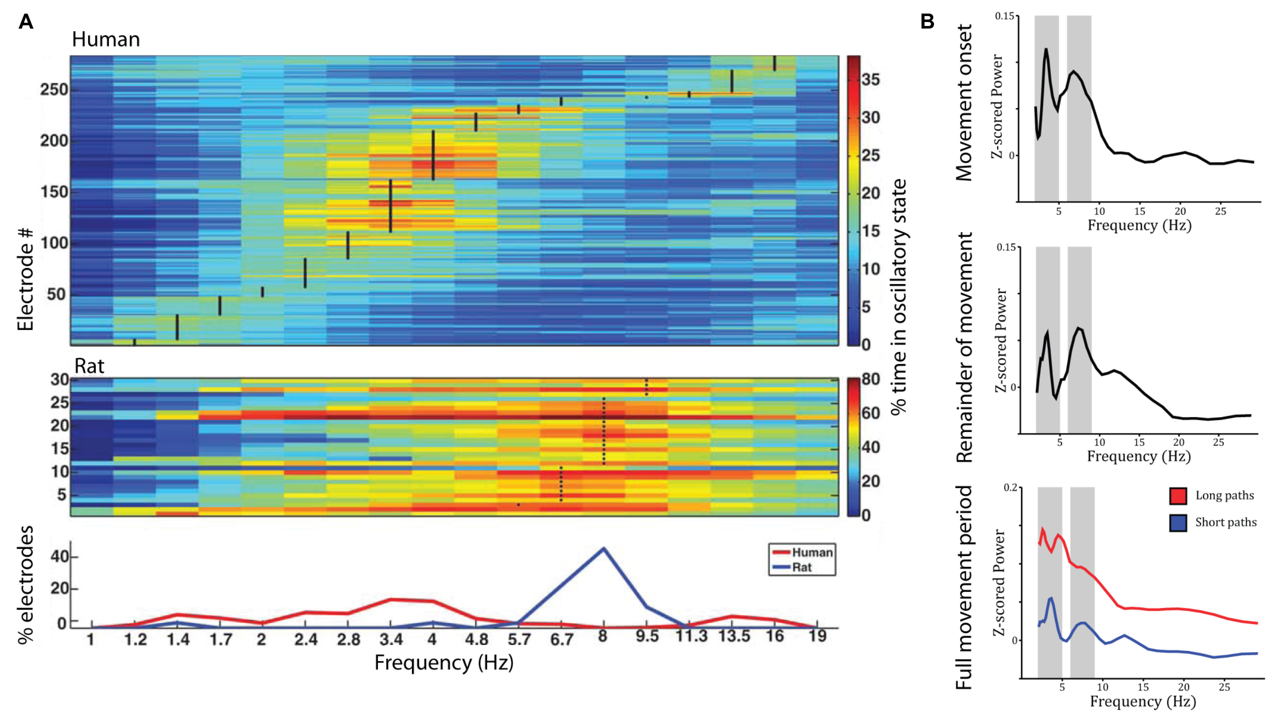

FIGURE 3 | Theta oscillations during virtual navigation. **(A)** The predominant frequency of oscillations occurring during virtual navigation appears to be lower in humans than rats. A clear peak around 8 Hz is evident in rats, while human data shows a peak around 3–4 Hz. Adapted with permission (Watrous et al., 2013a) from Wiley Periodicals. **(B)** Theta oscillations are evident in the power spectrum during movement onset (*top*), the remainder of the movement period (*middle*), and the full movement period (*bottom*) in two distinct frequency bands around 3–4 and 8–9 Hz, at the edges of the conventional theta rhythm. Theta oscillations are of higher amplitude during long compared to short paths (*bottom*).

Kaplan et al., 2012). Theta oscillations were observed likewise in the hippocampus and parahippocampal gyrus (Ekstrom et al., 2005; Cornwell et al., 2008) and co-occurred with an increase in hippocampal BOLD contrast (Kaplan et al., 2012; although other studies did not show a significant relation between hippocampal theta and BOLD: Ekstrom et al., 2009; Ekstrom, 2010). They were further indexed not only by increased power but also by examination of raw traces and an oscillation detection algorithm, which discriminates narrow band oscillations lasting several cycles from broad band and/or transient power increases (Ekstrom et al., 2005). Based on studies in rodents, most studies on human navigation *a priori* restricted their analyses to the theta band. Some studies have considered a wider spectrum of low-frequencies, and their findings suggest that the spatial navigation rhythm might be of lower frequency in humans than in rodents (**Figure 3A**). These studies observed a power spectral peak in the delta band around 2–3 Hz (Clemens et al., 2013; Watrous et al., 2013a; Miller et al., 2018) or both a low and a high frequency peak (Bush et al., 2017). While one study suggests that differences in frequency partly relate to virtual vs. real-word navigation (Bohbot et al., 2017), others have speculated that a shift toward lower frequencies relates to the larger size of the human hippocampus compared to that of the rodent (Jacobs, 2014).

Low frequency activity has been shown to be a function of movement speed (fast > slow; Watrous et al., 2011), navigational goal (fixed-location landmark > aimless navigation; Cornwell et al., 2008; Watrous et al., 2011), view (Watrous et al., 2011), path length (long > short, during movement onset and the remainder of the path; **Figure 3B**; Bush et al., 2017), and familiarity of the environment (familiar > novel; Kaplan et al., 2012). These findings shed some light on the role of low frequency oscillations during navigation. Specifically, two (not mutually exclusive) hypotheses have been discussed: Low frequency oscillations might coordinate sensory and motor areas during navigation (Bland and Oddie, 2001; Caplan et al., 2003) or might play a role for spatial coding and memory (Cornwell et al., 2008; Watrous et al., 2011). Modulations by movement speed can be easily explained by a sensorimotor integration account (Bland and Oddie, 2001). Modulations by view, however, were observed as stronger theta power during viewing of non-goal buildings compared to goal buildings or a relatively uniform background (Watrous et al., 2011). These results are difficult to reconcile with a pure sensorimotor account, as they seem to indicate that theta activity specifically increases when viewing landmarks, which can be used to plan routes to the goal location, i.e., when encoding and retrieval of spatial information is required. Similarly, enhanced theta power during goal-directed navigation compared to aimless navigation suggests a role for theta oscillations in spatial memory retrieval and route planning. The same is true for higher theta power during movement onset for long compared to short paths (which require retrieval of more spatial information and planning of a longer route). Finally,

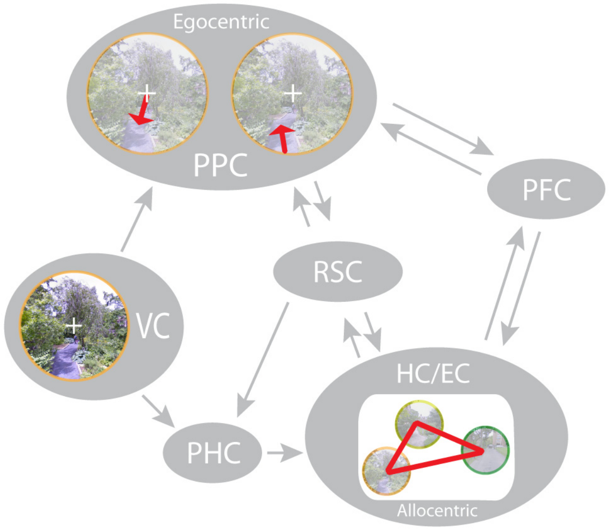

FIGURE 4 | Key regions involved in spatial memory and navigation. The PPC, situated along the dorsal visual stream, extracts spatial coordinates from visual input and translates between different egocentric reference frames (e.g., retinotopic or head-centered). These can be used to track motion and plan movements in coordination with the PFC. The PHC receives input not only via the ventral visual pathway but also from the dorsal pathway via the RSC. It projects to the HC via the EC, where allocentric coding pre-dominates. The RSC might translate between parietal egocentric and medial temporal allocentric representations. Prefrontal interactions with HC and surrounding MTL may facilitate goal-directed navigation. EC, entorhinal cortex; HC, hippocampus; MTL, medial temporal lobel; PHC, parahippocampal cortex; PPC, posterior parietal cortex; RSC, retrosplenial cortex; VC, visual cortex.

higher theta power in familiar environments may relate to the fact that more stored spatial information is available that can be retrieved to guide movement. Taken together, these results suggest that theta oscillations are involved not only in low-level sensory and motor processes but also in the encoding and retrieval of spatial information.

Further support for the spatial memory hypothesis has been obtained from both rodent and human studies. In rodents, it has been shown that theta oscillations orchestrate the firing of place-responsive cells. Specifically, a place cell fires at progressively earlier phases of the theta cycle while a rat traverses its place field (O'Keefe and Recce, 1993), a phenomenon that has been termed phase precession and implicates theta oscillations in representing allocentric spatial location. In humans, hippocampal theta-power has been associated with navigation performance across subjects (Cornwell et al., 2008) and with pre-navigation planning across trials: Upon instruction to find the location of a previously presented object, theta power was found to be higher for subsequently accurately vs. inaccurately placed objects (Kaplan et al., 2012). Miller et al. (2018) have associated slow theta power with successful encoding of object-location pairs. In their task, subjects navigated a virtual arena to reveal objects. During retrieval, they were cued with objects and had to recall the associated location. Subsequently successfully placed objects were associated with higher slow theta power during encoding. Finally, one study used a virtual environment equipped with multiple teleporters to decouple traveled distance from sensory input and motor output during navigation. Here, delta–theta oscillations were predictive of the spatial distance traveled during teleportation (i.e., in the absence of sensory-motor demands) while controlling for the time being teleported (Qasim and Jacobs, 2016; Vass et al., 2016).

While most studies *a priori* focused on low frequency oscillations, few studies have analyzed modulations in higher frequencies. These studies have found navigation-related increases in hippocampal and parahippocampal alpha (∼9–14 Hz), beta (∼15–30 Hz), and gamma (∼31–55 Hz) power (Ekstrom et al., 2005; Jacobs et al., 2009; Watrous et al., 2011). An increase in power, however, does not necessarily index underlying oscillations but may also be caused by transient, non-oscillatory amplitude changes (Whitten et al., 2011). While the presence of narrowband oscillations in the low frequency range has been established by multiple studies using oscillation detection algorithms (Caplan et al., 2003; Ekstrom et al., 2005; Watrous et al., 2011), it remains largely unclear to what extent effects in higher frequencies are due to broadband shifts in spectral power versus narrowband oscillations. Likewise, the functional role of medial temporal high frequency effects in navigation remains a subject for future study.

SPATIAL REPRESENTATIONS IN A BRAIN-WIDE NETWORK

Although place- and grid-like activity has mainly been associated with the hippocampus and entorhinal cortex, respectively, studies have also observed such signals outside the MTL. Specifically, cells in PFC showed place-selectivity (Ekstrom et al., 2003) and cells in cingulate cortex showed both, place and grid-like firing (Jacobs et al., 2013; **Figure 1E**). Using fMRI with whole brain coverage, wide-spread grid-like activity was observed in medial prefrontal, parietal, and lateral temporal cortices (Doeller et al., 2010). Similarly, navigation-related low- and high-frequency oscillations are prevalent not only in the MTL but also in frontal (Caplan et al., 2001, 2003; Ekstrom et al., 2005; Jacobs et al., 2009; Kaplan et al., 2012), lateral temporal (Kahana et al., 1999; Caplan et al., 2001; de Araujo et al., 2002; Ekstrom et al., 2005; Jacobs et al., 2009), parietal and occipital cortex (Jacobs et al., 2009). Theta oscillations are correlated between hippocampus and neocortex as well as between different cortical regions (Ekstrom et al., 2005). Further, low-frequency phase consistency between the parahippocampal gyrus and sub-regions in frontal and parietal cortex has been implicated in retrieval of spatial information (Watrous et al., 2013b). Taken together, these results demonstrate that spatial representations are not strictly confined to the MTL and that interactions between medial temporal and distant cortical brain regions support the encoding and retrieval of spatial relations to successfully orient oneself in and navigate the surrounding environment (**Figure 4**; Ekstrom et al., 2017).

Interactions between the MTL and posterior brain regions may underlie encoding of spatial relations to build a cognitive map and to relate current perceptual input to information stored in that map. Two separate neural pathways have been described in primate vision (Goodale and Milner, 1992), connecting visual with temporal areas (ventral "what" pathway) for object recognition and visual with parietal areas (dorsal "how" or "where" pathway) for object localization, respectively. While the latter pathway has traditionally been thought to mainly project to motor areas in dorsal frontal cortex for spatially accurate movement planning, anatomical, and functional evidence suggests that egocentric spatial maps in parietal cortex also provide strong inputs to MTL structures (especially to the hippocampus and parahippocampal cortex), both directly, and via the posterior cingulate and retrosplenial cortices (RSC) (Kravitz et al., 2011). This input carries information on egocentric distances and self-motion extracted from binocular disparity (Georgieva et al., 2009) and optic flow (Siegel and Read, 1997; Wall and Smith, 2008). Accordingly, the PPC is more active during virtual navigation than during viewing of static scenes as indexed by regional cerebral blood flow measured with PET (Maguire et al., 1998) and during active navigation compared to passive traversal of a repeated corridor as indexed by fMRI BOLD (Wolbers and Buechel, 2005). Furthermore, calculation of an egocentric versus an allocentric homing vector is associated with a more parietal versus temporal source activity distribution as obtained from scalp EEG (Gramann et al., 2006).

As a relay between PPC and MTL, the RSC contains head direction cells in rodents (Chen et al., 1994) and is strongly active during viewing familiar scenes, during identification of the location associated with a known scene, and during imagined navigation, as shown with fMRI BOLD (Ino et al., 2002; Epstein et al., 2007a,b; Epstein and Higgins, 2007). Based on these findings, it has been speculated that the RSC translates between parietal egocentric and medial temporal allocentric reference frames (Burgess, 2006; Epstein, 2008). The precise neurophysiological interactions between human PPC, RSC, and MTL, however, remain to be investigated.

Interactions between the MTL and frontal brain regions, in turn, may underlie retrieval of spatial information in the course of action planning with respect to current goals. Neuroimaging has shown that the PFC is more active during successful compared with unsuccessful navigation, during active compared with guided navigation and when an unexpected detour is required (Maguire et al., 1998; for a review see Spiers and Gilbert, 2015). Further, using fMRI and a model-based learning algorithm, Simon and Daw (2011) showed that the value associated with a chosen path was predictive of prefrontal BOLD signal. These studies specifically implicate the PFC in prospective evaluation and selection of possible routes. The PFC might thereby access stored information on goal location and available paths held in the MTL. Rodent studies show that hippocampal place cells exhibit spiking outside of their place fields (i.e., non-local place representations) at decision points (Johnson and Redish, 2007). In humans, single units in both frontal and medial temporal lobe represent current goal locations (Ekstrom et al., 2003), implicating coordinated activity between MTL and PFC in planning goal-directed behavior. More direct evidence for interactions between MTL and PFC during route planning has been provided with fMRI: Brown et al. (2016) showed that univariate activation in the frontopolar cortex, as well as the strength of orbitofrontal goal representations covaries with the strength of hippocampal goal representations. Coordination between these brain regions may rely on theta synchrony: During a cue period specifying the goal of a subsequent navigation period, prefrontal theta oscillations have been shown to exhibit phase-locking (i.e., a consistent phase-difference) to the hippocampal theta rhythm (Kaplan et al., 2014).

COGNITIVE MAPPING AND COMPLEMENTARY LEARNING MECHANISMS IN HUMAN SPATIAL NAVIGATION

Although electrophysiological evidence aligns with the concept of an allocentric spatial map, behavioral work supports the flexible use of multiple cognitive representations during navigation. In the present section, we highlight some of the central ideas related to this multiple-representations perspective (a more comprehensive treatment can be found in, e.g., Burgess, 2006; Khamassi and Humphries, 2012; Ekstrom et al., 2014; Wolbers and Wiener, 2014; Filimon, 2015).

Evidence consistent with the assumption of an allocentric spatial map has been provided by Manning et al. (2014) using a computational modeling approach. Their model accounts for navigational behavior under the assumption that subjects encode and retrieve associations between landmarks and their perceived location within an allocentric spatial map of the environment. Memory for these associations, which form and decay during navigation, is used to determine an optimal path toward a target location within the environment. Their model could accurately account for subjects' spatial knowledge expressed in excess path length and a pointing task. Moreover, pointing performance was higher while subjects' view was aligned with a salient axis of the environment (i.e., north–south or east–west), as compared with when it was unaligned. This alignment effect (which is not to be confused with the alignment of movement and grid direction discussed in section "Spatially Selective Single Cells – Observed via Invasive Recordings or Inferred from Population Activity") suggests that subjects rely (at least to some degree) on an allocentric spatial reference frame centered on these axes: The mental rotation required when pointing from an unaligned view introduces additional error compared to aligned pointing. Similar alignment effects were observed in other studies (McNamara et al., 2003; Brunyé et al., 2015). McNamara et al. (2003) further showed that the orientation and origin of the allocentric coordinate system used depends on egocentric heading during exploration. Simon and Daw (2011) compared a model-based algorithm to an opposing cue-response learning strategy. Here, values associated with responses to specific landmarks are learned based on a temporal difference reinforcement learning (TD-RL) algorithm that is blind to the global spatial structure of the environment. A direct comparison between these two revealed an average Bayes factor of 17, providing strong evidence in favor of model-based planning. Finally, Chen et al. (2015) examined failures in distance estimation following rescaling of a known virtual arena. They show that errors in path integration are predicted by the way grid cells rescale their firing fields upon such changes in environmental shape in rodents (Barry et al., 2007), providing a link between grid cell activity and human navigation.

A different set of studies, in contrast, suggests that human subjects acquire local spatial knowledge, but do not integrate that knowledge into a coherent global spatial map. In one study, Warren et al. (2017), created a virtual environment that contained "invisible wormholes," which teleported subjects between predetermined locations without any perceptual cue. The only way for subjects to detect the teleportation would therefore be an awareness for the geometric inconsistencies caused by the presence or absence of teleportation on different routes to a target location. Although subjects were able to navigate successfully to two locations A and B from a third location C (two paths not containing a wormhole), when being asked to walk from A to B (a path containing a wormhole during learning), subjects showed a strong bias toward the "experienced wormhole location" of the target location. None of the subjects, however, reported any experienced inconsistencies, suggesting that no global metric map of the environment was formed. Another study examined navigation in an environment consisting of several enclosed local spaces (i.e., buildings) and came to a similar conclusion: Here, subjects often failed to navigate to a correct global location while being able to locate an object correctly in local dimensions (i.e., they navigate to the correct location in the wrong building) (Marchette et al., 2017). Finally, two studies examined object-location memory within and across spatial boundaries. They showed that pointing across spatial boundaries (rooms or neighborhoods) is slower and less accurate compared to within-boundary pointing (Han and Becker, 2014; Meilinger et al., 2016). These findings highlight the impact of spatial scale on memory and navigation (Wolbers and Wiener, 2014) and suggest that subjects' spatial knowledge contains local geometric information which is not always integrated into a coherent Euclidean map.

Navigation in large-scale complex environmental spaces may depend on multiple learning strategies. A common taxonomy of navigation distinguishes a model-based allocentric place strategy from a model-free egocentric cue-response strategy. However, one can imagine situations in which the representational reference system (egocentric cue/allocentric place) is independent of the type of learning (model-free/model-based). Specifically, allocentric place representations can cue a habitual response (Foster et al., 2000) and associations between landmarks can be learned in a model-based rather than a model-free fashion (Khamassi and Humphries, 2012), allowing for graph-like knowledge of spatial relations (Chrastil, 2013; Warren et al., 2017). In addition, learning might take place at an intermediate level of flexibility and computational expense, using what has been introduced as the successor representation (Dayan, 1993; Momennejad et al., 2017). Instead of directly caching action-values (i.e., model free) or storing a full map of all possible state transitions that is combined with a value function during decision making (i.e., model based), agents might cache predictions about future states (i.e., how often each successor state will be visited in the future), which they can similarly combine with a value function during decision making. Caching the number of expected future visits is less expensive than storing a complete map of the world (i.e., model-based), but more flexible than model-free learning when changes to the reward structure (e.g., a change in goal) occur, since value function and spatial knowledge are stored separately. The successor representation has recently been used to explain the firing of place responsive cells (Stachenfeld et al., 2017), but has not yet been directly linked to human navigational behavior. Formal models that account for such alternative learning and decision mechanisms might help to develop a better understanding of navigation in large environmental spaces and, ultimately, its neural underpinnings.

FUNCTIONAL OVERLAP IN THE MTL: A COMMON MAP FOR PHYSICAL AND CONCEPTUAL SPACE?

The MTL is not only the major focus of electrophysiological studies investigating the neural signature of spatial memory, but, ever since the hallmark findings on patient H.M. (Scoville and Milner, 1957; Milner et al., 1968), it has also emerged in human neuroimaging as a central brain region for declarative memory more generally (Mayes et al., 2007; Battaglia et al., 2011). A study combining spatial navigation with episodic free recall has shown that place-responsive cells in the human MTL reinstate their activity during recall of items that were encoded in the cell's place field (**Figure 5A**; Miller et al., 2013), suggesting that place cells do not only code instantaneous spatial position but also represent a spatial code for remembering past episodes.

Besides coding instantaneous as well as remembered spatial locations, hippocampal and entorhinal cells have been shown to code a variety of other features. In rodents, hippocampal and entorhinal cells have been associated with the coding of elapsed time (Pastalkova et al., 2008; MacDonald et al., 2011; Kraus et al., 2013; for a review see Eichenbaum, 2014), behavior (i.e., approach), stimulus quality (i.e., odor identity), and task characteristics (i.e., match vs. non-match trials) (Wood et al., 1999). In humans, cells in the MTL are responsive to view of or search for a specific landmark irrespective of the position of the observer (**Figure 5B**; Ekstrom et al., 2003). Moreover, a subset of place-responsive cells has been shown to remap (i.e., change their place field) upon a change in goal location (Ekstrom et al., 2003), suggesting that the same cells are responsive to spatial and non-spatial features during navigation. Outside of navigation, human MTL cells are sensitive to the identity of individuals, landmarks or objects irrespective of the type of presentation (i.e., pencil sketches, photographs, letter strings, etc.) (Quiroga et al., 2005). Using fMRI, Constantinescu et al. (2016) further observed grid-like activity coding imagined trajectories in conceptual space (**Figure 5C**). Subjects first learned a conceptual two-dimensional space of visual bird features (i.e., neck and leg length) and subsequently viewed and imagined trajectories in this space (i.e., birds morphing along a given neck:leg length ratio). Grid-like modulation of BOLD was observed in entorhinal cortex, posterior cingulate and retrosplenial cortices, PPC, temporo-parietal junction, and PFC. Collectively, these studies implicate

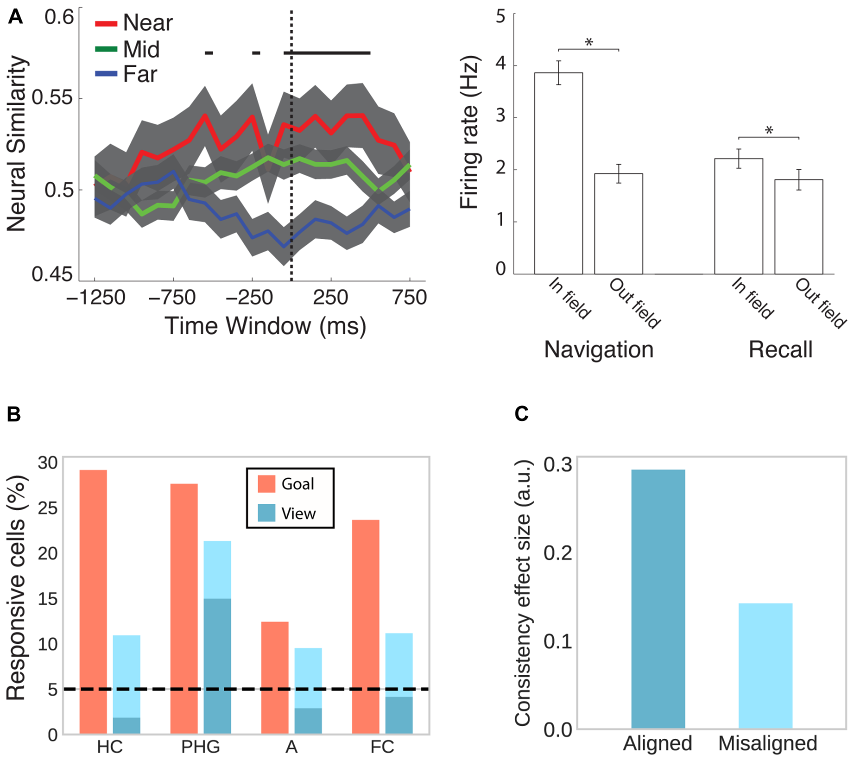

FIGURE 5 | Cells in the human MTL code non-spatial features as well as spatial features outside their respective spatial context. **(A)** While viewing a black screen, the activity of place cells is reinstated when subjects recall words that were encoded inside the cells' place field in a virtual city environment. This effect is evident at the population (*left*) and individual cell (*right*) level. Adapted with permission (Miller et al., 2013) from Science. **(B)** Goal- and view- responsive cells in the hippocampus (HC), parahippocampal gyrus (PHG), amygdala (A), and frontal cortex (FC). *Dark turquoise bars* indicate responsiveness to stores and *light turquoise bars* indicate responsiveness to both stores and passengers. Adapted with permission (Ekstrom et al., 2003) from Springer Nature. **(C)** Evidence from fMRI suggests that cells in the entorhinal cortex show grid-like activity that codes position in a conceptual space representing visual features of birds (neck length and leg length). BOLD contrast was higher for viewing or imagining morphing trajectories that were aligned with the common grid orientation as compared with misaligned trajectories. Data from Constantinescu et al. (2016).

the spatial memory network described above more broadly in coding associations between different kinds of features in the service of perception, memory, and prospective planning (Eichenbaum et al., 1999; Buzsáki, 2005; Buzsáki and Moser, 2013; Eichenbaum and Cohen, 2014).

One way to approach this high degree of functional overlap in the MTL is to identify functional subdivisions and link them to the encoding and retrieval of different classes of stimulus features. In the episodic memory literature, a popular model of MTL function assigns item processing to the perirhinal and lateral entorhinal cortex, (spatial) context processing to the parahippocampal and medial entorhinal cortex, and item-in-context processing to the hippocampus (Eichenbaum et al., 2012; see Buffalo et al., 2006 and Wixted and Squire, 2011 for evidence that perirhinal cortex also processes spatial information). This model has received support from studies on functional connectivity, which have embedded these structures into a broader anterior temporal (item) and posterior medial (context) network (Ranganath and Ritchey, 2012; Ritchey et al., 2015). The distinction between item processing in lateral and spatial context processing in medial entorhinal cortex in this model is in line with the finding that grid cells in rats are localized to the medial (rather than lateral) entorhinal cortex (Hafting et al., 2005; Moser et al., 2008). Studies on grid cells in humans, however, have so far been using a spatial resolution too coarse to identify such functional subdivisions. Ultra-high field MRI at 7T has recently been used to successfully differentiate an antero-lateral and a posterior-medial sub-region of the human entorhinal cortex based on resting state connectivity, as well as differential processing of objects and scenes (Maass et al., 2015; Schröder et al., 2015; for a review see Schultz et al., 2015), suggesting that future studies should in principle be able to study differential engagement of these entorhinal regions in coding spatial vs. non-spatial features.

An alternative (and complementary) approach is to develop a unifying framework that supports spatial and non-spatial memory functions with the same mechanisms. Buzsáki (2005) suggested that associations between spatial and non-spatial information are established through theta oscillations in the hippocampus, giving rise to episodic memory, unidirectional place cells, semantic memories, and omnidirectional place cells. Specifically, precession of hippocampal cells to the theta rhythm (i.e., progressively earlier spiking as the place field is traversed) results in multiple cells firing within a single

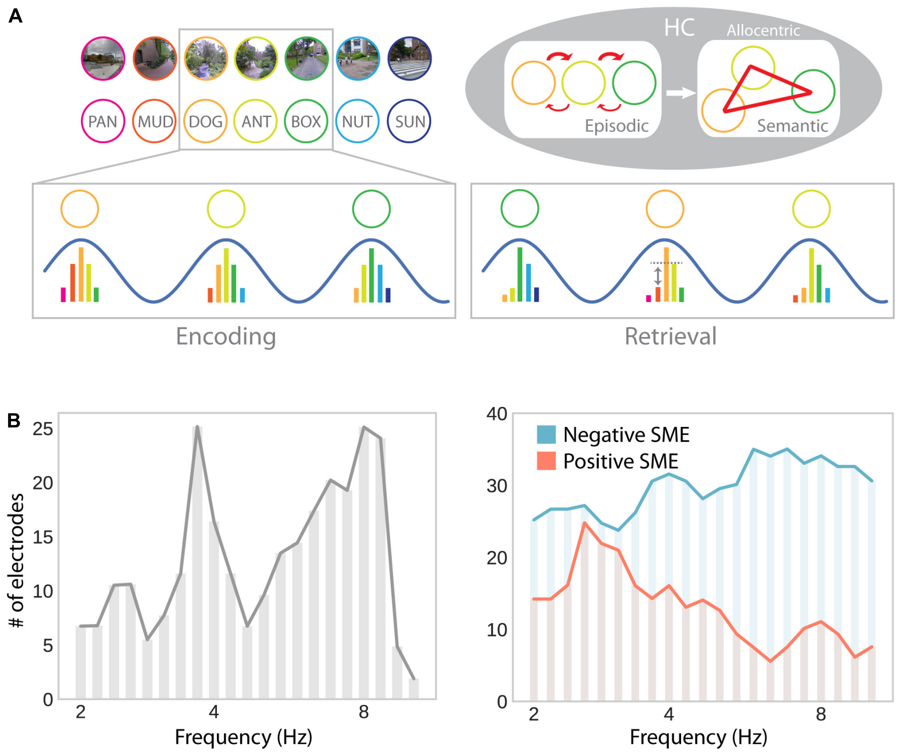

FIGURE 6 | Theta oscillations in episodic memory formation and retrieval. **(A)** Model suggesting a common role for hippocampal theta oscillations and phase precession in memory for spatial and non-spatial sequences (e.g., during navigation or a list-learning task; Buzsáki, 2005). Successive firing of hippocampal cells within a theta cycle establishes temporal associations between both place and item representations through synaptic plasticity, which favors associations in the forward direction. Multiple encounters of the same items/places in different serial order establishes semantic/allocentric representations of conceptual and physical space. In part adapted with permission (Buzsáki, 2005) from Wiley Periodicals. **(B)** Hippocampal electrodes showing theta oscillations around 3–4 and 8–9 Hz, analogously to theta effects during navigation (see **Figure 3B**; *left*), as well as positive and negative subsequent memory effects (SME; *right*). Positive SMEs predominate around 3–4 Hz. Adapted with permission (Lega et al., 2012) from Wiley Periodicals.

theta cycle. These cells represent successively visited places or successively presented items (e.g., in a non-spatial recall task; **Figure 6A**). Consequently, the synaptic connections between these cells get strengthened by spike timing-dependent plasticity, which favors associations in the forward direction. This time compression mechanism explains unidirectional place cells in one-dimensional navigation: As connections are specifically strengthened in the forward direction, traversal in the same direction reinstates firing of the same sequence of cells, whereas traversal in the opposite direction does not. Similarly, it explains two hallmark findings of episodic free recall: Temporal contiguity (i.e., stronger associations between items that were encoded in temporal proximity) and temporal asymmetry (i.e., stronger associations in the forward than the backward direction) (Kahana, 1996). Time-independent associations, which give rise to omnidirectional place cells and semantic memory, in this framework, are formed from multiple overlapping traversals of a given location, as well as multiple overlapping encounters of a given item (Buzsáki, 2005).

While this idea elegantly unites place cells, theta oscillations, spatial, episodic and semantic memory, it has yet to be verified experimentally. If theta oscillations provide a time compression mechanism that can act independently of spatial navigation and establishes temporal associations between successively experienced items, evidence consistent with this idea should be observable in electrophysiological studies of human recall and recognition. Although a large number of studies highlight a role for low-frequency oscillations in episodic memory encoding, they provide mixed results of increases (Guderian et al., 2009; Hanslmayr et al., 2011; Lega et al., 2012; Lin et al., 2017) and decreases (Sederberg et al., 2007; Lega et al., 2012; Burke et al., 2013; Lin et al., 2017; Solomon et al., 2018) associated with successful encoding in the MTL, as well as in cortical brain regions or at the scalp (increases: Klimesch et al., 1996; Osipova et al., 2006; Sederberg et al., 2007; Khader et al., 2010; Burke et al., 2013; decreases: Sederberg et al., 2007; Guderian et al., 2009; Burke et al., 2013). It is noteworthy that several of these studies simultaneously report both increases and decreases which are separated in time and/or precise localization (Sederberg et al., 2007; Guderian et al., 2009; Lega et al., 2012; Burke et al., 2013, 2014). Similarly, when looking at theta phase synchrony, rather than theta power, studies have observed increases (Burke et al., 2013; Solomon et al., 2017) as well as decreases (Burke et al., 2013) in brain-wide theta synchrony associated with successful memory formation.

The results reported by Lega et al. (2012) seem to be particularly interesting with respect to navigation-related theta effects: They show two distinct peaks in low (∼3–4 Hz) and high (∼8 Hz) frequency theta oscillations. Furthermore, subsets of hippocampal depth electrodes show increases and decreases in theta oscillations as a function of subsequent memory. The co-occurrence of these effects explains why both increases and decreases may be observed in average theta power depending on sampling and measurement procedures. Furthermore, positive and negative subsequent memory effects seem to be differentially linked to slow (∼3–4 Hz) and fast (∼8 Hz) theta oscillations, respectively (**Figure 6B**). These results thereby partially resolve the discrepancies between the navigation and episodic memory literature in suggesting that a localized slow hippocampal delta–theta rhythm is involved in successful encoding and navigation (see section "Oscillatory Activity"), whereas a faster theta rhythm is detrimental for episodic encoding (see Ekstrom and Watrous, 2014 and Watrous et al., 2013b for an alternative spectral fingerprinting account of slow and fast theta in spatial and episodic memory). Based on the idea that theta oscillations specifically facilitate inter-item or item-context associations (Buzsáki, 2005), one could further argue that the more informative contrast in this regard should involve some form of successful context encoding (rather than just successful item encoding). However, few studies report such a contrast and, again, provide mixed results: While Staudigl and Hanslmayr (2013) observe a theta (∼4 Hz) increase during successful item-in-context encoding, Long and Kahana (2017) observe no significant difference in theta power for items subsequently retrieved with or without temporal context information. Overall, one can say that the evidence for theta power increases associated with successful episodic encoding are far less robust and effects are less distributed across the brain, compared to findings obtained during navigation.

We have outlined above that theta oscillations play a role not only in encoding but also retrieval of spatial information from memory and imagined navigation in a familiar environment. Theta effects during episodic retrieval seem generally more coherent than encoding effects. Theta increases have been shown to precede spontaneous recall (Burke et al., 2014) and to differentiate successful recollection of contextual information from item recognition (Guderian and Düzel, 2005; Herweg et al., 2016). While MEG effects were source localized to the MTL (Guderian and Düzel, 2005), intracranial effects were localized mainly to the anterior temporal cortex (Burke et al., 2014). It remains an open question whether this difference is due to imprecise source localization or differences in the cognitive demands posed by the retrieval tasks (i.e., free recall vs. source memory judgment). Evidence for the role of hippocampal theta oscillations during memory retrieval has also been provided by studies investigating theta mediated synchrony. One study linked theta power increases in scalp EEG to hippocampal connectivity in BOLD data (Herweg et al., 2016). Specifically, a psychophysiological interaction analysis revealed connectivity between hippocampus and other brain regions in the core memory network to be positively associated with theta power. Another study observed increased brain-wide theta phase synchronization (involving the hippocampus) as measured with iEEG during successful episodic recall (Solomon et al., 2017). These findings highlight the role of theta oscillation during retrieval of non-spatial information, and thereby parallel findings on spatial memory.

A unifying account of MTL function should account for the role of theta during both encoding and retrieval of spatial and non-spatial memories. One possibility is that theta oscillations during retrieval organize spike timing (as they do during encoding) to represent temporal context and remembered or imagined serial order information (**Figure 6A**). Given the wealth of evidence demonstrating the importance of retrieval for learning (Karpicke and Roediger, 2008; Roediger and Karpicke, 2006a,b), it is likely that theta's role in spike-timing dependent plasticity ought to operate during retrieval as well as encoding. Specifically, theta oscillations during retrieval might facilitate re-encoding of temporal associations between retrieved/imagined items/places. These assumptions can be tested by linking theta oscillations during retrieval to immediate and future associative memory strength.

CONCLUDING REMARKS

We have reviewed converging evidence that the human MTL is equipped with a population of place and grid cells that provides an allocentric spatial map of the environment, similar to that observed in the rodent brain (see section "Spatially Selective Single Cells – Observed via Invasive Recordings or Inferred From Population Activity"). Furthermore, spatial coding in the human MTL seems to be supported by oscillatory activity in the theta frequency range (although this may be lower in humans than rodents; see section "Oscillatory Activity"). Recent findings strongly suggest that theta oscillations are not only involved in sensorimotor integration, as has previously been argued, but instead directly relate to the encoding and retrieval of spatial information. Their relation to spiking activity of place-responsive cells remains less clear and, hence, a subject for future study.

Despite the evidence for an allocentric spatial map in the human MTL, we have pointed out that the MTL does not work in isolation (see section "Spatial Representations in a Brain-Wide Network"). Connections with parietal brain regions provide input to the MTL that carries egocentric spatial information and prefrontal brain regions make use of the allocentric spatial map in the process of prospective thinking and action selection. Moreover, an allocentric spatial map alone does not fully account for the affordances of human spatial navigation in environmental spaces and, presumably, real-world settings (see section "Cognitive Mapping and Complementary Learning Mechanisms in Human Spatial Navigation"). The interactions of different spatial learning mechanisms and navigation strategies are currently not well understood, both at the behavioral and neurophysiological level. Clearer taxonomies along with stronger consideration of the cognitive demands posed by different environments will help to develop and refine formal models of navigational behavior that can be linked to neurophysiological phenomena.

Finally, a parallel line of research has implicated the MTL in declarative memory formation and retrieval (see section "Functional Overlap in the MTL: A Common Map for Physical and Conceptual Space?"). It remains to be determined to what degree this functional overlap can be either resolved by identifying sub-regions and networks in the MTL that preferentially process spatial vs. non-spatial information or explained with a common framework that integrates spatial and declarative memory. We believe that a critical step in developing and refining such a unified theory of MTL function will be to specifically link task-related phenomena at multiple temporal and spatial scales. Understanding how place- (and concept-) responsive single cell activity relates to ongoing theta oscillations during both the encoding and retrieval of spatial and non-spatial associations will significantly contribute to a more mechanistic understanding of memory processes in the MTL.

OUTSTANDING QUESTIONS

(1) What is the relation between spiking activity of place-responsive cells and the hippocampal theta rhythm in humans, and how is information coded in spiking-phase relations? Although Jacobs et al. (2007) found general evidence for phase-locking of single neurons to theta oscillations, this relation has not been specifically linked to spatially responsive neurons in the MTL. Furthermore, rodent work demonstrates that place (O'Keefe and Recce, 1993) and grid (Hafting et al., 2008) cells show phase precession to the hippocampal theta rhythm while rats traverse a place field. It remains unknown whether human place-responsive cells demonstrate similar spike-phase relations.

(2) Whereas studies of rodent spatial coding often use small-scale spaces, studies in humans often use large-scale virtual environments with constrained paths (Wolbers and Wiener, 2014). How do these different paradigms affect coding of space and navigational strategies? Can a closer examination of navigational paradigms reconcile some of the inconsistencies between electrophysiological findings supporting and behavioral findings contradicting a Euclidean metric map (e.g., Meilinger et al., 2016; Marchette et al., 2017; Warren et al., 2017)?

(3) Both rodents and humans preferentially navigate on flat surfaces and study of their spatial navigation system has consequently focused on two dimensional spatial representations. Place cells in the bat hippocampus, in turn, have been shown to exhibit isometric three dimensional place fields that are tuned to the affordances of volumetric navigation (Yartsev and Ulanovsky, 2013; Finkelstein et al., 2016). How do humans code spatial locations in multilayered navigation, on elevated surfaces, or during volumetric navigation (e.g., while diving or in an aircraft)? Preliminary evidence suggests speed but not accuracy costs associated with spatial memory in the vertical compared to the horizontal dimension of a 3D environment (Kim et al., 2017). Moreover, partially overlapping brain regions seem to encode vertical and horizontal space (Kim et al., 2017; Kim and Maguire, 2018). It remains to be shown, however, how the network of human place and grid cells codes 3D space. If the spatial representation system is not only used to code physical, but also conceptual spaces, how does the dimensionality of preferred navigation affect the representation of conceptual space (which is not always two dimensional)?

(4) Some studies suggest that the navigation-related theta rhythm is slower in humans than in rodents (Jacobs, 2014) or that oscillations occur in separate low- and high- frequency theta bands (Bush et al., 2017). Studies in the episodic memory domain provide mixed evidence on the direction of theta effects during successful encoding. Results reported by Lega et al. (2012) suggest that oscillations in the low-theta band facilitate encoding, while oscillations in the high-theta band are detrimental for performance, raising a potential way to reconcile the findings. Are there indeed two separate theta rhythms? What is their differential role in navigation and episodic memory?

(5) It has been shown that spiking activity of place cells is reinstated when subjects remember an item that was encoded within a cell's place field (Miller et al., 2013), implicating place cells in the retrieval of item-in-spatial-context information during episodic recall. Do grid cells show similar reinstatement effects during episodic memory retrieval or is their role more specifically tied to spatial navigation and path integration?

(6) Buzsáki (2005) has proposed an elegant theory explaining the emergence of spatial and semantic maps from episodic experience. Is there direct evidence in favor of the idea that theta oscillations provide a time compression mechanism that establishes associations between successively experienced items in an episodic memory task in humans?

AUTHOR CONTRIBUTIONS

NH and MK performed the literature search and discussed the results. NH drafted the manuscript. NH and MK revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work.

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Dynamic Neural Network Reconfiguration During the Generation and Reinstatement of Mnemonic Representations

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Mnemonic representations allow humans to re-experience the past or simulate future scenarios by integrating episodic features from memory. Theoretical models posit that mnemonic representations require dynamic processing between neural indexes in the hippocampus and areas of the cortex providing specialized information processing. However, it remains unknown whether global and local network topology varies as information is encoded into a mnemonic representation and subsequently reinstated. Here, we investigated the dynamic nature of memory networks while a representation of a virtual city is generated and reinstated during mental simulations. We find that the brain reconfigures from a state of heightened integration when encoding demands are highest, to a state of localized processing once representations are formed. This reconfiguration is associated with changes in hippocampal centrality at the intra- and inter-module level, decreasing its role as a connector hub between modules and within a hippocampal neighborhood as encoding demands lessen. During mental simulations, we found increased levels of hippocampal centrality within its local neighborhood coupled with decreased functional interactions between other regions of the neighborhood during highly vivid simulations, suggesting that information flow vis-à-vis the hippocampus is critical for high fidelity recapitulation of mnemonic representations.

Keywords: fMRI, graph theory, hippocampus, navigation, orientation, virtual environment

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INTRODUCTION

One of the most striking features of the human mind is our ability to re-experience the past in vivid detail. Memories pervade daily life, allowing us to develop a sense of self, find new and familiar locations, and identify more effective strategies for interacting with the world. The ability to encode and reinstate complex mnemonic representations by binding features from previous experiences is thought to be the primary function of an episodic memory system in humans (Tulving, 2002). These representations are hypothesized to be conjunctive in nature, integrating sensory features from the environment – such as people, places, and objects – into holistic representations that can be used to guide behavior into the future (Davachi, 2006; Byrne et al., 2007;

Chersi and Burgess, 2015). Theoretical and computational models suggest that these mnemonic representations are formed by integrating information processed throughout the neocortex in convergence zones (Marr, 1971; Damasio, 1989; Nadel and Moscovitch, 1997; Burgess, 2008; Meyer and Damasio, 2009), most notably the hippocampus (HC), where processes such as pattern completion allow representations to then be reinstated using a partial set of input features (Marr, 1971; Norman and O'Reilly, 2003; Rugg and Vilberg, 2013). Recent research has provided support for these models, showing that inter-regional communication dynamics assist to concentrate information flow to the HC (Mišić et al., 2014), and that the HC acts as a primary convergence zone during associative memory tasks (Gordon A.M. et al., 2014; Backus et al., 2016), allowing different types of information processed in the neocortex to be reinstated and integrated into a holistic representation (Staresina et al., 2013; Horner et al., 2015).

Although there is preliminary empirical evidence for hippocampal-based information integration during memory retrieval (Gordon A.M. et al., 2014; Iaria et al., 2014; Robin et al., 2014; Schedlbauer et al., 2014; Horner et al., 2015; Backus et al., 2016), key questions remain about how mnemonic representations are encoded across networks of brain regions. A critical but untested component of prominent theoretical models is that when encoding occurs, there is a heightened demand to integrate information processed in sensory and first-order association cortices into neural patterns within memory structures that form the basis of a mnemonic representation (Marr, 1971; Damasio, 1989; Squire and Zola-Morgan, 1991; McClelland et al., 1995; Nadel and Moscovitch, 1997; Meyer and Damasio, 2009). Recent work using functional magnetic resonance imaging (fMRI) analyses has shown that encoding associations between sensory features depends on neural activity in areas of the cortex specialized to the specific feature, which are encoded by neural indexes in the hippocampus (Horner et al., 2015), and that hippocampal–cortical functional interactions increase when stimuli features need to be combined into a single associative representation during retrieval (Zeithamova et al., 2012; Staresina et al., 2013; Gordon A.M. et al., 2014). This suggests that memory structures such as the hippocampus interact dynamically with other regions across the cortex during the initial encoding and subsequent reinstatement of a mnemonic representation. Surprisingly though, there has yet to be a systematic evaluation of global and local network topology during encoding using complex network measures such as graph theory. Graph theory allows for the quantification of more nuanced aspects of network processes (Bassett et al., 2012), specifically relating to communication dynamics and the integration of information across components of a network (Sporns et al., 2007; Bullmore and Sporns, 2009) that are of critical importance to understanding memory function in humans (Chrastil, 2012; Ekstrom et al., 2014). The central aim of this study is to provide such an investigation by quantifying putative changes in network topology and the dynamic role of the hippocampus within brain networks.

An important characteristic of brain network topology is modularity (Bertolero et al., 2015). Modular systems are sub-networks or communities defined by dense interconnections between intra-module components, with sparse or weak inter-module connections (Newman, 2006). Of importance here, the dynamic formation and interaction of modules and their components defined using functional interactions between brain regions has been proposed to provide a neural correlate for adaptability (i.e., learning) in the brain (Ghosh et al., 2008; Meunier et al., 2010; Werner, 2010), putatively through a reduced cost to rapidly change network configurations in response to environmental demands (Kirschner and Gerhart, 1998; Kashtan and Alon, 2005). Dynamic shifts in modularity have been associated with motor learning tasks (Bassett et al., 2011) and working memory paradigms such as the n-back task (Stanley et al., 2014; Cohen and D'Esposito, 2016). In the context of memory function, this view suggests that changes to the modularity of networks may allow the brain to regulate the degree to which sensory information is integrated into a neural index during encoding by altering the degree to which network modules communicate with one another. In the present study, we use this perspective on network modularity to investigate whether the dynamic reconfiguration of modular systems across the brain is associated with encoding and reinstating mnemonic representations based on the degree to which environmental features needs to be integrated over time. This tests the long held, but sparsely tested, perspective that information is integrated across sensory and associative cortices during representation encoding, and that this integration is mediated in part by the hippocampus (Nadel et al., 2000).

Drawing from theoretical models and empirical work, it is possible to formulate three key predictions about the basis of network reconfiguration and adaptability as mnemonic representations are encoded. First, when encoding demands are highest, the topology of brain networks should be organized in a manner that increases the capacity to integrate information processed across distributed systems in the brain. We term this the *global integration* hypothesis. Second, once representations are formed, there should be a reconfiguration of network topology from a state of global network integration to one of localized processing, as the need to integrate stimuli features lessens and the demand to reinstate and maintain neural representations within memory systems increases. We term this the *state transition* hypothesis. Third, critical convergence zones such as the HC should display flexibility in how they interact with global and local brain networks, such that when encoding demands are the highest, they act to integrate information across different systems in the brain, but change to localized processing as environmental feature integration demands decrease. We term this the *node flexibility* hypothesis.

Integrative processes additionally appear to play a role in the subsequent reinstatement and use of multi-featural representations (Gordon A.M. et al., 2014; Iaria et al., 2014; Robin et al., 2014; Schedlbauer et al., 2014; Horner et al., 2015; Backus et al., 2016). Prospection, the cognitive ability to think about, predict, and simulate possible future events is theorized to rely on a similar neurocognitive system dedicated to dynamically encoding experiences, extracting features from those memories, and actively combining those features into representations, or mental 'scenes,' that are used to optimize behavior (Buckner and Carroll, 2007; Schacter and Addis, 2007; Hassabis and Maguire, 2009; Moulton and Kosslyn, 2009; Schacter et al., 2012; Szpunar et al., 2013). As with the encoding of mnemonic representations, the HC is predicted to be critical to prospection, using a neural index to reinstate mnemonic representations through interactions with sensory and associative regions across the brain (Janzen and van Turennout, 2004; Horner et al., 2015). In humans, recent work has shown that goal-specific trajectories and intervening locations can be decoded during prospection using patterns of hippocampal activity (Brown et al., 2016), further supporting the role of the HC in coordinating the neural codes underlying the spatial context for prospective mental simulations. Importantly, however, prospective representations in humans appears to involve additional brain regions, including the parahippocampal, perirhinal, and retrosplenial cortices (Brown et al., 2016), suggesting that integrative and distributed information processes are also involved.

Although it appears that the HC dynamically interacts with other regions across the brain during prospection (Hassabis and Maguire, 2009; Schacter et al., 2012), fundamental questions remain about how this occurs and whether these interactions vary based on how featural information encoded in memory is integrated into a mnemonic representation subserving prospection. Variability in the fidelity of prospective mental simulations has been proposed as a measure of feature integration (Arnold et al., 2016), providing a quantifiable metric of how task-oriented mnemonic representations are generated through multi-feature reinstatement. Critically, this suggests that variance in the fidelity of prospective mental simulations may be associated with the degree of functional interactions within the hippocampal–cortical networks supporting prospection, rather than relying on neural processes occurring in the hippocampus alone, and may provide a window into how dynamic network processes support memory function.

As with encoding, it is possible to formulate specific research questions about how distributed and dynamic network processes provide a mechanism for prospection. First, we asked which regions of the brain coordinated information processing during mental simulations with the HC. Due to the putative role of the HC in coordinating the reinstatement of information processing in sensory and associative regions (Nadel et al., 2000; Horner et al., 2015; Backus et al., 2016), we hypothesized that simulations with high visual and spatial fidelity would be associated with increased functional connectivity between the HC and areas of the visual cortex, allowing for reinstatement of patterns of activity coding visual and spatial features of the route being simulated. We term this the *feature reinstatement* hypothesis. Second, we asked whether variance in the vividness and spatial coherence of mental simulations is associated with differences in hippocampal network topology. The capacity for both whole brain networks and the HC to efficiently coordinate information flow has been shown to facilitate the reinstatement of spatial contexts during retrieval tasks (Arnold et al., 2014b; Schedlbauer et al., 2014). This suggests that feature reinstatement and integration during prospection may also benefit from network topologies with increased communication efficiency, as features and their associative structure are recapitulated across the brain and integrated into a task-oriented mnemonic representation used to simulate behavior. Based on this perspective, we hypothesized that high simulation fidelity would require more widespread interactions between the HC and neocortex, and therefore demonstrate increases in graph theoretical measures quantifying the communication capacity of hippocampal networks. We term this the *feature integration* hypothesis.

To test the three outlined hypotheses on encoding mnemonic representations and the two on reinstating representations during prospection, we constructed a large-scale virtual city and calculated bivariate and graph theoretical measures using fMRI data acquired while people encoded the spatial layout of landmarks in the city and then conducted mental simulations of the different routes between landmarks. Spatial navigation is a model system for understanding how mnemonic representations are encoded and reinstated to guide behavior and inform decision making processes (Chersi and Burgess, 2015; Arnold et al., 2016), with past research demonstrating that the topology of resting-state (Arnold et al., 2014b) and task-active networks facilitate the accurate reinstatement of spatial representations (Watrous et al., 2013; Arnold et al., 2014a; Schedlbauer et al., 2014). **Figure 1** provides an overview of the task. The analyses herein were conducted on the navigation blocks from the encoding phase, and the simulation blocks from the simulation phase. For the *global integration* hypothesis during representation encoding, we calculated the modularity index Q, global efficiency, and global flow of distributed networks, and compared navigation blocks from the encoding phase where participants were unsure about landmark locations to trials in which they were highly confident of knowing the landmark location. Similarly, for the *node flexibility* hypothesis, we calculated and compared the betweenness centrality, participation, and flow coefficient for the HC between high and low confidence navigation blocks in the encoding phase. These graph theoretical metrics assess the centrality of the HC at the global, inter-module, and local network level, respectively. Third, for the *state transition* hypothesis, we calculated the local efficiency of the hippocampal networks during navigation blocks of the encoding phase to identify whether localized network processing increased as the need to integrate environmental information decreased. For prospection, we tested the *feature reinstatement* hypothesis on simulation blocks from the simulation phase using general psychophysiological (gPPI) models to identify areas of the brain showing increased functional connectivity with the HC during prospection based on high fidelity representations. For the *feature integration* hypothesis, we again used the node-based graph theoretical measures of betweenness centrality, flow coefficient, and local efficiency using hippocampal nodes to identify potential differences in communication efficiency relating to variance in representation fidelity observed during the simulation blocks of the simulation phase.

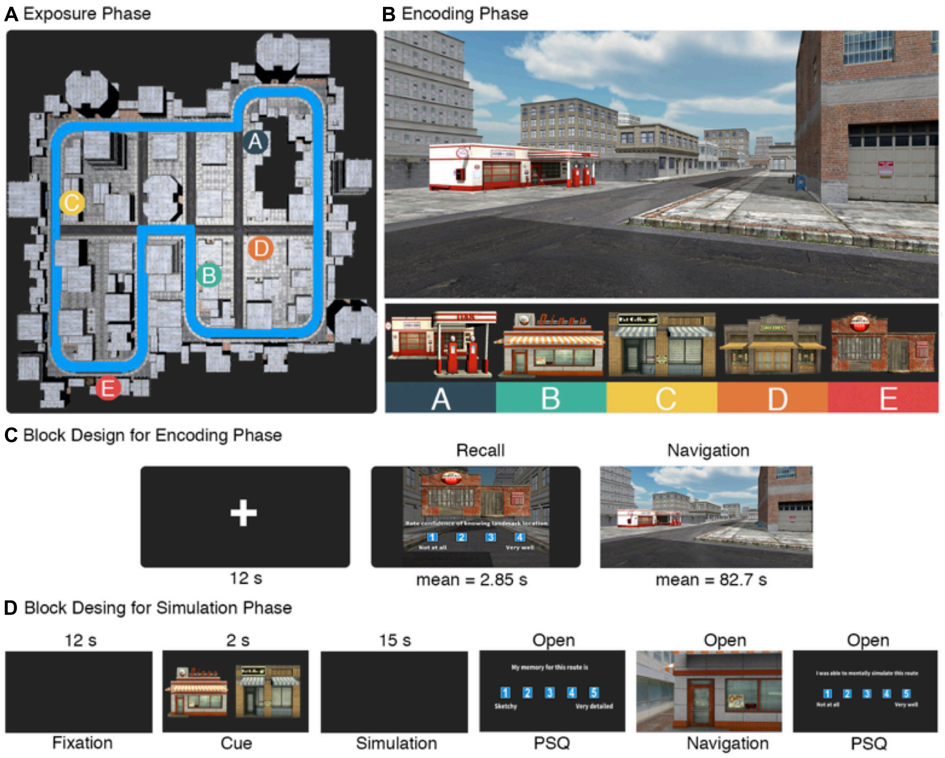

FIGURE 1 | Task design. **(A)** Top-down view of the city. During the exposure phase, participants viewed a video of passive first-person movement along the city perimeter outlined in blue. Also displayed are the locations of the five target landmarks. **(B)** During the encoding phase, participants navigated between the five target landmarks. The city was composed of buildings using variations of three architectural styles, while the target landmarks were selected to be visually salient. **(C)** Block sequence order during scanning of the encoding phase. Each trial began with a fixation cross, followed by a recall block in which one of the target landmarks was displayed and participants rated on a scale of 1–4 their confidence in knowing its location. A navigation block followed, where participants were instructed to navigate to the landmark as quick as possible. **(D)** Timing information for the simulation phase. After the initial 12 s fixation period, participants were cued with a starting landmark (left) and a target landmark (right). They were given 15 s to simulate movement between the two landmarks in as much detail as possible. Completion of the PS-Q was open ended as was the subsequent navigation period between the two cued landmarks and the two remaining questions of the PS-Q.

MATERIALS AND METHODS

Participants

Fourteen right-handed undergraduates (nine female; mean age = 21.64, *SD* = 2.56) recruited through the University of Calgary research participation pool participated in the study and the study was approved by the research ethics board at the university (CHERB 22848). Sample size was similar to previous studies on the function of memory networks (Ekstrom and Bookheimer, 2007; Libby et al., 2012; Watrous et al., 2013; Arnold et al., 2014b). Participants were pre-screened to exclude anyone who reported previously experiencing nausea while playing a videogame. All participants provided informed consent prior to scanning, received $50 reimbursement whether they completed the experiment or not, and were debriefed after the experiment.

Environment Design

The virtual city was designed using Unity3D (version 4.6[1]). The city was composed of an interconnecting series of roads lined with buildings (**Figure 1A**). The configuration of the roads was constructed to be nearly symmetric across the city to minimize the potential to derive location information based on global geometrical cues. The city buildings consisted of target landmarks and non-target buildings. The non-target buildings were variations of three architectural styles that were repeated throughout the city and selected to be visually similar in order to reduce their use as spatial cues during navigation trials. Five target landmarks were selected to be visually unique relative to the rest of the city (**Figure 1B**). The location of the target landmarks was selected by applying a 10×10 grid over the city layout and randomly selecting grid locations to place the landmarks. Numerous shortcuts were created by placing walkable paths between the buildings and a series of back alleyways. We also included two blockades on the main roads in order to ensure that the shortest path between any two target landmarks were only available by taking shortcuts. Movement speed was capped at 6 virtual m/s, which approximates to a 4.47× increase over an average real world walking speed of 1.34 m/s given the relative scale of the virtual city. Post-experiment interviews suggested that participants primarily used relative orientation of target landmarks to one another to guide navigation. Aside from the exposure phase (see below), participants viewed the city by

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[1] https://unity3d.com

projecting it on a mirror in the scanner and moved using four buttons coded to forward and backward movement, and left and right rotation.

Task Design

The task was divided into three phases: an exposure, encoding, and simulation phase. Prior to entering the scanner, participants were given an overview of the task and completed the exposure phase. The overview consisted of giving participants instructions on the mechanics of the task in each phase and provided time for them to ask the experimenter any questions. The exposure phase consisted of watching a video of first person movement along the perimeter of the city (**Figure 1A**). The video stopped for 5 s at each of the target landmarks and the experimenter pointed to the landmark on the screen and verbally confirmed that the participant had seen it before proceeding. The video stopped at the same point it had started, which was a randomly selected point along the perimeter and was consistent across participants. The exposure phase was designed to give the participants a sense of scale of the city and a baseline knowledge of the target landmark identities and locations.

Once inside the scanner, participants completed the encoding phase. This phase consisted of a sequence of fixation, reinstatement, and navigation blocks (**Figure 1C**). It began by placing participants at a random starting point in the city (randomized once and held consistent across participants), showing them an image of one of the target landmarks, and asking them to rate on a scale of 1–4 their confidence in knowing the location of the landmark (1: not at all, 4: very well). This is termed the reinstatement block. Afterward, the participants were instructed to find the cued landmark as quick as possible. This is termed the navigation block. Once located, the participants walked into the front of the building which prompted the next rest/reinstatement/navigation block sequence. We also included a helper arrow that was initiated once participants had taken more than 90 s to locate the landmark. The helper arrow always pointed in the cardinal direction of the cued landmark, requiring the participants to still make decisions on how best to navigate to it. The helper arrow was included based on results from an initial pilot study that showed trials where participants took longer than 90 s frequently resulted in getting lost. Optimal path time between each landmark pair was calculated by taking the quickest possible path between landmarks using available shortcuts (mean path time for optimal routes = 24.85 s, *SD* = 7.15; mean number of turns = 5.9, *SD* = 2.33). As with the starting point, the order of starting-goal landmark pairs was randomized once and held consistent across participants. The encoding phase lasted for 23 min and had an upper limit of 21 possible trials consisting of all pairwise combinations of landmarks in both directions, as well as the initial starting trial. At the end of the 23 min, scanning stopped irrespective if they had completed all the trials or not.

After the encoding phase, participants completed the simulation phase (**Figure 1D**). All participants conducted two practice trials prior to entering the scanner to ensure they properly understood the task instructions and provide them with the opportunity to ask the experimenter questions. Participants were instructed that the simulation portion would begin with the word ‘Simulation’ on the center of the computer screen. Afterward, they would be shown two images of the five target landmarks – one on the left and one on the right. Once the landmarks disappeared from the screen, they were instructed to mentally simulate in as much detail as possible moving through the city from the landmark on the left to the one on the right. The experimenter emphasized that it was important to mentally immerse themselves in the city and to take as much time as they needed to properly navigate the route. Participants were instructed to mentally navigate the quickest route between landmarks rather than trying to specifically recall the route they had previously taken.

Of critical importance here, participants were not instructed to simply try and remember their initial route between landmarks in the encoding phase. The reason for this is twofold. First, routes between landmarks in the encoding phase occurred with different levels of environmental familiarity due to their place in the trial order. As such, simple replay of past experiences during simulations are not in all cases representative of the fastest possible routes between two landmarks. Second, the interest here is in predictive simulations rather than memory replay. Simulations allow participants to incorporate spatial information they’ve learned throughout the experiment rather than trying to recall specific instances of an episode.

Inside the scanner, each trial of the simulation phase began with a fixation period for 12 s in which a white fixation cross was placed on top of a black background. Next, the word ‘Simulation’ displayed on the screen for 2 s. Following that, images of the starting and target landmark appeared for 3 s. Immediately afterward, the screen turned to black and the participants began to mentally simulate the route. The simulation period lasted for 15 s. The length of this block was determined using a larger behavioral study that recorded precise simulation times using the same experimental paradigm (Arnold et al., 2016). In that study, we observed that the average simulation period was approximately 15 s (*SD* = 11.21). Importantly, we also observed no statistical differences in simulation length comparing high (mean simulation time = 12.11 s, *SD* = 9.55) and low (mean simulation time = 14.5 s, *SD* = 14.03) vividness simulations [$t(127) = 0.96$, $p = 0.34$], nor were there when comparing high (mean simulation time = 12.94 s, *SD* = 10.72) and low (mean simulation time = 15.04 s, *SD* = 13.44) spatial coherence simulations [$t(98) = 0.8$, $p = 0.42$]. This suggests that potential confounds due to participants engaging in other forms of cognition after completing a simulation, but before the block has ended, are consistent across all levels of the analyses and therefore will have a minimal impact on the data. After the simulation, participants complete a 14 item post-simulation questionnaire (PostSQ). **Table 4** outlines the wording for each question/response and how they were grouped into different factors for analysis. The PostSQ included items modified from the Memory Characteristics Questionnaire (Johnson et al., 1988), as well as novel items, and was intended to probe qualitative aspects of the simulation experience. This included questions about spatial and temporal coherence, vividness, fractionation, confidence in knowing the starting/target locations, and perceived accuracy of their memory for the route. Each item was rated on a scale of 1–4. Immediately following the questionnaire, participants were placed within the virtual city facing the starting landmark and navigated to the target landmark as quick as possible. Once there, a post navigation questionnaire (PostNQ) was displayed where they rated two items on a scale of 1–4 assessing how well they simulated the route and how well the simulation matched their navigation experience. In total, 10 routes were included in the simulation phase. The starting-destination landmark pairs were pseudo-randomly selected such that each of the five landmarks were included as a starting point and destination only once.

Functional MRI Data Acquisition

All MRI data were collected using a 3T GE Discovery MR750w scanner with a 32-channel head coil. A single shot EPI sequence was used, consisting of 38 interleaved T2*-weighted slices per volume (flip angle: 77°, TR: 2000 ms, TE: 30 ms, 3.6 isotropic voxel size, 64×64 matrix size). The first five volumes were discarded to allow for T1 equilibrium. Additionally, a T1-weighted three dimensional FSPGR anatomical image using 1 mm isotropic voxels was collected to assist with normalization of the EPI data.

Functional MRI Preprocessing

All fMRI data were preprocessed through Nipype (Gorgolewski et al., 2011) using FSL (version 5.0.9[2]) and Advanced Normalization Tools (ANTs[3]). Data were first realigned with MCFLIRT, smoothed using a 7 mm FWHM Gaussian filter, intensity normalized, and temporally filtered using a 90-s high-pass filter for the encoding phase data and a 60-s filter for the simulation phase data. Next, all data were denoized using MELODIC to remove non-hemodynamic components based on inspection of the time course and power spectrum for each component. Anatomical and EPI data were then normalized into MNI152 space and resliced into 2 mm voxel space using ANTs by first computing a transformation matrix for registering each participant's anatomical image to the MNI152 2 mm template, and then applying a linear transform of each EPI volume using the computed matrix. To further minimize non-BOLD signal from the data and to normalize the distribution of correlation values between ROIs, anatomical images were segmented into gray matter, white matter, and cerebral spinal fluid (CSF) estimates. These tissue classes were then used to apply the CompCor noise correction method (Behzadi et al., 2007) by regressing out principle components obtained from each participant's white matter and CSF estimates from signal located in gray matter.

Node Definition

Three hundred and thirty-three regions of interest (ROIs) spanning across the entire cortex were obtained from resting-state functional connectivity boundary mapping conducted by Gordon E.M. et al. (2014). We additionally included subject-specific ROIs for the left and right HC for a total of 335 ROIs in the analyses. These hippocampal ROIs were obtained through segmenting subcortical regions in native space for each participant's anatomical scan using FIRST (Patenaude et al., 2011), and then applying the transformation matrix calculated from ANTs to resample and register each ROI to MNI152 2 mm space.

Graph Construction

Correlation matrices for all network analyses were calculated using the CONN toolbox inside SPM12. A series of general linear models (GLMs) were constructed using the encoding phase data by binning reinstatement and navigation periods at the trial level based on the confidence rating for each trial. That is, for each participant we binned their reinstatement and navigation blocks into four levels by how confident the participant was in knowing the target landmark location (1: not at all, 4: very well). For the simulation phase data, simulation period blocks were binned into four levels based on participant ratings for (i) simulation vividness (a composite measure of six questions; see **Table 4**), and (ii) the spatial coherence of featural information during a mental simulation (1: vague, 4: clear/distinct). Each GLM was then convolved with the canonical hemodynamic response function in SPM12 and used to calculate 335×335 correlation matrices using Fisher transformed *r*-values.

Graph Analyses

Calculation of all graph metrics was done using the brain connectivity toolbox for Python (version 0.4[4]). Briefly, a graph G (N,E) is characterized as a set of N nodes (here, 335 ROIs) and E edges (here, Fisher transformed r-values) representing the relationship between time varying data in any pairwise combination of nodes. Graphs are represented as a correlation matrix C_{ij} where i, j is defined by the number of nodes being analyzed. We analyzed a number of graph metrics for both global and local networks. A global network is composed of the entire set of nodes that share at least one direct connection with another node, while a local network is defined as a subset of nodes that share some form of connection with a specific node. Both left and right hippocampal nodes were used to define local networks in the present study.

Each graph metric was calculated across a range of density levels by thresholding each correlation matrix C_{ij} based on a series of cost values (k). Cost thresholds are applied to isolate a fixed percentage of edges (i.e., connections) between nodes in a graph. For the present study, we investigated each graph metric across a k value range of 0.1–0.25 at 0.05 increments representing the top 10–25% edges in each graph, a similar range used to identify developmental (Khundrakpam et al., 2013) and clinical (Bassett et al., 2008) changes in network topology. Each thresholded correlation matrix was then binarized by setting all supra-threshold edges to 1 and all sub-threshold edges to 0 to produce an adjacency matrix used for calculating different graph metrics.

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[2] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/

[3] https://github.com/stnava/ANTs

[4] https://github.com/aestrivex/bctpy

Global Network Metrics

We calculated three metrics to investigate reorganization of global network topology: modularity, global efficiency, and global flow. Modularity was calculated using a spectral community detection algorithm developed by Newman (2006). Modules are defined as a subset of nodes in a graph *G (N,E)* such that nodes within a module are more densely connected than between modules. Partitioning of a graph into modules is done by maximizing the modularity index Q by iterating over possible sub-divisions of a network. Q is obtained by first calculating a modularity matrix B_{ij} using the formula:

$$B_{ij} = A_{ij} - \frac{k_i k_j}{2m}$$

where A_{ij} is the observed number of edges between node i and j, and $\frac{k_i k_j}{2m}$ is the expected number of edges in a random graph where k_i and k_j are the degrees of each node and $m = \frac{1}{2}\sum_i k_i$ is the total number of edges in the graph. The modularity matrix is then used to find the most positive eigenvalue and corresponding eigenvector. Next, the graph is subdivided into two parts based on the signs of the elements in the vector and repeated for each of the parts using a general modularity matrix defined as:

$$B_{ij}^{(g)} = B_{ij} - \delta_{ij} \sum_{k \in g} B_{ik}$$

where $B_{ij}^{(g)}$ is the matrix indexed by *i,j* within group *g*. See Newman (2006) for a complete overview of the algorithm and a full description of the parameters used to optimize Q.

Global efficiency is the inverse characteristic path length in a graph ([.e., the average shortest path length between any two pairs of nodes (Watts and Strogatz, 1998)]. In functional brain networks, it represents the minimum number of statistical associations required to link any two brain regions and is indicative of the integrative and communicative capacity of a network to share information (Sporns et al., 2007; Bullmore and Sporns, 2009; van den Heuvel and Hulshoff Pol, 2010). Its inclusion in the present analysis is to provide a metric of global integration across all nodes in the network. Global flow is the average flow coefficient (Honey et al., 2007) across all nodes in a graph and represents the degree to which, on average, nodes act as hubs within local neighborhoods. Its inclusion here is quantify integration at a local scale.

Node Centrality Metrics for Left and Right HC

To investigate the role of the left and right hippocampal nodes within global and local networks, we calculated four commonly used metrics: betweenness centrality, flow coefficient, the participation coefficient, and local efficiency. Betweenness centrality is the number of shortest paths in a network that pass through a specific node and indicates the importance of a node to global processing in a network. It is calculated with the formula:

$$b_i = \frac{1}{(n-1)(n-2)} \sum_{\substack{h, j \in N \\ h \neq i, h \neq j, i \neq j}} \frac{\rho_{h,j}^{(i)}}{\rho_{h,j}}$$

where $\rho_{h,j}$ is the number of shortest paths in a graph that pass between h and j, and $\rho_{h,j}^{(i)}$ represents the number of shortest paths between h and j that pass through node i.

The flow coefficient is a measure of local efficiency (Honey et al., 2007) that quantifies the fraction of all paths with a length of two divided by the total possible number of paths with length two that traverse a node. It is calculated as:

$$FC = \frac{p_o}{p_p}$$

where p_0 is the number of actual paths with a length of two and p_p is the number of possible paths with a length of two.

The participation coefficient quantifies the amount of inter-module connections for a node such that nodes with a high participation coefficient act as connector hubs in a modular network by integrating processing across different communities. The participation coefficient is calculated as:

$$y^i = 1 - \sum_{m \in M} \left(\frac{k_i(m)}{k_i} \right)^2$$

where M is the set of modules identified using a community detection algorithm, and $k_i(m)$ is the number of edges between node i and all nodes in module m.

Local efficiency is similar to global efficiency but is calculated using a subset of nodes that share a direct connection with a particular node. As such, in functional networks it may be thought of as quantifying communication capacity of a network centered on a particular brain region. It is defined by Latora and Marchiori (2001) as the efficiency of a subgraph G_i composed centered on the ith node, where the subgraph is composed solely of nodes that are immediate neighbors of i. It is calculated using the formula:

$$E_{loc}(i) = \frac{1}{N_{G_i}(N_{G_i} - 1)} \sum_{j,h \in G_i} \frac{1}{l_{jh}}$$

where l_{jh} is the shortest path length between nodes j and h, and N_{Gii} is the number of nodes in the subgraph G_i.

gPPI Data Analysis

To address the *feature reinstatement* hypothesis, fMRI data were analyzed at the bivariate level using generalized psychophysical interaction (gPPI) models and at the multivariate level using graph theoretical measures. Generalized PPI models allow for the assessment of context-specific changes in functional connectivity between a seed region and sets of voxels across the brain (McLaren et al., 2012). Models are constructed by taking the interaction between the time course of the seed region and a GLM describing a task context, and searching for sets of voxels with a time course that correlates to the interaction model. Here, we use right and left hippocampal seeds defined using subject-specific segmentations generated using the FIRST algorithm in FSL to investigate context-specific changes in functional connectivity between simulation and navigation periods, as well as between simulation periods with different levels of reported vividness and spatial coherence. All gPPI analyses were conducted as whole brain analyses and used the standard corrections for multiple comparisons with a voxel height threshold of $p < 0.001$ and a cluster threshold of $p_{FWE} < 0.05$.

RESULTS

Behavioral Performance

The experiment began with an exposure phase in which participants viewed a video of passive first person movement along the perimeter of the city (**Figure 1A**). Following that, participants completed the encoding phase in the scanner (**Figure 1C**). Each trial began by cueing a target landmark and asking participants to rate their confidence in knowing its location within the city (termed the recall block), after which they were asked to navigate to the cued landmark as quickly as possible (termed the navigation block). All analyses in this manuscript that use data from the encoding phase were conducted on the navigation blocks. A total of 14 participants completed on average 13.14 trials (*SD* = 4.91) of 21 possible trials during the encoding phase. Mean path time for the navigation block was 82.7 s (*SD* = 69.24) and the average length of time during the recall block was 2.85 s (*SD* = 2.09). There was a total of 69 trials in the low confidence bin and 50 in the high confidence bin. Path number (i.e., whether a path occurred at the beginning or end of the encoding phase) and confidence rating were significantly correlated [$r(117) = 0.55$, $p < 0.001$], indicating that low confidence trials occurred early in the encoding phase and confidence ratings increased with exposure to the environment. Confidence ratings were negatively correlated with observed path time [$r(117) = -0.32$, $p < 0.001$] and path efficiency [$r(117) = -0.31$, $p < 0.001$], indicating that higher confidence in knowing landmark locations was associated with more efficient navigation.

Following the encoding phase, participants performed the simulation phase. Here, participants were cued with a starting and destination landmark from the encoding phase and given 15 s to mentally simulate a route between them in as much detail as possible. After the simulation, they were placed in front of the starting landmark within the virtual city and asked to navigate to the target landmark as fast as possible. Participants completed an average of 7.79 trials (*SD* = 2.26) out of 10 possible trials and spent an average of 1112.37 s (approximately 18 min and 30 s; *SD* = 84.2 s) completing the simulation phase. Mean path time was 60.8 s (*SD* = 53.98). Simulation vividness (mean rating = 2.96, *SD* = 0.75) and spatial coherence (mean rating = 2.9, *SD* = 0.99) were significantly correlated [$r(102) = 0.52$, $p < 0.001$], suggesting that highly vivid mental simulations are also spatially ordered. We also investigated whether simulation vividness and spatial coherence correlated to observed path time for each of the subsequent routes. Here, we found a statistically significant negative correlation [$r(102) = -0.41$, $p < 0.001$] between simulation vividness and observed path time, as well as one between simulation spatial coherence and observed path time [$r(102) = -0.2$, $p = 0.044$]. This demonstrates that aspects of feature reinstatement are relating to behavioral performance on the task, where more vivid and spatially coherent simulations relating to quicker subsequent path times. We have outlined and discussed similar findings with a larger behavioral dataset more widely in a previous study (Arnold et al., 2016), where we suggest a model in which more effective feature integration relates to quicker simulation times and subsequently more efficient wayfinding. Importantly, 44 of the 102 (40%) routes completed in the simulation phase were not navigated during the encoding phase, and there was a non-significant correlation for path time between identical routes in the encoding and simulation phase [$r(58) = 0.18$, $p = 0.14$]. Together, these findings suggest that participants were not simply replaying memories from the routes in the encoding phase during mental simulations but instead simulating novel routes (Arnold et al., 2016).

Global Network Reorganization During Encoding

Our *global integration* hypothesis predicts that functional networks across the brain will demonstrate dynamic reorganization as mnemonic representations are encoded, increasing in modularity and decreasing in the amount integration as encoding occurs. Briefly, graph theoretical measures are calculated primarily at three levels: (1) across a global network, where the number of nodes and edges being analyzed is the total set of nodes and edges in a network; (2) across local networks, which are subsets of nodes and edges within a global network that share some specific criteria (e.g., all nodes in a local network have a direct connection with a certain node); or (3) on individual nodes and the direct connections between that node and others in a global or local network. To investigate this hypothesis, we calculated three graph metrics at the global network level that are proxies for the degree of integration occurring at different stages of the encoding phase. These metrics were calculated first by binning trial-level navigation blocks (mean path time = 82.7 s) based on the confidence rating for knowing the target landmark location and compared them across a range of density thresholds. Confidence ratings during memory retrieval has been shown to act as an effective proxy for the engagement of memory-selective neurons in the HC that are involved in indexing mnemonic features within declarative memory systems (Eichenbaum et al., 2007; Rutishauser et al., 2015). Here, they are used to infer encoding demands. We reasoned that low confidence judgments indicate higher encoding demands as the participants need to encode more environmental information into their representations of the city, whereas high confidence judgments are the result of feature rich representations. Importantly, we included a choice during confidence ratings (confidence rating = 1; see "Materials and Methods") for when participants were unsure of the target landmark location, in attempts to remove trials from the low confidence bin where the participant was simply guessing or did not attempt to retrieve the landmark location. In this context, we believe that the low confidence level (i.e., confidence level = 2) analyzed here is inclusive of only trials in which the participants had some sense of where the landmark may be located, but did not have a detailed memory of how to navigate there and therefore had higher demands on encoding spatial information.

The first graph metric analyzed was the modularity index Q (Newman, 2006), a measure of the degree of modularity observed in a network. Briefly, higher values of Q indicate that a global network has a more robust modular structure (see "Materials and Methods" section on global network metrics for details on the algorithm used to compute Q). Modularity is theorized to provide a mechanism for adaptability in the brain (Ghosh et al., 2008; Meunier et al., 2010; Werner, 2010), with low levels of modularity relating to a higher capacity to integrate information across a global network. Previous research has associated changes in modularity with motor learning tasks (Bassett et al., 2011) and working memory paradigms such as the n-back task (Stanley et al., 2014; Cohen and D'Esposito, 2016). Our *global integration* hypothesis uses this perspective to predict that there would be an increased modular structure within the brain as mnemonic representations of the virtual city are encoded. We found support for this hypothesis with the modularity index Q. For the navigation blocks, there was a statistically significant difference using paired-samples t-tests the majority of density thresholds (see **Table 1** for complete list of statistics). We also computed a summary metric by collapsing across all density thresholds and comparing differences of Q. There were also statistically significant differences in Q using this summary metric, [$t(55) = -4.87$, $p < 0.001$]. **Figure 2A** summarizes these results.

Next, to complement the modularity analysis, we computed the global efficiency values for each graph across the different density thresholds. Global efficiency is calculated at the global network level and represents the integrative and communication capacity of a network by indicating, on average, how interconnected nodes in a network are (Sporns et al., 2007; Bullmore and Sporns, 2009; van den Heuvel and Hulshoff Pol, 2010). More generally, high global efficiency networks are characterized by short path lengths (i.e., the number of edges needed to connect any two nodes in a network), indicating high levels of information integration, and has been linked to the capacity to recall spatial features from memory (Arnold et al., 2014b). As with modularity, our prediction here was that higher encoding demands on low confidence trails compared to high confidence ones would require more integration of information processed across the brain and therefore be related to higher levels of global efficiency. We found support for this prediction across all density thresholds (**Figure 2B**). There were statistically significant differences across all density thresholds (**Table 1**) and for the summary metric [$t(55) = 5.23$, $p < 0.001$].

TABLE 1 | Statistical results across density thresholds for the global integration hypothesis.

Hypothesis	Graph metric	Density *(k)*	*t*-statistic	*p*-value
Global integration				
	Q	0.1	−1.85	0.087
		0.15	−2.57	0.023
		0.2	−2.63	0.021
		0.25	−2.5	0.026
	Global efficiency	0.1	2.5	0.027
		0.15	2.64	0.02
		0.2	2.66	0.02
		0.25	2.65	0.02
	Global flow	0.1	2.32	0.38
		0.15	2.54	0.024
		0.2	2.69	0.019
		0.25	2.72	0.018

Thus far the data suggest that as encoding demands decrease, brain networks reorganize into a more modular state coupled with a reduction in global integration. Another important aspect of information flow in networks is based on the topological structure of local networks (i.e., neighborhoods). Local networks in the brain are subsets of nodes (i.e., parcellated brain regions) that share some characteristic, such as a statistically significant functional correlation with a certain node, and do not incorporate information about the spatial distribution of nodes. That is, local networks can consist of spatially distant regions of the brain that have similar functional activations in response to a task. In the context of encoding mnemonic representations, it is plausible to suggest that higher encoding demands are also associated with increased need for processing within local networks early on. More specifically, as features of an environment are encoded into a representation, there may be a higher demand placed on not only integrating between, but also processing within, task-relevant systems such as the visual, somatosensory, and attentional subnetworks. To quantify and compare this, we calculated the global flow coefficient (Honey et al., 2007). This metric is the average flow coefficient of the complete set of nodes within a global network. The flow coefficient (Honey et al., 2007) represents how efficiently information flows between neighboring nodes and is therefore representative of integration within local networks. As such, the global flow coefficient represents the amount of integration occurring within the complete set of local neighborhoods in a global network rather than one neighborhood in particular. Here, the prediction was that higher values of global flow (and therefore more local integration) would be associated with the increased encoding demands of low confidence trials. As with modularity and global efficiency, we found support for our hypothesis (**Figure 2C**). There were statistically significant differences for all density thresholds (**Table 1**) and for the summary metric [$t(55) = 5.28$, $p < 0.001$].

Hippocampal Centrality During Encoding

The *node flexibility* hypothesis predicts that critical convergence zones such as the HC dynamically change functional interactions with other brain regions to alter the degree to which environmental information is integrated into a neural index. To test this, we investigated how the HC acts as a network

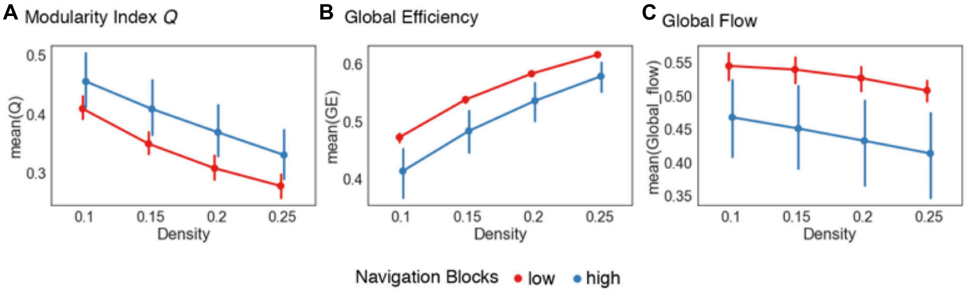

FIGURE 2 | Global network reconfiguration during representation encoding. Graph metrics evaluating the *global integration* hypothesis. **(A)** Increases in the modularity index Q were observed across the whole 335 ROI network during high confidence navigation blocks across all the density thresholds (upper 10–25% of connections in the network). **(B)** Similarly, there were increased global efficiency values across the entire density range during the low confidence trials during navigation blocks. **(C)** Low confidence trials were also associated with increased values of global flow for each density threshold. Error bars represent 95% confidence intervals.

hub at the global, inter-module, and local network level, and whether change in these measures relate to the reorganization of global brain networks while representations are formed. This was done by calculating four node-based metrics that quantify different aspects of hubness in a network using the navigation blocks (mean path time = 82.7 s) from the encoding phase that were binned by confidence rating, similar to the global graph metrics. The first metric was betweenness centrality, a common measure of global network centrality that quantifies the number of shortest paths between nodes that pass through a given node. This metric is calculated at the global network level, and indicates the importance of a node (i.e., here, the HC) to information flow in a global network by serving to connect any two nodes in a network. **Table 2** and **Figure 3A** summarizes these results. Here, we found no statistically significant differences at the different density thresholds during navigation blocks for the right [summary statistic: $t(55) = -0.38$, $p = 0.7$], or left HC [summary statistic: $t(55) = -1.12$, $p = 0.27$]. The lack of statistical differences here suggests that when considering the brain as a single, global network, there are no differences in HC centrality. However,

TABLE 2 | Statistical results across density thresholds for the node flexibility hypothesis.

Hypothesis	Graph metric	Hemisphere	Density *(k)*	*t*-statistic	*p*-value
Node flexibility					
	Betweenness centrality	Right	0.1	0.32	0.75
			0.15	0.5	0.63
			0.2	0.07	0.95
			0.25	0.25	0.81
		Left	0.1	0.07	0.95
			0.15	1.13	0.28
			0.2	0.66	0.52
			0.25	0.85	0.41
	Flow coefficient	Right	0.1	3.08	0.009
			0.15	3.15	0.008
			0.2	3.26	0.006
			0.25	3.07	0.009
		Left	0.1	2.44	0.03
			0.15	3.05	0.009
			0.2	3.42	0.005
			0.25	3.09	0.009
	Participation coefficient	Right	0.1	1.97	0.07
			0.15	2.79	0.015
			0.2	2.92	0.01
			0.25	1.45	0.17
		Left	0.1	0.77	0.46
			0.15	1.65	0.12
			0.2	1.9	0.08
			0.25	1.31	0.21

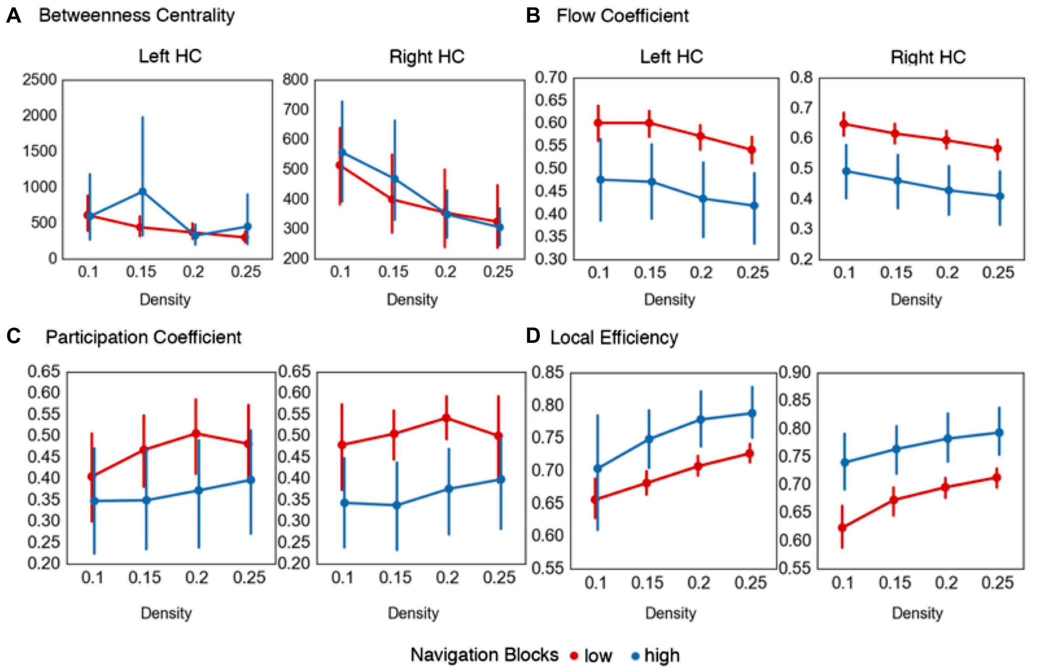

FIGURE 3 | Centrality measures for hippocampal nodes during representation encoding. Graph metrics evaluating the *node flexibility* and *state transition* hypotheses. **(A)** No differences were observed across the density thresholds for the betweenness centrality of the left and right HC during navigation blocks. The summary statistic (betweenness centrality values averaged across density thresholds) was significantly increased during high confidence trials for the left HC during memory reinstatement. **(B)** Increased values of the flow coefficient were observed for both the left and right HC in low confidence trials during navigation blocks. **(C)** Across the majority of density thresholds (0.15–0.25) there were increased participation coefficient values during low confidence trials for the right HC during navigation blocks, but only for the summary statistic in the left HC. **(D)** Across all density thresholds in the right HC and for the majority (0.15–0.25) for the left HC, there were increased local efficiency values for the hippocampal sub-network during high confidence navigation blocks. Error bars in all graphs represent 95% confidence intervals.

as demonstrated in the previous section, the brain displays a modular structure during this task and therefore changes in HC centrality may only occur within and between modules.

To expand on this, we calculated the flow coefficient (Honey et al., 2007), a graph theoretical measure that quantifies the centrality of a node within a local network. High values of the flow coefficient indicate that a particular node (here, the HC) is involved in connecting any other two nodes in a local network, and therefore acts as hub for information flow. **Table 2** and **Figure 3B** shows the results. We found statistically significant differences across all density thresholds for the right [summary statistic: $t(55) = 6.45$, $p < 0.001$] and left HC [summary statistic: $t(55) = 6.45$, $p < 0.001$].

The two analyses so far suggest that the HC displays increased centrality during navigation when encoding demands are high within a local neighborhood composed of regions that share a functional connection with the HC, but not when treating the brain as a global network. Given that there were observed shifts in modularity associated with encoding demands, it is plausible that the HC is acting as a connector hub integrating information across these modules rather than as a hub across a singular whole brain network. To investigate this, we calculated the participation coefficient (Guimerà and Amaral, 2005). The participation coefficient quantifies the amount of inter-module connections of a node compared to the amount of intra-module connections, and is representative of the degree to which a node participates in and integrates across different subnetworks. These results are summarized in **Table 2** and **Figure 3C**. The participation coefficient increased when encoding demands were high across most of the density thresholds and the summary statistic for the right HC [$t(55) = 4.54$, $p < 0.001$], but only with the summary statistic for the left [$t(55) = 2.85$, $p = 0.006$].

Global to Local State Transitions

Lastly, the local efficiency for hippocampal subnetworks was calculated to test the *state transition* hypothesis. Local efficiency (Latora and Marchiori, 2001) is conceptually similar to global efficiency, in that it quantifies the degree to which any two nodes in a network are connected, but is calculated on a local network defined as nodes sharing a direct connection with the HC. High values of local efficiency represent an increased capacity to integrate information across nodes in a local network (Rubinov and Sporns, 2010). As outlined previously, the prediction was that as participants form representations during encoding, there should be reconfiguration of network topology during navigation from a state supportive of global integration to one based on local network processing. Again, we used the navigation blocks from the encoding phase (mean path time = 82.7 s) binned by confidence rating. We found support for this prediction (**Table 3** and **Figure 3D**) with increased local efficiency in high

TABLE 3 | Statistical results across density thresholds for the state transition hypothesis.

Hypothesis	Graph metric	Hemisphere	Density (*k*)	*t*-statistic	*p*-value
State transition					
	Local efficiency	Right	0.1	−3.76	0.002
			0.15	−3.15	0.008
			0.2	−3.25	0.006
			0.25	−3.08	0.009
		Left	0.1	−1.04	0.32
			0.15	−2.58	0.022
			0.2	−3.36	0.005
			0.25	−3.04	0.01

confidence navigation blocks for the right [summary statistic: $t(55) = -6.76$, $p < 0.001$] and across the majority of density thresholds for the left HC [summary statistic: $t(55) = -4.21$, $p < 0.001$].

Hippocampal–Cortical Interactions During Prospective Mental Simulation

Retrieval and integration of environmental features from memory into the spatiotemporal context for prospective mental simulation is believed to operate through the reinstatement of regional activity in sensory and associative areas of the cortex, coordinated primarily through pattern completion and separation mechanisms in the HC (Norman and O'Reilly, 2003; Stokes et al., 2014; Horner et al., 2015). Based on this perspective, we formulated the *feature reinstatement* hypothesis and predicted that there would be increased functional coupling between the HC and areas of visual cortex during simulations with high visual and spatial fidelity. To test this, we binned the 15-s simulation blocks based on how participants rated the simulation vividness and spatial coherence in the post-simulation questionnaire (PS-Q; **Table 4**). This binning strategy was done on the simulation phase data that was collected at the completion of the encoding phase. The binned simulation blocks were then used to construct gPPI models (McLaren et al., 2012) by multiplying the time course of BOLD signal in the left and right HC with GLMs denoting trials with low (PS-Q rating value of 1) and high (PS-Q rating value of 4) vividness and spatial coherence. All gPPI analyses were conducted across the whole brain and were data driven (Biswal et al., 2010), as opposed to using *a prior* ROIs, due to the novelty of research into the neural mechanisms supporting mental simulations which putatively involve interactions across a wide set of brain regions (Brown et al., 2016).

During highly vivid simulation blocks, we found evidence for increased functional connectivity between the right HC and the superior portion of the left lateral occipital cortex [$t(13) = 4.81$, $p < 0.001$; 128 voxels; peak MNI coordinates: −46, −64, 46] (**Table 5** and **Figure 4a**). For spatial coherence, high ratings for spatial coherence during simulations were associated with increased functional connectivity between the left HC and areas within the left angular gyrus and the superior division of the left lateral occipital cortex [$t(13) = 4.34$, $p < 0.001$; 118 voxels; peak MNI coordinates: −40, −56, 42] (**Table 5** and **Figure 4b**). There were no statistically significant increases in functional connectivity with the right or left HC in low vividness or spatial coherence simulation blocks. Considered together, these results support the *feature reinstatement* hypothesis that increased hippocampal–cortical functional coupling is associated with a high degree of simulation fidelity, putatively through more effective feature integration coordinated by the HC through selective functional coupling with areas of the brain associated with higher-order visual processing.

TABLE 4 | Post simulation questionnaire (PS-Q) items listed by feature integration process.

Post-simulation Questionnaire
Vividness
My memory for this route is (1: sketchy – 4: very detailed)
*My memory for this route is (1: entirely in color – 4: black and white)
My memory for this route involves visual detail (1: little or none – 4: a lot)
Overall vividness of this route is (1: vague – 4: very vivid)
My memory for this route is (1: dim – 4: sharp/clear)
When imagining this route, it was so vivid I felt I was actually navigating it (1: not at all – 4: a great deal)
Spatial Coherence
*The relative spatial arrangements of buildings along the route is (1: clear/distinct – 4: vague)
Temporal Coherence
The order of buildings along the route is (1: confusing – 4: comprehensible)
Fractionation
Simulating the route was like watching a movie in my mind's eye (1: not at all – 4: very much)
The route was a collection of separate images (1: very much – 4: not at all)
Simulation Confidence
I have doubts about the accuracy of my memory for this route (1: a great deal – 4: no doubts)
Post Route Accuracy
My memory for this route matched my experience (1: not at all – 4: very well)
I was able to mentally simulate this route (1: not at all – 4: a lot)
Other
The route seems (1: long – 4: short)
*My memory of the starting location for this route is (1: clear/distinct – 4: vague)
My memory for the destination location for this route is (1: vague – 4: clear/distinct)

**Indicates response that was inverted prior to analysis.*

TABLE 5 | List of brain regions showing increased functional connectivity related to simulation fidelity.

Analysis				Peak MNI coordinates (mm)				
	Source	Region	Hemisphere	*X*	*Y*	*Z*	Cluster size	Z-score change
Vividness	Right hippocampus	Superior lateral occipital cortex	Left	−46	−64	46	115	0.028
		Angular gyrus	Left				11	
Simulation	Left hippocampus	Angular gyrus	Left	−40	−56	42	62	0.058
		Superior lateral occipital cortex	Left				36	

Table shows results for differences in functional connectivity between a source region and a multi-regional cluster. Anatomical regions for each cluster are listed by voxel size. All clusters were identified using a peak voxel threshold of $p < 0.001$ and a cluster correction threshold of $p_{FWF} < 0.05$.

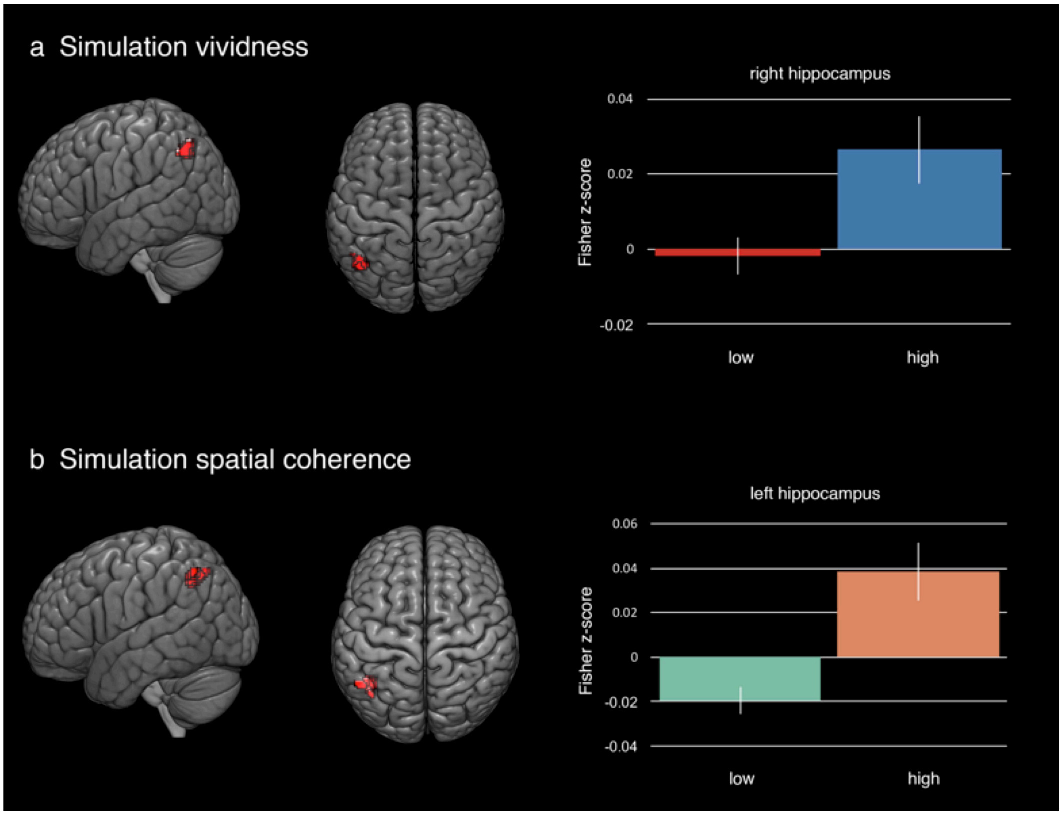

FIGURE 4 | Results from general psychophysiological interaction analyses on mental simulations. **(a)** Simulations with high visual vividness were found to have increased functional connectivity between the right HC and a cluster located in the superior division of the left lateral occipital cortex. Graph on right shows Fisher transformed z-scores for the low vividness and high vividness simulation periods. **(b)** Similarly, increased functional connectivity was observed between the left HC and a cluster within both left angular gyrus and the superior division of the lateral occipital cortex. Fisher transformed z-scores for high and low spatial coherence simulations are on the right. **Table 5** lists regions and number of voxels per region for each cluster. Statistically significant clusters were identified using a voxel height threshold of $p < 0.001$ and a cluster threshold of pFWE < 0.05. Error bars represent standard error of the mean.

Network Topology and Simulation Fidelity

In the next analysis, we sought to extend the findings on changes in hippocampal–cortical functional coupling relating to simulation fidelity by testing the *feature integration* hypothesis. This hypothesis predicts that high simulation fidelity would be associated with hippocampal-based network states conducive to information integration. While bivariate techniques such as gPPI can elucidate the functional coupling between a seed region and a cluster of voxels sharing similar BOLD response patterns, multivariate techniques such as graph theory allow for the assessment of more complex patterns of information communication and integration by considering the functional interactions between more than two sets of regions in the brain (Sporns et al., 2007; Rubinov and Sporns, 2010; Bassett et al., 2012). Of importance here, graph theoretical measures allow for assessment of network dynamics in local neighborhoods (i.e., sub-networks characterized by shared patterns of functional interactions), and how a particular region (e.g., the HC) coordinates the information flow between multiple sets of regions. To assess how hippocampal network topology relates to simulation fidelity, we calculated node-based graph theoretical measures of betweenness centrality, flow coefficient, and local efficiency for the right and left hippocampal nodes. These measures quantify the centrality of the HC at the global and local network level, and assess the communication efficiency of local HC networks, respectively. Similar to the gPPI analysis, these measures were calculated by using the 15-s simulation blocks binned by either vividness or spatial coherence.

The first measure calculated was the betweenness centrality of the right and left HC. Comparing high and low vividness simulations (**Table 6** and **Figure 5A**), there were no statistically significant differences between betweenness centrality values across the density thresholds in the right [summary statistic: $t(55) = 0.9$, $p = 0.37$] or left HC [summary statistic: $t(55) = 1.7$, $p = 0.09$]. Similarly, comparing high and low spatial coherence simulations, there were no statistically significant differences across the density thresholds in the right [summary statistic: $t(55) = 1.27$, $p = 0.21$] or left HC [summary statistic: $t(55) = -0.02$, $p = 0.99$]. As with the confidence judgment analysis on the encoding phase data, there appears to be no differences in HC centrality when considering the brain as a single global network. However, given the modular structure of networks during the task, it is plausible that there are dynamic alterations in how the HC interacts between modules and within its local neighborhood.

Next, we calculated the flow coefficient for the left and right hippocampal nodes (**Figure 5B**). In this analysis, the flow coefficient represents how central information flow vis-à-vis the HC is within its local network. Here, we found statistically significant increases in flow coefficients during high vividness simulations at the higher density thresholds (**Table 6** and **Figure 5B**) for the right [summary statistic: $t(55) = -5.22$, $p < 0.001$] and left HC [summary statistic: $t(55) = -5.38$, $p < 0.001$]. Comparing high and low spatial coherence trials, we found no statistical differences at the individual density thresholds (**Table 6** and **Figure 5B**). The summary statistic was statistically significant for the left [$t(55) = -2.52$, $p = 0.01$] but not the right HC [$t(55) = -1.73$, $p = 0.09$].

Thus far, the data show that there are no differences between the centrality of the HC at the global network level in mental simulations with high vs. low vividness and spatial coherence. However, there was evidence for increased hippocampal centrality within its local neighborhood during mental simulations with high vividness. Next, we sought to further evaluate information flow within hippocampal neighborhoods. As previously outlined, the HC is theorized to coordinate the selective reactivation of sensory and associative areas of the cortex using a neural index to reinstate environmental features from memory and integrate them into a representation used during mental simulation. A plausible prediction from this is that in trials with low hippocampal centrality (i.e., trials which tended to be correlated with low-vividness ratings), the coordination of feature reinstatement and integration is compensated by increases in functional interactions between other regions of the memory system supporting mental simulations (Fornito et al., 2012). To evaluate this, we calculated the local efficiency of hippocampal networks. Local efficiency represents the efficiency of information flow in a subnetwork composed only of immediate neighbors of a specific node (i.e., a neighborhood). Comparing simulations of high and low vividness (**Table 6** and **Figure 5C**), there were statistically significant decreases in local efficiency values for high vividness simulations in the right hippocampal neighborhood [summary statistic: $t(55) = 5.17$, $p < 0.001$], and across higher density thresholds in the left hippocampal neighborhood [summary statistic: $t(55) = 5.22$, $p < 0.001$]. We also investigated differences in local efficiency values of hippocampal networks between simulations with high and low spatial coherence. For the individual density thresholds, there were no statistically significant differences for the right or left hippocampal neighborhoods (**Table 6**). The summary statistic was significant for the left hippocampal neighborhood [$t(55) = 2.6$, $p = 0.011$], but not the right [$t(55) = 1.6$, $p = 0.11$]. Importantly, comparing the increased flow coefficient and decreased local efficiency of the right HC network during highly vivid simulations and the left HC for spatial coherence indicates that information flow vis-à-vis the HC, rather than increased information flow between all nodes in the HC network, is vital for highly vivid simulations.

DISCUSSION

Theoretical and computational models of memory function posit that mnemonic representations are generated by integrating sensory features processed across the neocortex into neural patterns within memory structures, and the retrieval of these representations involves reinstatement of feature-specific activity in the neocortex via pattern completion mechanisms in the HC (Marr, 1971; Damasio, 1989; McClelland et al., 1995; Nadel and Moscovitch, 1997; Norman and O'Reilly, 2003; Meyer and Damasio, 2009). While there is increasing evidence for these models during memory retrieval (Staresina et al., 2013; Watrous et al., 2013; Gordon A.M. et al., 2014; Schedlbauer et al., 2014; Horner et al., 2015; Backus et al., 2016), empirical evidence for how brain networks interact dynamically during encoding has been lacking. Here, using confidence ratings as a proxy of processing demands within memory networks (Rutishauser et al., 2015), we test a series of three hypotheses relating to dynamic network processes and how mnemonic representations are encoded and reinstated. The *global integration* hypothesis predicts that brain networks are in state of increased integration when encoding demands are highest. The *state transition* hypothesis predicts that as encoding progresses, brain networks transition from a state of global and inter-module integration into one emphasizing local processing within hippocampal networks. The third hypothesis, termed the *node flexibility* hypothesis, predicts that the convergence zones such as the HC flexibly alter functional connections with global and local networks, increasing in centrality as a global network and inter-module connector hub when encoding demands are high, and transitioning to local network processing once representations are formed. Collectively, the results from this study support these hypotheses and demonstrate for the first time that the

TABLE 6 | Statistical results across density thresholds for the global integration hypothesis.

Hypothesis	Graph metric	Fidelity metric	Hemisphere	Density *(k)*	*t*-statistic	*p*-value
Feature integration						
	Betweenness centrality	*Vividness*	Right	0.1	1.91	0.08
				0.15	0.43	0.67
				0.2	0.34	0.74
				0.25	−0.32	0.76
			Left	0.1	0.17	0.11
				0.15	1.02	0.33
				0.2	1.23	0.24
				0.25	−0.17	0.87
		Spatial coherence	Right	0.1	0.7	0.5
				0.15	0.37	0.71
				0.2	1.58	0.14
				0.25	0.11	0.91
			Left	0.1	−0.1	0.92
				0.15	0.39	0.71
				0.2	0.22	0.83
				0.25	1.02	0.33
	Flow coefficient	*Vividness*	Right	0.1	−1.31	0.21
				0.15	−3.21	0.007
				0.2	−3.45	0.004
				0.25	−3.34	0.005
			Left	0.1	−1.51	0.16
				0.15	−2.73	0.017
				0.2	−3.12	0.008
				0.25	−3.22	0.007
		Spatial coherence	Right	0.1	−0.77	0.46
				0.15	−0.99	0.34
				0.2	−0.74	0.47
				0.25	−0.88	0.4
			Left	0.1	−0.5	0.62
				0.15	−1.06	0.31
				0.2	−1.54	0.15
				0.25	−1.88	0.08
	Local efficiency	*Vividness*	Right	0.1	2.19	0.047
				0.15	3.76	0.002
				0.2	3.69	0.003
				0.25	3.42	0.005
			Left	0.1	1.42	0.18
				0.15	2.66	0.02
				0.2	3.07	0.009
				0.25	3.21	0.007
		Spatial coherence	Right	0.1	0.73	0.48
				0.15	0.86	0.41
				0.2	0.69	0.5
				0.25	0.87	0.4
			Left	0.1	0.74	0.47
				0.15	1.12	0.28
				0.2	1.48	0.16
				0.25	1.86	0.09

topological structure of brain networks reconfigures from a state of global integration to localized processing based on the degree of integration of environmental information into a putative representation, and that the HC flexibly changes its role as an inter- and intra-module connector hub in response to these integrative demands. The subsequent use

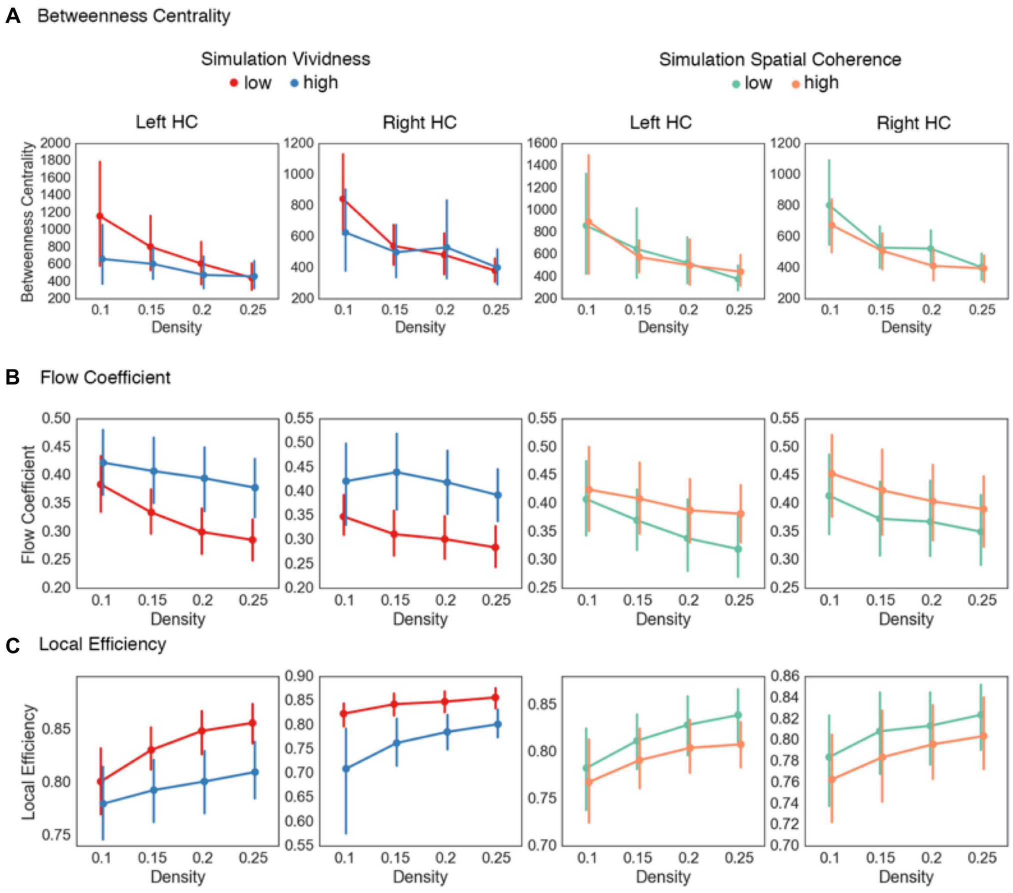

FIGURE 5 | Results from hippocampal network analyses on mental simulations. **(A)** No statistically significant differences were found in the betweenness centrality of the left or right HC comparing either low and high vivid or spatially coherent mental simulations. **(B)** Increased flow coefficient values were found during highly vivid simulations in the right and left HC across higher density thresholds. **(C)** Decreased local efficiency values were found during highly vivid mental simulations in the right and across the higher density thresholds in the left HC. No statistical differences were observed between high and low spatial coherence mental simulations. Density thresholds represent the percentage of strongest connections in each network. Error bars represent 95% confidence intervals.

of mnemonic representations during prospection was also investigated using two hypotheses and shown to be associated with dynamic changes in network topology. During highly vivid and spatially coherent simulations, the HC was found to increase functional interactions with areas of left occipital cortex and angular gyrus that have previously been associated with object recognition, manipulation of mental imagery, and awareness of intended action sequences. Highly vivid simulations were also found to increase hippocampal centrality in local memory networks, indicating that the HC is critical for supporting multi-regional integration of visual information during prospection. Collectively, these results suggest that dynamic shifts in global and local network topologies, coordinated in part by changes to functional interactions with the HC, relate to the degree to which environmental information is encoded in a mnemonic representation.

Adaptability of complex networks is thought to operate in part through the dynamic formation and interaction of different network communities (Ghosh et al., 2008; Meunier et al., 2010; Werner, 2010; Bassett et al., 2011), allowing the network to optimize its output based on relevant environmental demands. Using 335 ROIs distributed across the brain, we found support for network adaptability during the encoding and retrieval of mnemonic representations. During navigation trials in which participants had low confidence in knowing the target landmark location, we observed lower values of the modularity index Q compared with trials in which they had high confidence in knowing the landmark location. This suggests that the brain displays an increasingly stable modular topology as the need to integrate environmental features lessens and can dynamically reconfigure its community organization based on changing task demands. This result was extended at the global and local network level, with low confidence navigation trials associated with increased values of global efficiency and global flow across the brain. This pattern of results supports the *global integration* hypothesis and provides empirical support at the network level for the long held but sparsely tested hypothesis that encoding features into mnemonic representations increases the integration of information processed in a distributed set of systems across the brain (Marr, 1971; Damasio, 1989;

Squire and Zola-Morgan, 1991; McClelland et al., 1995; Nadel and Moscovitch, 1997; Meyer and Damasio, 2009). Building on the perspective of Bassett et al. (2011), as well as research on motor learning (Bassett et al., 2011) and working memory (Stanley et al., 2014; Cohen and D'Esposito, 2016), we suggest that adaptability in network topology underlies changes in how domain-specific information is integrated into holistic representations in a manner that allows the contents of a specific representation to become more stable over time. Further, decreases in global efficiency and increases in hippocampal community local efficiency indicate that as a representation is encoded, there is a decreased need to integrate across sensory and associative systems in the brain and an increased need to rapidly propagate information within the hippocampal sub-network. Although more research is needed, particularly in non-spatial memory paradigms, these findings provide a tentative experimental framework for understanding the neural basis of the dynamic formation of networked representations (Eichenbaum, 2000).

The HC has long been thought to be a primary convergence zone (Eichenbaum, 2000; Meyer and Damasio, 2009; Mišić et al., 2014; Backus et al., 2016), receiving multisynaptic inputs from both sensory cortices and associative systems in the perirhinal and parahippocampal cortex. This allows for conjunctive coding of high-level sensory and associative environmental features, such as spatial information to specific locations (O'Keefe and Nadel, 1978; Ekstrom et al., 2003) and the temporal sequence of places and events that form the basis of episodic memories (Eichenbaum, 2004, 2013; Davachi, 2006; MacDonald et al., 2011). Although the results of the current study are consistent with the role of the HC as a convergence zone, the current findings extend past results and support the *node flexibility* hypothesis by showing that the HC demonstrates flexibility during representational encoding by altering the degree to which it acts as a connector hub within local networks, as well as between network modules. On low confidence trials where encoding demands are highest, we observed increased values of the flow coefficient, indicating that the centrality of the HC within its local network is associated with the need to integrate sensory and associative information. Importantly, we also observed increased values of the participation coefficient on low confidence trials in the right HC, supporting its role as an inter-module hub, combining information processed within different modules across the brain into a putative mnemonic representation. Conversely, on high confidence trials, we found evidence for the *state transition* hypothesis local efficiency increased within a hippocampal sub-network. Considered together, these results suggest that the convergence of information into the HC is mediated in part by associative demands during the encoding of a representation, and operates dynamically by changing the functional interactions within and between network modules. As representations are formed, the centrality of the HC decreases while the efficiency of information flow within hippocampal sub-networks increases. This finding builds upon past work positing that the learned associations of a mnemonic representation are related to the topological composition of functional interactions between brain regions (Buchel et al., 1999; Eichenbaum, 2000), putatively through the reconfiguration of hippocampal interactions that initially allow sensory and associative information to be bound into a holistic representation that is subsequently coded by the functional interactions between components of a hippocampal based sub-network. Additionally, the dynamic nature of cognition during navigation (Spiers and Maguire, 2008; Ekstrom et al., 2017) may provide additional demands on network reconfiguration by requiring that the brain rapidly apply different cognitive operations that are critical to wayfinding. In the context of the present study, this suggest that the navigation blocks during the encoding phase contain instances of different cognitive processes, such as periodic reinstatement periods, that cumulate in observable navigation behavior. However, this is speculative and future research using time sensitive imaging methods such as multi-band MRI or magnetoencephalography may be able to further detail how different components of navigation behavior relate to alterations in network processing.

The reinstatement of mnemonic representations is not a binary process. Rather, recapitulation of task-oriented representations during prospection vary in how orderly and vivid encoded information appears subjectively. Variability in representation fidelity is theorized to be associated with how effectively environmental features from previous experiences can be recapitulated into a mnemonic representation underlying prospection (Arnold et al., 2016). Based on this and other outlined theoretical perspectives (Hassabis and Maguire, 2009; Schacter et al., 2012), we formulated the *feature reinstatement* hypothesis that the representational fidelity of a prospective mental simulation would require increased coordination between the HC and visual areas of the brain, as the neural codes of the spatial context in the HC putatively coordinates the recapitulation of environmental features needing to be integrated in a task oriented manner. The results from the current study provide support for this hypothesis by showing that highly vivid and spatially coherent simulations involve increased functional coupling between the HC and cortical areas associated with object representation and the manipulation of mental simulations. Comparing simulations with high and low vividness ratings using gPPI models, we observed increased functional connectivity during highly vivid simulations between the right HC and the superior division of the left lateral occipital cortex and the left angular gyrus. Similarly, we found increased functional connectivity during simulations with high ratings of spatial coherence between the left HC and the left angular gyrus and the superior division of the left lateral occipital cortex, similar to the area identified in the vividness analysis. Lateral occipital cortex has previously been implicated in representing high-level visual features of objects and how they are localized in spatial contexts (Kourtzi and Kanwisher, 2001; Xu and Chun, 2006; Silk et al., 2010). Additionally, this area has been found to uniquely increase activity during mental simulations that involve self-referential processes in non-present timeframes (i.e., past, future, and imagined) (Nyberg et al., 2010). Angular gyrus has more widespread functional roles, acting as a multi-modal hub integrating multisensory information to allow for the manipulation of mental representations (Seghier, 2013) and subjective awareness of intended action sequences and their consequences in spatial contexts (Farrer et al., 2008; Arnold et al., 2014b). Considered together, these functional interactions suggest that the neural codes in the HC representing the spatial context of a location interact with visual and associative areas of the cortex to reinstate and organize environmental features from memory. Critically, the degree of these functional interactions relate to how effectively environmental features can be reinstated, integrated, and manipulated during simulation of movement within a spatial context. This suggests that the neural codes underlying prospection involve changes in interactions between the hippocampus and other cortical regions, particularly those previously shown to integrate multisensory information and act as a representational buffer for high level spatial information, rather than resulting from neural processes located solely in the hippocampus.

Prospection is theorized to rely on functional interactions between a multi-regional network across the brain (Hassabis et al., 2007; Schacter et al., 2012; Brown et al., 2016). To characterize the topological structure of these networks and how the HC is involved in coordinating information flow between network components, we sought to complement the gPPI analysis by investigating changes in hippocampal network topology associated with representational fidelity. Here, we tested the *feature integration* hypothesis that predicts feature reinstatement and integration requires network states allowing more efficient communication (Arnold et al., 2014b), particularly with increased hippocampal involvement in coordinating information flow. We did not find support for this hypothesis at the global network level, with no statistical differences in betweenness centrality values for the HC when comparing mental simulations with high or low vividness or spatial coherence ratings. However, within hippocampal neighborhoods, the right HC had increased centrality as measured by the flow coefficient during mental simulations with high vividness ratings and the left HC with spatial coherence, albeit only the summary statistic. Additionally, we observed decreased local efficiency, a measure of information flow between any two nodes in a neighborhood, in simulations with high vividness ratings within the right HC neighborhood, and those with high spatial coherence within the left HC neighborhood. The presence of increased hippocampal centrality and decreased local efficiency within hippocampal neighborhoods suggests that coordination of information flow vis-à-vis the HC within memory networks during prospection is critical, facilitating the recapitulation and integration of spatial features from memory into a goal-oriented mnemonic representation. Conversely, in simulations with low visual fidelity, the decreased role of the HC in coordinating information flow appears to be compensated for by increased functional interactions between other regions in the memory network. This compensatory mechanism may allow for partial recapitulation of environmental features from memory, albeit at a lower visual resolution than simulations with increased hippocampal coordination (Rosenbaum et al., 2009; Yonelinas, 2013).

CONCLUSION

The present study provides novel empirical support for critical predictions by theoretical models on how mnemonic representations are formed and subsequently used in a goal-oriented manner. We show that on low confidence trials, which we infer as having increased encoding demands, the topological structure of the brain is organized to facilitate global and local information flow. As representations are encoded, the HC flexibly changes its functional interactions across the brain, decreasing its role as connector hub within its local sub-network and across network modules, while the information flow within the hippocampal community increases in efficiency. The ability to subsequently use mnemonic representations for prospection was also related to dynamic changes in network topology. As predicted, both aspects of representational fidelity were related to increased functional coupling between the HC and visual and associative areas of the brain, putatively allowing for more effective feature integration during mental simulation. Highly vivid and spatially coherent simulations were also found to be associated with both increased hippocampal centrality and decreased local efficiency within a hippocampal sub-network, suggesting that the visual basis of a mental simulation requires coordination of information processing via the HC into high-resolution mnemonic representations (Rosenbaum et al., 2009; Yonelinas, 2013). This provides a tentative theoretical framework to understand the dynamic nature of representational encoding and retrieval, through assessing changes in topological structure across global and hippocampal based brain networks. Critically, this study also provides the first direct empirical evidence that the neural representations underlying prospection are generated and manipulated through hippocampal–cortical functional interactions rather than neural codes in the HC alone. Future research will be able to use this framework to understand how the pathology of cognitive and neurodegenerative disorders impacts the topological structure of global and local brain networks during memory encoding and retrieval, and how neurostimulation methods enhance the ability to form accurate mnemonic representations.

AUTHOR CONTRIBUTIONS

AA and GI conceived the project and designed the task and environment. AA collected the behavioral and fMRI data. AA, GI, and AE wrote the manuscript and outlined the analysis pipeline and AA was responsible for analyzing the data.

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Perspective: Assessing the Flexible Acquisition, Integration, and Deployment of Human Spatial Representations and Information

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Studying human spatial navigation in the lab can be challenging, particularly when including non-invasive neural measures like functional magnetic resonance imaging (fMRI) and scalp encephalography (EEG). While there is broad consensus that human spatial navigation involves both egocentric (self-referenced) and allocentric (world-referenced) coding schemes, exactly how these can be measured in ecologically meaningful situations remains controversial. Here, we explore these two forms of representation and how we might better measure them by reviewing commonly used spatial memory tasks and proposing a new task: the relative vector discrimination (RVD) task. Additionally, we explore how different encoding modalities (desktop virtual reality, immersive virtual reality, maps, and real-world navigation) might alter how egocentric and allocentric representations manifest. Specifically, we discuss desktop virtual reality vs. more immersive forms of navigation that better approximate real-world situations, and the extent to which less immersive encoding modalities alter neural and cognitive codes engaged during navigation more generally. We conclude that while encoding modality likely alters navigation-related codes to some degree, including egocentric and allocentric representations, it does not fundamentally change the underlying representations. Considering these arguments together, we suggest that tools to study human navigation in the lab, such as desktop virtual reality, provide overall a reasonable approximation of *in vivo* navigation, with some caveats.

Keywords: spatial representations, spatial information, navigation, egocentric, allocentric, virtual reality, relative vector discrimination (RVD) task

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INTRODUCTION

Cognitive neuroscience provides a wide variety of behavioral and neural tools to assay cognitive processes and neural systems that underlie human spatial navigation. However, like any measurement tool in science, there are limitations to how they can be applied and exactly what information they provide. In terms of behavioral measures for spatial knowledge, two pointing tasks have been widely used: the scene and orientation-dependent pointing (SOP) task and the judgments of relative direction (JRD) pointing task. In the SOP task, shown in **Figure 1A**, participants are oriented within the environment and then asked to point to target objects. In the VR version, all targets are removed, and background information provides visual orienting information (e.g., Zhang et al., 2014). In the real-world version, participants are blindfolded but oriented within the environment via body-based input (e.g., Wang and Spelke, 2000). Conversely, the JRD task is conducted with participants either disoriented within the environment, or moved to a different environment, where they are provided a triad of targets (delivered via text or by the experimenter, verbally; "Imagine standing at A, facing B; point to C."). The first two targets serve to established an imagined heading to orient to while participants point to the third target in the triad (Shelton and McNamara, 2001; Mou et al., 2004; Waller and Hodgson, 2006; Starrett et al., in press). An example trial is shown in **Figure 1B**. There are systematic differences in what is measured by each task, and both tasks have limitations related to exactly what they measure in terms of underlying spatial representations (Mou et al., 2004; Kelly et al., 2007; Ekstrom et al., 2014; Zhang et al., 2014).

In terms of neural assays, functional magnetic resonance imaging (fMRI) requires participants to lay supine while navigating in virtual reality (VR), and challenges remain for conducting scalp EEG during real-world exploration (but see Gramann et al., 2010). Our main focus in this perspective is therefore to consider the limitations imposed by the SOP and JRD tasks and studying navigation in VR more generally. We also consider the valuable information we can nonetheless glean from them in terms of how we navigate and suggest a new relative vector discrimination (RVD) task (see **Figure 1**) aimed to better describe spatial memory for allocentric reference frames and the flexibility of representations across various spatial task demands.

One way to consider the relative demands of the SOP and JRD tasks is along an egocentric to allocentric continuum (see **Figure 2**), which also allows us to consider how different levels of immersion in VR might affect where they fall on this spectrum. We suggest that future experiments should focus on how spatial information manifests and is accumulated during various encoding modalities (e.g., route versus map learning). Separately, we consider how this information might be strategically deployed depending on flexible task demands during retrieval (e.g., SOP, JRD, map drawing, etc.). We can potentially better model and understand the nature of representations underlying human spatial navigation by considering how spatial information is first encoded along the egocentric to allocentric continuum, and then subsequently retrieved depending on the task demands.

THE EGOCENTRIC TO ALLOCENTRIC SPECTRUM: WHERE DO THE DIFFERENT POINTING TASKS SIT?

One of the most widely used distinctions in spatial navigation involves the idea of two fundamentally different forms of representations, egocentric vs. allocentric. Briefly, navigation involving an egocentric representation employs a coordinate system referenced to one's current position and facing direction and is most familiar in navigating our immediate, peripersonal space. Examples include knowing where a chair is in front of us so that we can avoid colliding with it when we get up or reaching for a mug next to us. One disadvantage of egocentric coordinates, however, is they change constantly as the navigator moves, requiring continuous updating of one's position. In contrast, an allocentric representation involves reference to objects that remain constant in the external world. For example, using other landmarks to remember how to get to a goal. A disadvantage of an allocentric representation is that it requires reference, and memory for, multiple landmarks.

There is at least some evidence that the SOP task assays primarily egocentric forms of spatial representation while the JRD task assays primarily allocentric forms of representation (**Figure 2**). In particular, there is general agreement that the SOP task is primarily egocentric, provided that participants are oriented when pointing and that the dependent measure is absolute pointing error (Wang and Spelke, 2000; Holmes and Sholl, 2005; Waller and Hodgson, 2006; Zhang et al., 2014). In contrast, there is significantly less agreement regarding the JRD task and the extent to which it provides primarily allocentric, or some complex combination of egocentric and allocentric, information (Ekstrom et al., 2017). Specifically, given that imagined, first-person headings are a fundamental part of the task ("imagine you are facing X"), it seems difficult to fully discount the contributions of egocentric viewpoint information from JRDs (Ekstrom et al., 2014). Indeed, previous work has demonstrated a bias to perform better when pointing at targets in the forward hemifield of the imagined heading and that this bias is weaker or absent when information is learned from a map (Sholl, 1999; Kelly and McNamara, 2009), suggesting that spatial information is either acquired or deployed differently across learning modality even for the same retrieval task. In addition, a recent article by Wang (2017) demonstrated that tasks like the Morris Water Maze, often argued to rely on allocentric representations (Morris et al., 1986), can also be solved using egocentric coordinates (Wang, 2017). Finally, the JRD task does not involve an estimate of distance, an important component of allocentric representation more generally (because egocentric representations are more likely to involve viewpoint and bearing-dependent "snapshots," distance is likely less relevant).

THE RELATIVE VECTOR DISCRIMINATION (RVD) TASK: A MORE ALLOCENTRIC "ALLOCENTRIC" TASK

We propose a new RVD spatial memory task to provide a fundamentally more (although still not purely) allocentric task than the JRD task and thus a better foil for the SOP task (see **Figure 1**). Inspired by the task used by Han and Becker (2014), the RVD task is framed in the third-person, with participants receiving a top–down view of the locations of two target stores and placing a third freely (**Figure 1C**). In the RVD task, participants are presented with a blank screen showing two "anchor" landmarks positioned relative to one another on the screen. The position of these landmarks on the screen is fixed. Depending on the vector defined by the positions of the anchor landmarks, participants will be required to place a third target landmark on the screen relative to the anchor landmarks (**Figure 1C**). One benefit of the RVD task is that it provides a

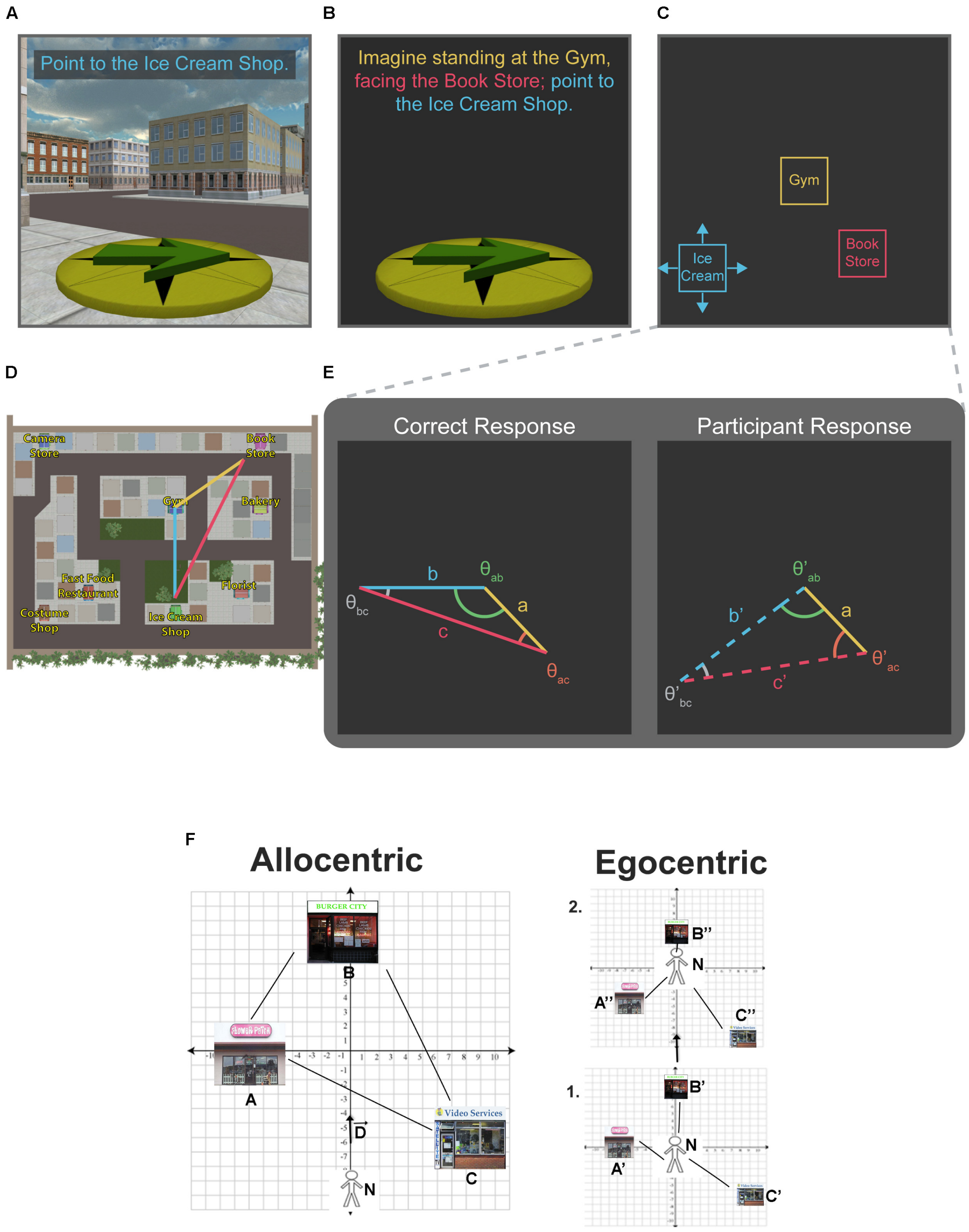

FIGURE 1 | Pointing tasks. Single-trial examples for computer versions of the scene and orientation-dependent (SOP) pointing task **(A)**, the judgments of relative direction (JRD) pointing task **(B)**, and the proposed relative vector discrimination (RVD) task **(C)**. In each example, participants' memory for the location of the Ice Cream Shop (blue text) is being tested. Example trials are based on the virtual environment used by Starrett et al. (in press) **(D)**. Unlike the JRD and SOP tasks, which only yield angular precision estimates, the RVD task yields both angular and distance information [note that the anchor vector (yellow line) is common across the correct and participant response, and the placement of the target store establishes the remaining two legs of a triangle (red and blue lines)] **(E)**. A reproduction of Figure 1 from Ekstrom et al. (2017) shows the cartesian relationship between allocentric (left panel) and egocentric (right panel) as a displacement vector from the navigator **(F)**.

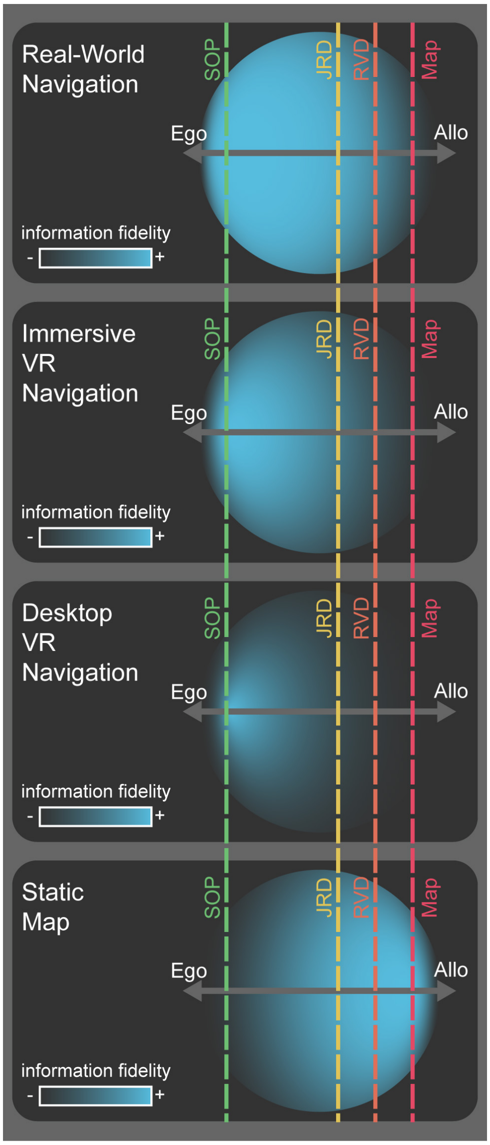

FIGURE 2 | Conceptual model for the encoding and deployment of spatial information. Hypothetical spatial information (blue circles) acquired during early encoding of a novel environment via various encoding modalities (labels, left). Each example shows the fidelity of spatial information acquired (density and center of mass for blue circles) along an egocentric-to-allocentric continuum (dark gray, horizontal axes). The extent to which the circles project outward from the egocentric-allocentric axis illustrates information that, while not strictly spatial in nature (e.g., semantic or episodic memory), can be used to derive spatial information or drive inferences about the environment. The offset of the vertical, dashed, lines from the center of the egocentric-allocentric axis represents the hypothetical proportion to which that task depends more on egocentric or allocentric reference frames for its optimal solution (SOP: green, JRD: yellow, RVD: orange, map drawing: red).

measure of both angle and distance, as well as latency, within the same task. Error can be quantified by comparing the geometry of the triangle created by the anchor vector and the correct placement vectors with the anchor vector and the participant's placement vectors (**Figure 1E**).

While the RVD task differs in several important ways from the SOP and JRD, performance on all three tasks is dependent on similar spatial memory principles such as environmental geometry, salient landmarks, and learned viewpoints or routes (depending on learning modality). For example, the anchor vector in the RVD task can be thought of as an analog to the imagined heading in JRD task or the oriented perspective in the SOP task. Therefore, the same types of independent manipulations can be applied to the RVD task (e.g., alignment with learned perspectives or environmental geometry). In fact, as suggested by the title of this section, the primary objective in creating this task is to yield a dependent variable comparable to that of the JRD, but with intrinsically more allocentric demands based on how the task is framed. This is illustrated in **Figures 1A–E**, where the orientation, imagined heading, and anchor vector in the SOP, JRD, and RVD, respectively are identical. The linearly transformable relationship between egocentric and allocentric cartesian coordinates is also illustrated in Figure 1 of Ekstrom et al. (2017), shown in **Figure 1F**. Therefore, if these tasks were identical, the triangles derived from responses on any of them should theoretically be geometrically similar (i.e., the corresponding angles should be equal), if not identical. Any deformation would be indicative of differences in task demands. Notably, with the inclusion of distance estimates in the RVD, other metrics comparing the deformation of entire shapes may be used to compare triangles derived from participants' responses against those derived from the correct response, such as those put forward by Basri et al. (1998).

When implementing the RVD task, there are several important parameters and aspects of the task to consider. (1) The degree of potential egocentricity can be manipulated even within the parameters of the RVD task (further supporting the idea of flexible spatial demands for retrieval tasks). For example, the anchor vector could be constrained to always originate from the center of the screen (as in the example trial shown in **Figure 1C**). While this may prove useful for experimental designs that require fixation, such as fMRI or eye tracking paradigms, doing so also limits the extent to which experimenters can rule out participants' reliance on a central "self-" centered anchor within their visual field. Other parameters that may affect the egocentric versus allocentric demands of the RVD task include length of the anchor vector relative to a learned viewpoint (particularly for map learning), the orientation of the anchor vector relative to learned viewpoint (global map orientation for map learning or possibly initial or final viewpoints during navigation), and potentially others. (2) Whether RVD performance is being compared with performance on other spatial memory tasks such as the SOP, JRD, or map drawing. In the case of the SOP and JRD tasks, which traditionally do not include distance estimates, it may prove beneficial to constrain the anchor vector to originate from the origin (as in **Figure 1C**) to provide a clear comparison angle and analog for imagined heading used in the SOP and JRD. Additionally, the length of the anchor vector could be constrained either to be identical on every trial or scaled to corresponding lengths relative to the geometry of the environment if the experimenter wishes to attempt to control for angular biases related to distance. Ultimately, the consideration of these parameters will depend on the design of the experiment and the questions being addressed (Waller and Hodgson, 2013).

The RVD task thus provides an additional position along the egocentric to allocentric continuum of spatial information (see **Figure 2**) that can be probed during recall. This will allow future experiments to expand on previous findings comparing the JRD and SOP tasks (Waller and Hodgson, 2006; Zhang et al., 2014) by observing and contrasting performance on the RVD task across encoding modalities (routes/maps) relative to the JRD and SOP tasks. We hypothesize that the RVD task can be used to coerce the deployment of more allocentric spatial information in well-learned environments or the conversion of egocentric information to make inferences from an imagined or low-fidelity allocentric reference frame (**Figure 2**), consistent with previous suggestions regarding how participants often utilize allocentric representations (Mou et al., 2006; Newman et al., 2007).

THE SPACE BETWEEN REFERENCE FRAMES: ENCODING MODALITIES, RETRIEVAL DEMANDS, AND HOW THEY INTERACT WITH SPATIAL KNOWLEDGE

As suggested by the BBB model (Byrne et al., 2007) but worked out in detail in a recent computational paper (Wang, 2017), the primary difference between egocentric and allocentric representations involves keeping track of one's displacement (**Figure 1F**; reproduction of Figure 1 from Ekstrom et al., 2017) (see also Ekstrom and Isham, 2017, **Figure 1**; Wang, 2017, **Figure 2**). As described earlier, in an egocentric reference frame, the coordinates for one's position stay constant while those for landmarks continuously change. In contrast, in an allocentric reference frame, the positions of landmarks stay constant while those of the self continuously change. Thus, the allocentric reference seems computationally more efficient because only the movement of the navigator needs to be maintained, and thus eventual conversion of egocentric to primarily allocentric coordinates would appear advantageous. Consistent with this idea, during navigation of well-known environments, participants appear to prefer allocentric reference frames, but when allocentric information is not reliable or is of low fidelity, egocentric reference frames dominate (Mou et al., 2006; Newman et al., 2007).

While it is possible to define and distinguish egocentric and allocentric reference frames mathematically and anecdotally, and why an allocentric reference in particular might be most advantageous for navigating, in practice, the interaction and dynamic use of either or both can be difficult to parse, particularly given that the main difference involves a simple linear transformation (adding/subtracting one's displacement). Consider the example of driving with a global positioning system (GPS). In this scenario, it is unlikely that the GPS or the driver's view of the road will be used in isolation. Most likely, attention will constantly shift from the road to the GPS and back, all the while updating and integrating information from each source. This example illustrates how navigation in the modern world rarely involves a static egocentric or allocentric reference frame.

Moreover, the specific reference frames used may not be purely egocentric or allocentric. While GPS devices do show a map view of the environment, this map is often updated such that an icon indicating the user's current position is constantly centered and sometimes even facing the current direction of travel, introducing an egocentric element. The GPS represents an example of a hybrid reference frame that may be integrated with, translated to, or even represented independently from more egocentric and allocentric reference frames as one navigates (Trullier et al., 1997; Eichenbaum, 2017). Such hybrid information could facilitate more rapid integration with real-world egocentric information in lieu of actual topological or survey knowledge by placing the onus of any computational conversions or representations on the GPS rather than areas proposed to be important for egocentric to allocentric conversion like retrosplenial cortex (Burgess, 2006; Byrne et al., 2007; Epstein, 2008; Ekstrom et al., 2017).

In **Figure 2**, we present a conceptual model for describing spatial information along the egocentric-to-allocentric continuum. Spatial information is indicated by the blue area of the circle for which density denotes more high-fidelity information and the center of mass shows the utility of that information for task demands ranging from egocentric to allocentric. The position, density, and dispersion of the spatial information circles are largely influenced by learning modality (illustrated by contrasts between panels in **Figure 2**), but for both egocentric and allocentric information, participants acquire varying amounts and fidelity in each learning condition. Various retrieval task demands are depicted by vertical, dashed lines, with the offset from the center of the continuum illustrating the relative egocentric-allocentric dependence of the task. As emphasized in the figure, not only are the learning modality and retrieval task demands critical individually, but so is the interaction between two. Here, spatial information is represented by a 2-dimensional circle along a 1-dimensional egocentric-allocentric axis. The extent to which the circle projects outward, orthogonally, from the egocentric-allocentric axis is intended to represent memory or knowledge that may not be specific to the environment being learned, like semantic (many cities are arranged in blocks or grids) or episodic memory (a car almost hit me when I crossed that street once). Thus, this conceptual model attempts to account for not only spatial information categorized from the "primary" reference frame, but also from the non-dominant reference frame and more abstract information like Bayesian priors or heuristics.

The model illustrates several important properties of how we encode and deploy spatial information, which can be impacted by (1) the encoding modality (e.g., routes or maps), (2) the strength or fidelity of the spatial information encoded (also partially dependent on the encoding modality), (3) the optimal reference frame used for solving a specific spatial memory task (note that none of these tasks can guarantee how participants will solve a retrieval task, rather only encourage selection of a desired, optimal solution), and (4) the ability to deploy prior knowledge and heuristics to make inferences using one reference frame when spatial information is encoded primarily from the other reference frame.

Here, we define heuristics as "up is north" (Brunye et al., 2012) or the well-described advantage that comes with remembering facing locations aligned with the axes of a rectangle compared to misaligned (e.g., Mou and McNamara, 2002; Starrett et al., in press). In the case of using rectangles as a heuristic, memory for the location of a target can be bound to the geometry of the rectangle, in that any points defined by its orthogonal distance to each side of the rectangle share the same principle axes relative to the environment. The selection of a singular, bipolar axis or two primary axes, akin to cardinal directions on a map, is consistent with how we often learn from and interpret maps and is thus a familiar and efficient way to remember any space with rectangular properties. In terms of our model, this would involve using information in denser areas or from other spatial representations to fill in less dense areas (**Figure 2**), perhaps temporarily while more high-fidelity information is acquired to establish that reference frame. In this way, our model helps explain several previously described phenomena in the human spatial navigation literature that lack a clear theoretical connection with egocentric vs. allocentric representation.

HOW EGOCENTRIC AND ALLOCENTRIC REPRESENTATIONS INTERACT WITH ENCODING MODALITY

Understanding the neural basis of egocentric and allocentric representations is an important research endeavor (for recent review, see Ekstrom et al., 2017). One important limitation inherent in most neural recordings from humans is that they have traditionally been limited to desktop interfaces, which lack many of the characteristics of real-world navigation. Namely, desktop VR does not provide idiothetic, self-motion cues because participants sit stationary, and desktop VR may introduce conflict between real-world and virtual allothetic cues. Even the rendering of optic flow, while still 3-dimensional, lacks the exact stereoscopic immersion of real-world experiences (see Snow et al., 2014). Specifically, in the context of navigation as a means for encoding spatial representations, the removal of such self-based information could fundamentally alter the neural processes and mechanisms being studied under such conditions relative to real-world (for review, see Taube et al., 2013). For example, desktop VR lacks true head-turns, resulting in little or no vestibular information during such navigation tasks. Vestibular lesions have been shown to significantly alter hippocampal theta oscillations in rats (Russell et al., 2006), an important neural signal related to spatial navigation, raising the possibility that the lack of head-direction input could fundamentally alter these codes. In humans, diminished vestibular information relative to real-world navigation may have downstream effects on other types of spatial processing neurons such as path cells, boundary-vector cells, or head-direction cells (Ekstrom, 2010; Jacobs et al., 2010; Taube et al., 2013).

To what extent does the lack of head-direction input limit the nature of spatial representations that can be assayed with desktop VR in humans? Invasive recordings of the hippocampus in humans, monkeys, and rats have all identified place cells, with Miller et al. (2013) showing that during later free recall of items associated with locations in a virtual environment, the same or nearby hippocampal place cells fired. These findings suggest that desktop VR, and even desktop presented stimuli in the absence of immersive scene information, do capture sufficient information to recapitulate neural codes from the real world. Notably, view-coding cells are also present in both monkeys and humans, suggesting a specific mechanism that could favor view-dependent, VR-based navigation (Ekstrom, 2015). Thus, the presence of place cells across modalities and species as well as view-coding mechanisms in primates, argue against the idea that the lack of explicit head-direction input during desktop VR somehow fundamentally changes how we code space during navigation.

Similarly, low-frequency, movement-related theta oscillations in the hippocampus, semi-periodic fluctuations in the local field potential that manifest during navigation, are present during desktop VR (Watrous et al., 2011, 2013; Bohbot et al., 2017), retrieval of spatial information (Ekstrom et al., 2007), encoding and retrieval of verbal associations (Sederberg et al., 2003; Yaffe et al., 2014), and during real-world navigation (Aghajan et al., 2017; Bohbot et al., 2017). One possibility is that the frequency of theta oscillations during real-world navigation in humans might be higher than VR, similar to higher frequency theta oscillations in rodents (Yassa, 2018). This in turn might seem to bolster the argument that VR and real-world navigation alter underlying neural representations (Aghajan et al., 2017). It is important to note, however, that the wireless hippocampal recordings used by Aghajan et al. (2017) could not detect oscillations below 4 Hz due to hardware-enforced, bandpass filtering. Indeed, Bohbot et al. (2017) used wired recordings during free ambulation and analyzed frequencies as low as 1 Hz, finding that low frequency oscillations were present across the range of 1–12 Hz, with only a slight difference in frequency across all electrode recordings for VR vs. real-world movements (see also Aghajan et al., 2017, Supplementary Figure 4 for examples from their wired recordings). Thus, low-frequency hippocampal theta oscillations, an important navigation-related neural signal, are present during a variety of immersed and non-immersed memory and navigation tasks to comparable extents, all of which appear sufficient to induce its presence.

If the lack of vestibular and other whole-body input did dramatically affect our underlying spatial codes, we might expect significant changes in how we learn environments with a full range of body-based cues compared to an impoverished set, such as navigating in desktop VR. Past behavioral studies have investigated these issues, with one early study suggesting that VR learning transfers only minimally to real-world environments (Kozak et al., 1993). A later study, however, by Richardson et al. (1999) only observed diminished performance when pointing tasks required participants to remember spatial relationships from different floors of a virtual building. One major issue with these early studies, however, is that VR technology was in its relative infancy and the complexity of visual displays and environmental geometry were relatively limited. With VR capturing real-world environments to only a limited extent, it is not surprising that transfer was minimal.

Recent experiments have begun to test learning in VR under a richer set of conditions than simply comparing desktop VR to real-world navigation, and in particular, the advent of the head-mounted display has allowed researchers to render complex visual environments as a participant freely ambulates within it. In one set of experiments participants had to search virtual birdhouses for a target. Importantly, they tested participants either while standing still and using a controller for rotations and translation, standing still but physically rotating while using a controller for only translations, or physically walking and turning. Results showed that physically walking and turning with the head-mounted display, i.e., the combination of vestibular, proprioceptive, and somatosensory information, significantly improved performance (Ruddle and Lessels, 2006, 2009) compared to the other conditions; thus, vestibular input, on its own, did not seem to be as important as the combination of multimodal cues.

More recently, Chrastil and Warren (2013) used a hedge-maze navigation task and assessed performance based on the later use of shortcuts to target locations. Participants learned the maze either by watching a video, being moved through the environment in a wheelchair, or by walking. Performance in the wheelchair condition, which provided rich vestibular information, was statistically equivalent to performance in the video condition, which was slightly above chance. In contrast, performance was better in the walking condition, which provided vestibular and proprioceptive input, than video condition. Other studies aimed at dissociating the contributions of proprioception (walking) and vestibular (turning) information have found that rotational information alone contributes minimally to performance on spatial estimates (Ruddle et al., 2011). While other studies have yielded conflicting results with regard to the importance of translational versus rotational body-based cues (see Chance et al., 1998), one common finding across these studies is that the full-range of multimodal body-based input seems to boost performance during navigation with the majority of findings suggesting that vestibular input alone is not necessary for the normal expression of spatial representations in humans. The question becomes even more complex when accounting for the plethora of ever-evolving interfaces used for immersive interaction with large-scale virtual environments, (head-mounted displays, CAVEs, omnidirectional treadmills), which introduce further nuances to the information available for encoding during spatial learning and should be considered when developing navigation and spatial learning paradigms (for a somewhat recent review, see Waller and Hodgson, 2013; see also: He et al., 2017; Paris et al., 2017; Starrett et al., in press).

While it is clear that there are some behavioral differences between learning with the full-range of body-based input vs. an impoverished set of cues, importantly, at least some of this may be attributable to memory-related effects (Tulving and Thomson, 1973). In other words, when we have a richer set of cues to encode information in the first place, we will benefit from these multiple cues during retrieval to a greater extent than when encoding and retrieval occur with a smaller number or different set of cues. A greater number of modalities also mean that different learning systems can work in parallel, providing the potential for faster learning. Thus, we believe that the evidence argues strongly against the idea that vestibular input is necessary for "normal" spatial navigation, by which we intend to say that navigation derived from visual input alone is largely sufficient for the types of modality independent spatial representations we form during navigation (see Waller and Hodgson, 2013). Nonetheless, vestibular (and other body based) cues clearly serve to enhance the fidelity of these representations (Klatzky et al., 1998). In this way, modality independent navigational representations can operate largely in the absence of vestibular cues, although such representations are more flexible and enriched in the presence of modality-dependent forms of representations involving vestibular and other body-based cues (Wolbers et al., 2011).

Another issue to consider is passive vs. active engagement with the environment. Past behavioral studies have provided mixed results regarding whether active navigation results in better performance on spatial tasks like map-drawing and shortcut-taking (Chrastil and Warren, 2012). Neurally, active engagement with stimuli alters neural codes in brain areas important to navigation and memory like the hippocampus (Voss et al., 2011). Even here, though, hippocampal mechanisms like pattern completion/separation (Stokes et al., 2015) still operate under conditions of passive navigation. It remains to be determined, then, the extent to which active vs. passive navigation significantly alters navigation-related neural coding in humans. Furthermore, while we have described how encoding modality might affect spatial representations more generally, exactly how it might differentially affect egocentric vs. allocentric representations both neurally and cognitively remains largely untested. We hope, however, that our discussions above, and **Figures 1**, **2**, will provide some possible theoretical predictions for testing these issues in the future.

CONCLUSION

To simplify the complexity of our considerations in cognitive neuroscience, it is often helpful to reduce the cognitive processes under consideration to more "elemental" ones, such as the frequently employed dichotomy in spatial navigation between egocentric vs. allocentric spatial information. As discussed above, however, we lack process pure measures of these codes, and must rely on tasks that are more likely to require one reference frame or the other for the optimal solution. To address this issue, we propose the RVD task that we believe utilizes more allocentric information than the commonly used JRD task. We then consider how encoding modality might influence egocentric and allocentric codes, and in particular, how we translate between them. We conclude that while studying human spatial navigation with ongoing neural recordings requires some compromise based on using fMRI/scalp EEG and desktop VR, with some expected changes in how these representations manifest, overall, these will not dramatically alter human navigation codes. Together, we hope the discussion provided here can provide useful considerations for research paradigms involving evaluating how spatial information will be acquired and deployed during encoding and retrieval from different modalities, such as desktop VR vs. real-world navigation.

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MS developed these perspectives under the supervision of AE. MS drafted the manuscript and AE provided critical revisions.

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Extrahippocampal Contributions to Age-Related Changes in Spatial Navigation Ability

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Age-related decline in spatial navigation is well-known and the extant literature emphasizes the important contributions of a hippocampus-dependent spatial navigation system in mediating this decline. However, navigation is a multifaceted cognitive domain and some aspects of age-related navigational decline may be mediated by extrahippocampal brain regions and/or systems. The current review presents an overview of some key cognitive domains that contribute to the age-related changes in spatial navigation ability, and elucidates such domains in the context of an increased engagement of navigationally relevant extrahippocampal brain regions with advancing age. Specifically, this review focuses on age-related declines in three main areas: (i) allocentric strategy use and switching between egocentric and allocentric strategies, (ii) associative learning of landmarks/locations and heading directions, and (iii) executive functioning and attention. Thus far, there is accumulating neuroimaging evidence supporting the functional relevance of the striatum for egocentric/response strategy use in older adults, and of the prefrontal cortex for mediating executive functions that contribute to successful navigational performance. Notably, the functional role of the prefrontal cortex was particularly emphasized via the proposed relevance of the fronto-locus coeruleus noradrenergic system for strategy switching and of the fronto-hippocampal circuit for landmark-direction associative learning. In view of these putative prefrontal contributions to navigation-related functions, we recommend future spatial navigation studies to adopt a systems-oriented approach that investigates age-related alterations in the interaction between the prefrontal cortex, the hippocampus, and extrahippocampal regions, as well as an individual differences approach that clarifies the differential engagement of prefrontal executive processes among older adults.

Keywords: spatial navigation, cognitive aging, associative learning and memory, executive functioning, prefrontal cortex

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INTRODUCTION

Spatial navigation ability is crucial for everyday living, allowing us to be cognizant of our position and orientation in our environment, as well as helping us to maintain a sense of direction when navigating to and from various locations (Wolbers and Hegarty, 2010; Chersi and Burgess, 2015). Even though spatial navigation seems effortless at the behavioral level, it is a multimodal activity that draws upon a multitude of cognitive and neural resources (Moffat, 2009, 2016; Wolbers and Hegarty, 2010; Wolbers, 2015; Zhong and Kozhevnikov, 2016; Lester et al., 2017). Numerous behavioral studies of spatial navigation in the cognitive aging literature have identified age-related declines or deficits in *navigation strategies* (Moffat and Resnick, 2002; Bohbot et al., 2012; Harris et al., 2012; Wiener et al., 2013; Harris and Wolbers, 2014; Colombo et al., 2017; Zhong et al., 2017), *associative learning/memory* (Head and Isom, 2010; Liu et al., 2011; Wiener et al., 2012, 2013; Zhong and Moffat, 2016; Allison and Head, 2017; O'Malley et al., 2018), and *working memory* (Mahmood et al., 2009; Taillade et al., 2013a,b, 2016; Ariel and Moffat, 2018). Complementary neuroimaging studies that investigated age-related declines in spatial navigation performance and memory have largely linked them to age-related reduction in the volume or activation of the hippocampus (e.g., Driscoll et al., 2003, 2005; Astur et al., 2006; Moffat et al., 2006, 2007; Antonova et al., 2009; Yuan et al., 2014; Daugherty et al., 2015, 2016), a region that has long been proposed as the neural basis of a "cognitive map" (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978).

Notwithstanding the pertinence of the hippocampus for spatial navigation, the complexities of navigation-related cognition and behavior cannot be traced to one region alone, and the functional relevance of extrahippocampal brain regions should not be minimized (Doeller et al., 2008; Chersi and Burgess, 2015). Navigationally relevant extrahippocampal regions encompass the striatum, the prefrontal cortex, the parietal cortex and the retrosplenial cortex (RSC; see Moffat et al., 2006, 2007; Moffat, 2009, 2016; Wolbers and Hegarty, 2010; Wolbers, 2015; Lester et al., 2017). Moreover, navigation depends on the contributions of cognitive domains/brain systems that are not specifically navigation-related (e.g., working memory, attention, motor control, etc.) and age differences in these cognitive domains may contribute to and manifest as deficits in navigation tasks. With advancing age, spatial learning and navigational performance start to become more dependent on extrahippocampal regions instead of the hippocampus *per se* (Moffat et al., 2006, 2007; Lester et al., 2017). With a focus on extrahippocampal regions and processes, the current review presents an overview of some key cognitive domains of spatial navigation that are adversely affected by normal aging and relates them to changes in the functional integrity of both hippocampal and extrahippocampal regions. To facilitate organization, we surveyed the literature on aging and navigation strategies and associative learning before turning to a discussion of other processes that are generally executive in nature and largely dependent on the prefrontal cortex. We acknowledge the inherently complex nature of spatial navigation and do not intend to suggest that these cognitive processes and the sections herein are mutually exclusive. **Table 1** shows a summary of the main cognitive aging studies covered by this review and the cognitive domains and brain systems investigated or discussed.

NAVIGATION STRATEGIES AND STRATEGY SWITCHING

A major theme in the discussion of spatial navigation pertains to navigation strategies, which commonly take the form of mental imagery techniques that require the primary engagement of an egocentric (i.e., first-person) or allocentric (i.e., third-person) frame of reference (see, e.g., Zhong and Kozhevnikov, 2016; He and McNamara, 2018; McCunn and Gifford, 2018; see also Colombo et al., 2017; for a review). While an egocentric navigation strategy requires the moving agent to visualize scenes and gauge self-to-object relationships from a body-centered viewpoint, an allocentric navigation strategy requires the agent to visualize scenes and map out object-to-object relationships from a disembodied or environment-centered viewpoint (Zhong and Kozhevnikov, 2016; Colombo et al., 2017; see also Klatzky, 1998). Previous neuroimaging work by Iaria and colleagues (based on samples of young adults) showed double dissociation between allocentric and egocentric/response strategies, with activation in the hippocampus corresponding with the former (Iaria et al., 2003, 2007), and activation in the caudate nucleus/striatum corresponding with the latter (Iaria et al., 2003). An alternative egocentric spatial strategy, requiring the tracking and spatial updating of movements away from a point of origin during path integration (Loomis et al., 1999; Mahmood et al., 2009; Wiener et al., 2011; Zhong and Kozhevnikov, 2016), depends on the stability of grid cell firing patterns in the entorhinal cortex of both humans (Stangl et al., 2018) and mice (Gil et al., 2018). Following the thematic emphasis on extrahippocampal functions, this review shall not discuss age differences in path integration that are contingent on entorhinal or hippocampal functions (see Mahmood et al., 2009; Wiener et al., 2011; Harris and Wolbers, 2012; Stangl et al., 2018), but on age differences in non-spatial egocentric/response strategy use.

In the cognitive aging literature, the proportion of older adults preferring an egocentric/response strategy for wayfinding has been shown to be higher than the proportion of younger adults preferring the same strategy (Bohbot et al., 2012; Rodgers et al., 2012; Wiener et al., 2013). For instance, in a virtual Y-maze that can be solved by either an egocentric/response (i.e., traversing the same route learned during training irrespective of the absolute location of the goal) or allocentric (i.e., judging the absolute location of the goal area relative to the origin regardless of the learned route) strategy, Rodgers et al. (2012) found that the great majority of older adults (83%) preferred the egocentric/response strategy whereas younger adults' preferences were relatively evenly divided between egocentric (46%) and allocentric (54%) strategies. Similar, but less striking statistics were also reported by Bohbot et al. (2012) in a study involving a virtual radial-arm maze task. In this task, egocentric/response strategy use involved counting the number of arms from the origin to find the goal objects at the end of different radial arms, whereas allocentric strategy use involved the use of surrounding cues to judge the locations of the goal objects. Post-test surveys showed that most older adults (60.7%) reported preferring an egocentric/response strategy while younger adults' preferences were more evenly divided between egocentric (53.7%) and allocentric (46.3%) strategies.

Older adults' lower preference for the allocentric strategy can be traced to fMRI studies comparing both young and

TABLE 1 | Main cognitive aging studies that investigated and/or discussed extrahippocampal cognitive domains in spatial navigation.

Extrahippocampal cognitive domain	Study	Brain region/system involved or implicated	Regional activation: Old > Young	Regional activation: Young > Old
Egocentric/response-based navigation strategy use	Antonova et al. (2009) Bohbot et al. (2012) Harris et al. (2012) Harris and Wolbers (2014) Iaria et al. (2003) Konishi et al. (2013) Konishi and Bohbot (2013) Rodgers et al. (2012) Schuck et al. (2015) Wiener et al. (2012, 2013) Zhong et al. (2017)	Striatum/caudate nucleus Hippocampal-striatal circuitry	✓ (see Konishi et al., 2013; Schuck et al., 2015)	
Switching between allocentric and egocentric/response strategies	Harris et al. (2012) Harris and Wolbers (2014)	Locus coeruleus Fronto-locus coeruleus noradrenergic system Fronto-hippocampal circuitry	N.A.	N.A.
	Moffat et al. (2006)	Retrosplenial cortex (BA 29/30)		✓ (in BA 29, see Moffat et al., 2006)
Associative learning/memory	Allison and Head (2017) Head and Isom (2010) Liu et al. (2011) O'Malley et al. (2018) Wiener et al. (2012, 2013) Zhong and Moffat (2016)	Dorsolateral striatum Fronto-hippocampal circuitry	N.A.	N.A.
Executive functioning and attention	Ariel and Moffat (2018) Dowiasch et al. (2015) Driscoll et al. (2005) Hartmeyer et al. (2017) Merriman et al. (2018) Moffat and Resnick (2002) Moffat et al. (2006, 2007) Szturm et al. (2017) Taillade et al. (2013a,b, 2016)	Medial prefrontal cortex (BA 9/10)	✓ (in BA 10, see Moffat et al., 2006)	

Note. The listed studies involved both young and older human participants. Studies showing comparatively higher activation in a specific brain region in one age group over the other are indicated by relevant check marks. "N.A." denotes "not applicable" for the studies of strategy switching and associative learning without published neuroimaging findings.

older subjects in navigating virtual environments; these studies generally showed that older adults have either reduced (Meulenbroek et al., 2004; Moffat et al., 2006; Konishi et al., 2013) or absent activation (Antonova et al., 2009) in the hippocampal formation. Lower allocentric strategy use among the older adults could also be attributed to smaller hippocampal volumes in older than younger adults, which in turn may undermine older adults' accuracy in spatial learning and navigational performance (Driscoll et al., 2003; Moffat et al., 2007; Konishi and Bohbot, 2013; Yuan et al., 2014; Daugherty et al., 2015). By contrast, when searching for previously encoded goal locations in virtual environments, increased activation in the striatum (mainly the caudate nucleus) was found among older egocentric/response strategy users (Konishi et al., 2013), and when older adults were focused on processing local landmark information as compared to processing allocentric boundary information (Schuck et al., 2015). This elevated striatal activity reflected a change in information processing in the hippocampal-striatal circuitry with advancing age—with spatial learning and performance in older adults being more associated with the striatum, as well as with the prefrontal cortex (Moffat et al., 2006, 2007), than with the hippocampus (Moffat et al., 2007; Konishi et al., 2013; Schuck et al., 2015). Consequently, increased engagement of the striatum, complemented by decreased engagement of the hippocampus, may offer a credible source of support for explaining older adults' "egocentric bias" in strategy use.

Another approach to understanding why older adults find it easier to implement egocentric/response strategies was performed by Harris and colleagues (Harris et al., 2012; Harris and Wolbers, 2014). In their studies, the researchers applied a virtual plus maze that allowed flexibility in configuring goal locations and the paths of travel. Egocentric/response strategy use involved making repetitive turning responses regardless of the whereabouts of the goal, whereas allocentric strategy use involved judging the absolute location of the goal regardless of the turning responses. Older adults attained comparable performance as the young when implementing the egocentric/response strategy but became less accurate when implementing the allocentric strategy (Harris et al., 2012). Crucially, the decline in search accuracy, as well as in the number of trials learning and implementing a specific strategy, were most prominent after the older adults were instructed to switch to allocentric strategy use from previous egocentric/response strategy use (Harris et al., 2012). This egocentric-to-allocentric strategy switching deficit further applied to finding shortcuts when navigating a larger virtual town (Harris et al., 2014). Unlike the young adults who overwhelmingly reported the consistent use of shortcuts or switching to shortcuts at some time during testing, none of the older adults did so. Instead, three-quarters of the older adults reported using shortcuts inconsistently and the remaining quarter reported the consistent use of an egocentric route strategy. A re-administration of the virtual plus maze with a smaller number of trials showed that older adults' search accuracy declined significantly (relative to younger adults) when they were attempting allocentric-to-egocentric strategy switches, suggesting an impairment in making allocentric-to-egocentric spatial transformations could also apply to older adults.

These observed deficits in strategy switching were suggested to represent an age-related degradation of the axonal circuitry in the prefrontal cortex (Pfefferbaum et al., 2005; as cited in Harris and Wolbers, 2014), and/or an age-related dysregulation of noradrenaline production and function along the anatomical pathways linking the locus coeruleus to the prefrontal cortex (Harris et al., 2012; Harris and Wolbers, 2014). Moreover, it was speculated that an age-related reduction of the functional connectivity between the prefrontal-noradrenergic network and the hippocampus may specifically account for the egocentric-to-allocentric strategy switching deficit (Harris et al., 2012; Harris and Wolbers, 2014). As for the allocentric-to-egocentric strategy switching deficit, the researchers did not associate it with the potential degradation in prefrontal-hippocampal connectivity but instead associated it with dysfunction within the noradrenergic system linking the prefrontal cortex and the locus coeruleus (Harris and Wolbers, 2014). The locus coeruleus is strongly implicated in strategy switching in view of its tonic and phasic outputs of noradrenaline to the prefrontal cortex (Aston-Jones and Cohen, 2005). Specifically, it has been proposed that tonic locus coeruleus-noradrenergic activity facilitates disengagement from a current behavior and the selection of alternative behavior (Aston-Jones and Cohen, 2005), whereas phasic locus coeruleus-noradrenergic activity promotes the adoption of behavioral alternative(s) and the organization of functional neural networks for tackling specific tasks (Aston-Jones and Cohen, 2005; Bouret and Sara, 2008).

Worthy of extra consideration was that older adults' difficulties with bidirectional switching between egocentric and allocentric strategies might be attributed to lower activation in the RSC (i.e., when encoding spatial information regarding the relative locations of landmarks, see Moffat et al., 2006, **Table 1**). This relates well to proposals of the RSC as being involved in translating between egocentric and allocentric reference frames (Maguire, 2001; Byrne et al., 2007; Vann et al., 2009; Mitchell et al., 2018), and in mediating between different spatial representations and modes of processing (Mitchell et al., 2018). Recent studies supported these proposals by showing that the RSC is crucial for: (a) judging egocentric views of target objects from rotated viewpoints that require the retrieval of allocentric spatial information (Sulpizio et al., 2016), and (b) the implementation of allocentric reference frames for integrating egocentric heading directions across separate locales (Shine et al., 2016).

Furthermore, using multi-voxel pattern analysis (MVPA), Marchette et al. (2014) showed that RSC activity patterns were similar when participants faced similar directions or imagined similar locations across four virtual museums that are geometrically similar but separated perpendicular to each other in global space. Reaction times were also faster for homologous/matching directions and locations than for non-matching directions and locations both within and across museums. Interestingly, these findings offer an alternative view of the RSC as being involved in anchoring internal spatial representations to local topographical features. However, Marchette et al. (2014) did not assess the extent to which their participants integrated local spatial representations into a global schematic map of the environment, and thus there remains the possibility (as pointed out by the authors) that the so-called "local" spatial representations of some participants could be environment-centered in nature, encompassing the spatial relationships between all landmarks imaginable. Interestingly, Mitchell et al. (2018) did not regard these findings as refuting the proposed role of the RSC in mediating between spatial reference frames and suggested that there may be RSC cells that are separately responsible for local/egocentric and global/allocentric orientation.

ASSOCIATIVE LEARNING

In addition to the challenges faced by older adults in implementing allocentric navigation strategies and switching between strategies, they also experience difficulties with the association of the correct heading directions (to goal) with landmarks or locations at which directional changes are required (Head and Isom, 2010; Liu et al., 2011; Wiener et al., 2012, 2013; Zhong and Moffat, 2016; Allison and Head, 2017; O'Malley et al., 2018). Specifically, older adults have been found to be less competent than younger adults at selecting correct headings or turns at intersections (Wiener et al., 2012, 2013; Zhong and Moffat, 2016), especially when approaching intersections from directions that are reversals of the directions encountered during route learning (Wiener et al., 2012, 2013). Notably, Wiener et al. (2013) showed that older adults' difficulties with finding the correct heading direction when traveling the route in reverse were associated with older adults' implementation of an associative cue strategy (i.e., "Turn left/right at"), and proposed that this strategy engaged the dorsolateral striatum.

Also noteworthy are the findings by Zhong and Moffat (2016), which showed that older adults exhibited a landmark-direction associative memory deficit at intersections, inasmuch that older adults performed poorer than younger adults at associating correct/goal-directed heading directions with varying views of landmarks at intersections but did *not* perform poorer than younger adults when tested on the recognition memory of landmarks alone. The authors speculated that this selective deficit in "binding" landmark and directional information was related to senescent changes in the fronto-hippocampal circuitry

(Li et al., 2001, 2005), as characterized by degraded functional connectivity between the prefrontal cortex and the hippocampus in older adults (Grady et al., 2003). Interestingly, this proposed involvement of the fronto-hippocampal circuitry in forming landmark-direction associations parallels the relevance of the same system in making successful egocentric-to-allocentric strategy switches (Harris et al., 2012; Harris and Wolbers, 2014).

EXECUTIVE FUNCTIONING AND ATTENTION

The proposed involvement of the prefrontal cortex in both navigation-related associative learning and strategy switching necessitates a closer look at its relevance for spatial navigation. When navigating towards a specific goal location, the prefrontal cortex mediates many goal-directed processes (Spiers, 2008). Spontaneously thinking about the goal location and the best route or path to reach it have been shown to be related to increased activity in the anterior prefrontal cortex (BA 10), the dorsomedial prefrontal cortex (BA 9; in middle-aged London Taxi drivers, Spiers and Maguire, 2006, 2007), and the ventrolateral prefrontal cortex (in a college-aged sample, Carrieri et al., 2018). On the other hand, the ventromedial prefrontal cortex has been related to maintaining the intention to reach the goal in working memory and suppressing irrelevant information [as suggested by Spiers (2008), based on evidence from a patient with ventromedial prefrontal damage documented by Ciaramelli (2008)], and exerting top-down control in mediating between a hippocampus-dependent boundary processing strategy and a striatum-dependent landmark-based strategy (in a college-aged sample, Doeller et al., 2008).

When comparing young and older adults in learning the spatial layout of a virtual environment from self-directed navigation, Moffat et al. (2006) showed that older adults exhibited higher activations in the medial frontal gyrus (BA 10; see **Table 1**) and the anterior cingulate gyrus than younger adults, whereas younger adults exhibited higher activations than older adults in the hippocampal formation and posterior extrahippocampal areas such as the RSC, parietal cortex (i.e., inferior parietal lobule, precuneus) and angular gyrus. The authors suggested that these findings reflected a potential age-related compensatory shift in spatial memory performance toward anterior frontal systems away from medial temporal and posterior brain systems.

Notably, the authors also considered the possibility that the higher frontal activations of older adults could simply reflect age group differences in performance, since the older adults made slower virtual movements and more errors when recalling landmark locations. This alternative view relates well to other findings showing that older adults performed poorer than younger adults *even on the first trial* of a virtual Morris water maze (vMWM) when either group had no prior knowledge of the hidden platform's location (Moffat and Resnick, 2002; Driscoll et al., 2005; Moffat et al., 2007). This suggests that older adults may possess impaired executive or strategic functions that are mediated by frontal areas at the outset of a navigational task (Moffat, 2009). Maintaining a high integrity of prefrontal gray and white matter in old age may help to attenuate or offset such executive declines, as greater volumes of lateral prefrontal gray matter and white matter have been shown to correlate positively with accurate vMWM search performance in in the first trial and onwards (Moffat et al., 2007). These findings corresponded well with additional findings showing robust negative associations between perseverative errors from the Wisconsin Card Sorting Test and vMWM search accuracy, reinforcing the proposed role of the prefrontal cortex in mediating successful navigational/search performance (Moffat et al., 2007).

In addition, recent findings by Ariel and Moffat (2018) showed that older adults attained lower metacognitive confidence judgments than younger adults in a cognitive mapping task, and that these confidence judgments mediated the relationship between age and allocentric strategy use. As the prefrontal cortex has been widely implicated as the neural basis of metacognition (see Fleming and Dolan, 2012), these findings suggest that the differential engagement of prefrontal processes in metacognition could partially account for robust age-related differences in allocentric strategy use.

Furthermore, it is important to acknowledge the effects of motor control on age-related differences in navigational performance, particularly in virtual environments. When navigating virtual environments, older adults have been observed to move more slowly when completing learning trials than younger adults (e.g., Driscoll et al., 2005; Moffat et al., 2006; Taillade et al., 2013a). This has been dealt with by using movement speed or some motion-related variables as covariates (e.g., Moffat et al., 2001, 2006; Zhong et al., 2017). While important, this only partially addresses potential qualitative effects of motor control on older adults' navigational performance. This is because older adults' slower movements effectively increase the delay or retention intervals across learning trials, and sets up dual tasking scenarios (e.g., attending to stimuli on screen and manipulating the control device simultaneously) for older adults that may not necessarily apply to younger adults. More specifically, prefrontal executive resources have been shown to be vital for older adults in mediating the dual task demands of visual and motor processing (Taillade et al., 2013a), as well as in supporting gait (Szturm et al., 2017). Declines in these functions may thus predispose older adults to slower movements and poorer cognitive performance in both virtual (Taillade et al., 2013a,b, 2016; Szturm et al., 2017) and real-world (Taillade et al., 2016) environments.

Together with these concerns, age-related executive declines have also been suggested to adversely affect the allocation of attentional resources (Hartmeyer et al., 2017; Merriman et al., 2018). Specifically, older adults were slower than younger adults in responding to auditory probes at intersections when simultaneously deciding on the correct heading directions to take, especially when turning movements were required (Hartmeyer et al., 2017). Older adults were also distracted by crowds of moving pedestrians and demonstrated lower accuracy in finding the correct heading directions at intersections in the presence of such crowds (Merriman et al., 2018). This susceptibility to distraction in the presence of other moving agents may have been brought about by a corresponding age-related reduction in goal-tracking eye movements or saccades (Dowiasch et al., 2015).

Overall, it is important to understand the challenges older adults experience under dual task and attention-demanding scenarios because such knowledge will invariably inform future efforts at investigating how such challenges can be managed or ameliorated.

SUMMARY AND FUTURE DIRECTIONS

Taken together, this survey of spatial navigation studies in the cognitive aging literature suggests a shift away from hippocampal engagement toward increased engagement of extrahippocampal areas, notably the striatum and the prefrontal cortex, with advancing age. While extant neuroimaging studies have provided reliable findings showing that an increased engagement of the striatum, coupled with reduced engagement of the hippocampus, could account for older adults' egocentric/response strategy use (Konishi et al., 2013; Schuck et al., 2015), the findings concerning age-related deficits in strategy switching (Harris et al., 2012; Harris and Wolbers, 2014), and landmark-direction associative learning (Zhong and Moffat, 2016) were behavioral in nature and speculative. It thus remains unknown as to whether dysfunctions in the fronto-hippocampal and the fronto-locus coeruleus circuits (as implicated in associative learning and strategy switching) would indeed be related to age-related declines in navigational ability. It is also possible that dysfunctions in these circuits would adversely affect navigational ability regardless of age and they may be *essential* for successful navigation. Moreover, we do not yet know whether the association of landmark and directional information is distinct from the association of other types of information (e.g., paired word associates, name-picture pairs, see Cabeza and Dennis, 2012). It thus remains possible that the brain systems related to the associations of these different pieces of information may be dissociable. Further investigations are definitely needed to clarify all these possibilities.

In addition, considering the importance of the prefrontal cortex for strategy switching, associative learning and mediating executive functions, future spatial navigation studies can take a system-oriented approach that investigate the interaction between prefrontal cortex, the hippocampus, the striatum, and/or other navigationally relevant regions (e.g., the RSC and precuneus; see, e.g., Brown et al., 2012; Sherrill et al., 2013; Chrastil et al., 2017) in both young and older adults. Most likely, this endeavor will present a broader picture of how age-related changes in prefrontal activity mediates or coordinates corresponding changes in activities in both hippocampal and extrahippocampal regions during spatial navigation.

Finally, it may also be important to clarify the significance of increased prefrontal activity in older adults during spatial navigation. Specifically, *does higher (pre)frontal activation in older adults represent an adaptive (or maladaptive) compensation mechanism among older adults?* (cf. Grady et al., 1994; Gutchess et al., 2005). To address this question, further investigations can adopt an individual differences approach when assessing older adults, as some recent studies have demonstrated that older adults with relatively high cognitive functions (O'Malley et al., 2018) or intact spatial learning ability (Zhong et al., 2017) can perform as well as younger adults in virtual navigation tasks. Consequently, the separate analysis of frontal activation profiles of older adults with differential levels of navigational performance or strategy preference shall provide greater insight into how older adults engage navigationally relevant executive processes.

AUTHOR CONTRIBUTIONS

JZ and SM conceived the framework for the review. Both authors conducted literature review and drafted the manuscript. Both authors edited the manuscript and finalized it for publication.

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Virtual Orientation Overrides Physical Orientation to Define a Reference Frame in Spatial Updating

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Previous studies showed that people could use either an egocentric or allocentric reference frame in spatial updating with body-based cues (i.e., physical body movements), but the adopted reference frame was anchored by the physical egocentric front when body-based cues were constrained. A recent study (He et al., 2018) showed that even without body-based cues, the orientation participants initially faced in the virtual environment (VE; initial heading) could be used to establish a reference frame, suggesting that the physical egocentric front could be overridden by a virtual orientation. In the current project, we aimed to: (a) replicate He et al.'s (2018) finding; (b) examine when the reference frame defined by the virtual initial heading was established; and (c) investigate the cognitive processes in establishing the initial heading as a reference frame. In four experiments, we were able to replicate the previous findings and found that the reference frame defined by the initial heading was established during spatial updating. More importantly, the reference frame defined by the initial heading was egocentric and participants did not need to know the orientation of their initial heading at the beginning of spatial updating to be able to use it. We discuss the cognitive processes of reference frame selection in spatial updating when body-based cues are absent.

Keywords: spatial navigation and memory, spatial updating, spatial reference systems, virtual reality, idiothetic cues

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INTRODUCTION

Spatial navigation is a ubiquitous and an important task in daily life. In a familiar environment with distinct landmarks, navigators can use these landmarks as beacons or associative cues (Waller and Lippa, 2007) to find their way. In an unfamiliar environment, however, navigators have not associated landmarks with locations of interest and spatial updating plays an important role in maintaining orientation (Gallistel, 1990). Spatial updating is a cognitive process that involves continuously computing the spatial relations between the navigator and objects in the environment as the navigator moves (Rieser, 1989; Amorim and Stucchi, 1997; Amorim et al., 1997; Farrell and Robertson, 1998). These computations must be implemented within a spatial frame of reference.

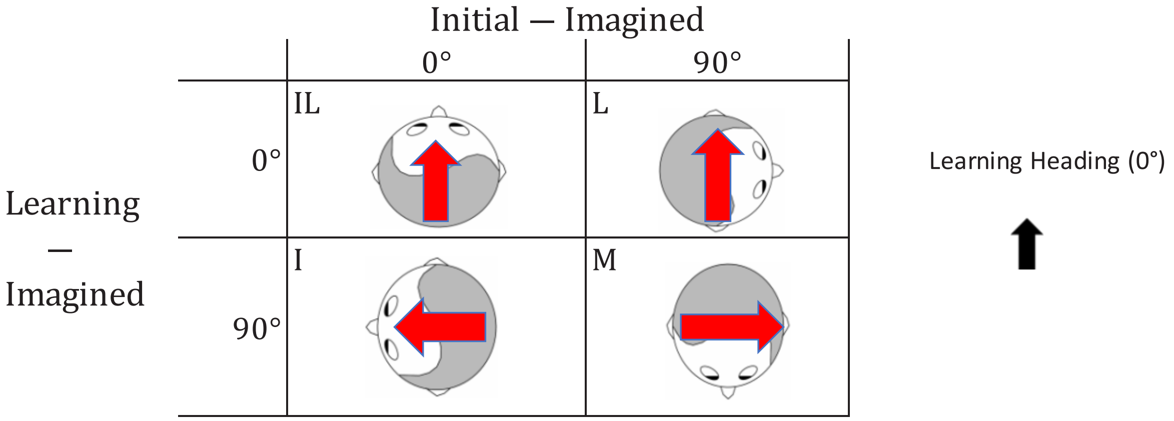
For the purposes of understanding spatial updating, spatial reference systems are typically divided into two categories (e.g., Klatzky, 1998): egocentric, or body-centered, and allocentric, or environmentally-centered. In spatial updating in an egocentric reference frame, or egocentric spatial updating, the navigator updates each object's location with respect to the body using a reference system centered on the body and typically defined by the reference directions of front, back, right and left (e.g., Wang, 2016). In contrast, in spatial updating in an allocentric reference frame, or allocentric spatial updating, the navigator updates his or her position in the environment using a reference system external to the body and anchored in the environment (e.g., using canonical directions of north, south, east, or west; Gallistel, 1990).

Previous studies have indicated that humans can use an egocentric or an allocentric reference frame for spatial updating, depending on the nature of the environment and complexity of the path, if they can physically locomote in the environment (e.g., Waller et al., 2002; Mou et al., 2004; Hodgson and Waller, 2006; Wang et al., 2006; Kelly et al., 2007). However, the reference frames used in spatial updating seem to be more constrained when body-based cues to locomotion (e.g., proprioceptive, vestibular, efferent information) are absent. Performance in imagined spatial updating deteriorates with the angular disparity between the participant's physical facing direction and the imagined facing direction (e.g., Rieser, 1989; Farrell and Robertson, 1998). Similarly, Klatzky et al. (1998) found that participants failed to update their heading in a triangle completion task if they could not rotate their bodies (see also, Chance et al., 1998). Results such as these indicate that the reference frame in spatial updating without body-based cues to locomotion is determined by the physical orientation of the navigator's body.

An important feature of Klatzky et al.'s (1998) study is that the virtual environment (VE) used in the critical "visual-turn" and "real-turn" conditions did not have environmental cues to orientation (by design). Spatial updating seems to be somewhat more efficient in complex, feature-rich environments, even when body-based cues are limited (e.g., Riecke et al., 2002; Ruddle et al., 2011; Chrastil and Warren, 2013). Such findings indicate that the reference frame used in spatial updating may not always be fixed by the navigator's physical orientation. Developing a better understanding of spatial updating in the absence of body-based cues to self-motion is important because such paradigms are required in most neuroimaging investigations of human spatial orientation and navigation even though their external validity has been questioned (e.g., Taube et al., 2013).

In a recent project (He et al., 2018; see also, He et al., 2017), we conducted two experiments that were designed to reveal the spatial reference systems used during navigation in a familiar, feature-rich environment when body-based cues were limited. Participants first learned a layout of objects from a single perspective (learning heading) in a VE. Participants then were placed in the same VE and navigated to two of the learned objects before pointing to a third object. Because the navigation was implemented by keyboard and participants were required to maintain a fixed body orientation throughout the task, body-based cues were reduced to a minimum He et al. (2018, Experiment 1) observed that when the imagined heading for pointing judgments was misaligned with the original learning heading, pointing performance was better if the imagined heading was aligned with the initial heading (the facing direction in the VE at the start of navigation; Condition I in **Table 1**) than if the imagined heading was misaligned with the initial heading (Condition M in **Table 1**). Because the axis of the initial heading (**Table 1**, human figures) was different from that of the physical and learning headings (**Table 1**, black arrow) in these conditions, this finding suggested that the physical egocentric front could be overridden, at least to some extent, by a virtual heading. In the current project, we aimed to replicate

TABLE 1 | Design of the experiments in He et al. (2018) and the current study.



Notes: the learning heading (black arrow to right) was 0° in all conditions. The initial heading corresponded to the facing direction in the virtual environment at the beginning of navigation, indicated by the orientation of the human figure. The imagined heading corresponded to the heading in the virtual environment from which participants made their pointing judgments, indicated by the orientation of the red arrow. In the present experiments, the imagined heading was the same as the facing direction in the virtual environment at the end of navigation, or final heading. Differences in headings are absolute values. The letters in each cell identify the experimental conditions: IL is the condition in which the imagined heading (= final heading) is aligned with the initial heading and the learning heading. L is the condition in which the imagined heading is aligned with the learning heading but misaligned with the initial heading. I is the condition in which the imagined heading is aligned with the initial heading but misaligned with the learning heading. M is the condition in which the imagined heading is misaligned with both the learning heading and the initial heading.

this finding, investigate the nature of this reference frame, and investigate the cognitive processes involved in producing this effect[1].

At least two important questions were left unanswered by He et al.'s (2018) study. The first question is when the reference frame defined by the initial heading was established. In He et al.'s (2018) study, the virtual room was square and participants could have used the 0° ↔ 180° axis or the 90° ↔ −90° axis (or both) to organize the object-to-object spatial relations (e.g., Rump and McNamara, 2013). Because the initial heading was parallel to the 90° ↔ −90° axis in that study, it was possible that the initial heading effect would only be observed when the initial heading had been used to represent object-to-object spatial relations at the time of learning; that is, when it corresponded to a reference direction established during learning. If the initial heading effect occurred under conditions in which it was not likely to have been used as a reference direction at the time of learning, we would have evidence that the corresponding reference direction was established during spatial updating.

A second question is the way in which participants utilized the initial heading for memory retrieval. He et al. (2018) hypothesized that at the beginning of a navigation trial, participants reconstructed in working memory the layout of objects from the perspective corresponding to the initial heading. This representation functioned similarly to the representation formed at the time of learning, and hence, pointing performance benefited when the imagined/final heading was parallel to the initial heading or to the learning heading (there was no additional benefit for an imagined heading aligned with both; see Mou et al., 2004). This explanation is predicated on the assumption that participants know their allocentric orientation at the beginning of a navigation trial. In the current project, we tested He et al.'s (2018) explanation by eliminating all cues to allocentric orientation at the beginning of the navigation trial.

Three experimental paradigms have been used to examine reference frames in spatial memory and navigation: (a) one paradigm involves comparing performance across various actual and imagined headings (e.g., Waller et al., 2002; Mou et al., 2004; Kelly et al., 2007). (b) A second paradigm compares configuration error before and after disorientation (e.g., Wang and Spelke, 2000; Mou et al., 2006; Xiao et al., 2009). Configuration error is a measure of the internal consistency of errors of pointing to objects. (c) The third paradigm examines performance as a function of the complexity of the environment (e.g., Hodgson and Waller, 2006; Wang et al., 2006). The present study used the first approach. This approach is founded on four pre-theoretical assumptions and one theoretical claim. The pre-theoretical assumptions are (see also, Klatzky, 1998): (a) spatial relations that are represented in memory can be retrieved from memory; (b) spatial relations that are not represented in memory must be inferred; (c) retrieval is computationally simpler than is inference; and (d) mental work produces costs in performance. The theoretical claim is that (e) object-to-object spatial relations are represented in memory in terms of one or more reference directions at the time of learning. For example, the angular direction from object A to object B might be represented relative to a reference direction parallel to the learning heading (e.g., Mou et al., 2004; Rump and McNamara, 2013). Based on these assumptions, actual or imagined headings that produce facilitated performance in pointing or perspective-taking tasks are assumed to correspond to reference directions in a spatial reference system.

In the current project, we followed the procedures of He et al.'s (2018) study and compared performance across different imagined headings to determine which headings were established as reference directions (**Table 1**). Participants learned a layout of objects from a heading of 0° (the learning heading) in a VE. After learning, they used a keyboard to navigate sequentially to two of the learned object locations. The initial heading (the heading that participants faced in the VE the beginning of navigation) and the imagined heading (which was the same as the final heading in the VE after reaching the second object) varied across experimental conditions. As a result, the alignment between the imagined heading and the learning heading, and the alignment between the imagined heading and the initial heading were manipulated to test the learning and initial heading effects, respectively (**Table 1**). The purpose of Experiment 1 was to replicate He et al.'s (2018) study to ensure that the findings were reliable.

The purpose of Experiment 2 was to reduce the likelihood that the 90° ↔ −90° axis would be used as a reference direction at the time of learning. Previous research has shown that people can use the 0° ↔ 180° axis (corresponding to the learning heading) and the orthogonal axis, 90° ↔ −90°, to establish reference directions when they learn a layout of objects in square or rectangular spaces (e.g., Shelton and McNamara, 1997, 2001; Mou and McNamara, 2002). However, if the room is cylindrical, the 90° ↔ −90° axis is much less likely to be established as a reference direction (e.g., Mou and McNamara, 2002; Experiment 3; Shelton and McNamara, 2001, Experiment 6). By rendering the room geometry as a circle and observing whether the initial heading effect still persisted, we hoped to determine when the reference frame defined by the initial heading was established.

In Experiment 3, we removed all orientation cues at the beginning of navigation so participants could not know their location or orientation. This manipulation was designed to discourage participants from imagining the layout at the beginning of the navigation trial. If the initial heading effect still persisted, this finding would suggest that the virtual initial heading could override the physical egocentric front, similar to the automatic spatial updating when full body-based cues are available (e.g., Farrell and Robertson, 1998; May and Klatzky, 2000).

Although we controlled the path complexities across experimental conditions, it was still possible that differences in the trial composition across experimental conditions produced the initial heading effect. For example, the object-to-object spatial relations could be more complex in the M condition

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[1] In the present experiments, the imagined heading was the same as the final heading at the end of navigation. These headings need not be the same, however, and were different in Experiment 2 of He et al. (2018).

than in the I condition, leading to inferior performance in the M condition. To test this possibility, in Experiment 4, participants performed a judgment of relative direction task (JRD; e.g., "Imagine you are standing at the cup, facing the plant, and point to the fish".) instead of navigating to objects and then pointing. The JRD task involved no spatial updating or navigation. If the initial heading effect observed in He et al.'s (2018) study were caused by differences in object-to-object spatial relations, then we would observe similar patterns of results in Experiment 4 as in the other experiments. Otherwise, the performance in the I and M conditions should be comparable when the task was switched to JRD.

The sample size of the current study was determined by a power analysis based on He et al.'s (2018, Experiment 1) data. The effect size was above 0.80 in the key comparison (I condition vs. M condition) and the observed power was above 0.95 with a sample size of 24 participants. Due to the large effect size, we considered that a sample size of 24 participants should reach a statistical power no smaller than 0.80 and therefore recruited 24 participants for each experiment except for Experiment 3 (for reasons explained in the "Results" section in Experiment 3).

To anticipate our results, the results of the current study replicated the initial heading effect, and showed that the initial heading effect could also be induced in a circular enclosure and without any orientation cues at the beginning of navigation. In addition, the initial heading effect could not be attributed to the differences in trial composition across experimental conditions.

EXPERIMENT 1

Method

Participants

Twenty-four students (12 women) from Vanderbilt University and the Nashville community participated in this experiment in return for extra credit in psychology courses or monetary compensation.

Materials and Design

The experiment was conducted on a 21.5-inch Apple iMac Desktop computer. The VE (**Figure 1**) consisted of eight virtual objects (dog, ball, cup, fish, car, lamp, plant and shoe) placed on identical red pillars that were 60 cm tall. Objects were arranged in five columns, as shown in **Figure 1**. In addition, a square (7 m × 7 m × 3 m) virtual room surrounded the scene. The four walls of the virtual room were textured with different colors and materials, so that participants could use the texture of the wall to determine their initial heading at the beginning of a trial. All participants learned the object locations from a fixed location and perspective (defined as 0°), which was 2 m away from the layout (**Figure 1**, Left). This viewing perspective ensured that participants could see all objects simultaneously.

To investigate the adopted reference frame, we used a 2 × 2 factorial design by manipulating the alignment between the imagined heading and the initial heading (i.e., initial heading effect), and the alignment between the imagined heading and the learning heading (i.e., learning heading effect) as shown in **Table 1**. The initial heading was the heading participants faced at the beginning of a test trial in the VE. The imagined heading was the heading that participants were required to imagine they were facing before responding, and was always the same as the final heading participants occupied at the end of a test trial in the VE. Ten trials were constructed for each experimental condition, resulting in 40 total trials. These 40 trials were divided into 10 blocks of four trials each, with one trial from each condition in each block and presented randomly.

Finally, to ensure that any significant differences observed between the aforementioned experimental conditions were

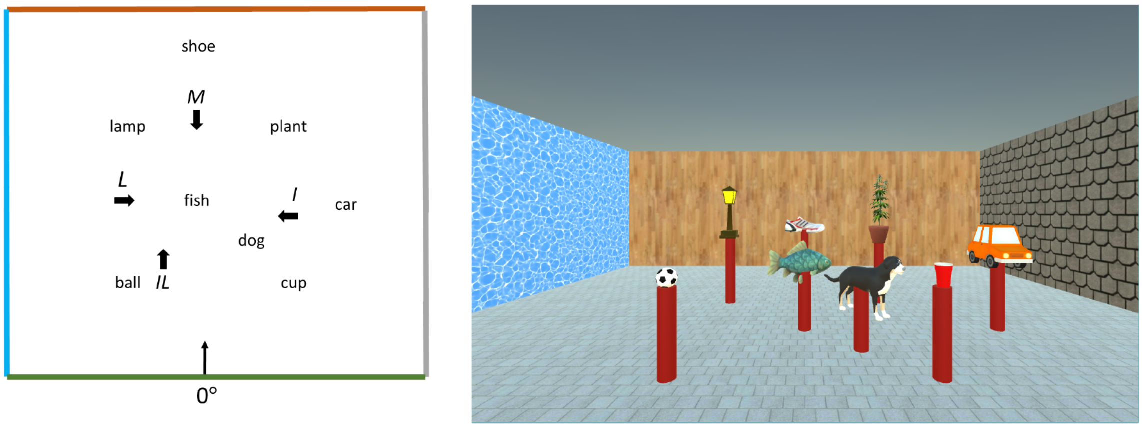


FIGURE 1 | Left. Plan view of the layout of objects. The thin arrow indicates the learning position and orientation in the learning phase. The thick arrows indicate the starting locations and orientations for the spatial updating trials in all experiments. The letters stand for the corresponding experimental condition. An example trial in the I condition would be: I -> plant -> lamp and point to car. An example trial in the L condition would be: L -> fish -> shoe, and point to lamp. An example trial in the M condition would be: M -> ball -> cup, and point to fish. An example trial in the IL condition would be: IL -> ball -> lamp, and point to plant. Right. Participants' actual view in the learning phase in Experiment 1.

not due to path complexity differences across conditions, we controlled the outbound path length (the shortest distance from the starting location to the first object plus the shortest distance from the first to the second objects), outbound path turning angle (the shortest turning angle from the starting location to the first object plus the shortest turning angle from the first to the second objects) and the correct pointing angle (the shortest angle from the second to the third object) across conditions. Details of the path complexity can be found in He et al. (2018).

Procedure

Learning Phase

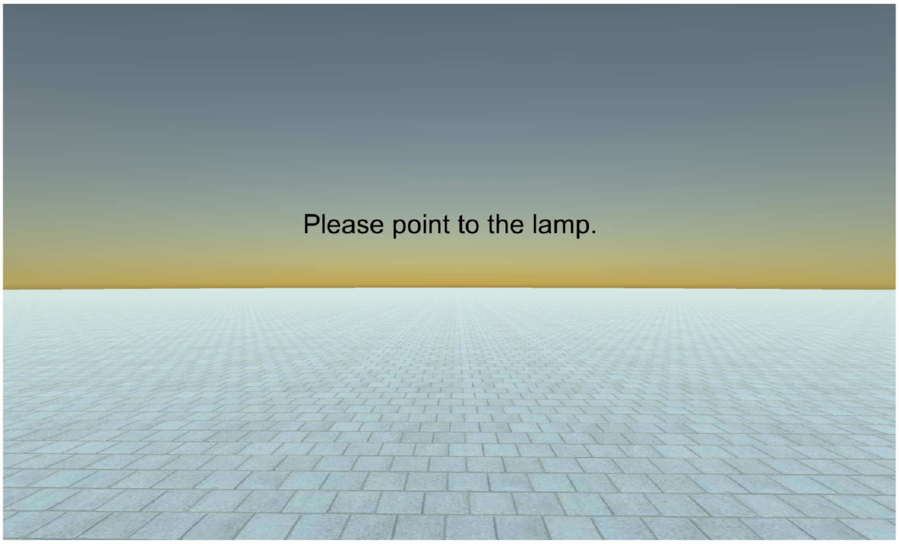
The layout of eight objects was displayed (**Figure 1**, Right) on a computer monitor and the experimenter named each of the objects for the participants. After all of the objects were named, the participants were instructed to study the layout for 2 min. During learning, participants were told not to move from the study location. After learning, both the objects and pillars were hidden and one of the pillars, but not objects, would appear randomly. Participants named the corresponding object on that pillar. This learning sequence was repeated until the participant successfully named all the objects twice.

Test Phase

After learning the layout, participants performed the test trials in front of the same computer using keyboard and joystick. Participants started at the location corresponding to the trial condition (I, L, IL or M). All objects and pillars were hidden but room walls and the floor were present at the beginning, so that participants could use the wall textures to identify their orientation in the VE (**Figure 1**, Left). Participants could not change their orientation or position before they pulled the trigger on the joystick. After participants pulled the trigger, the room walls were removed and one of the learned objects and the pillar beneath it appeared. Participants used the arrow keys on the keyboard to navigate to that object. Participants were instructed to first rotate the viewing perspective to face to the object, and then use the forward key to reach the object. The object disappeared upon arrival and the second object would appear. Participants were instructed to release the forward key upon arrival and use the left or right key to look for the second object. Participants reached the second object in the same way. Upon arrival at the second object, the second object and the pillar underneath it disappeared and a text message appeared at the center of screen displaying the name of the third object to point to (e.g., "Please point to the lamp"; **Figure 2**).

When participants saw the text message, they were told to imagine the environment from their final location (i.e., standing at the position and facing the orientation in the VE they had been before the screen was blanked), and to use the joystick to point to the third object from that perspective. The pointing response was chosen in favor of a navigation or turning response because the final heading was a key manipulation and we wanted to ensure that participants adopted and maintained their final heading during response. In addition, participants were told not to rotate their bodies during the test phase. If the joystick was deflected vertically or horizontally by more than 1 cm, the response would be recorded and participants would be teleported to the next position and orientation corresponding to the experimental condition to start the next trial.

Before the test trials, participants performed three practice trials that were identical to the test trials, except that the objects in practice trials were randomly selected from the remembered layout. No practice trials were provided after the first test trial.



Please point to the lamp.

FIGURE 2 | Participants' view of the response prompt in Experiment 1.

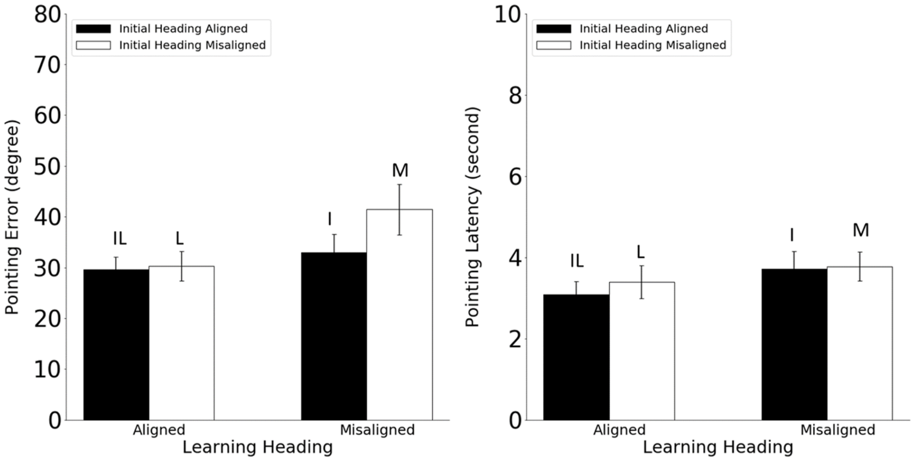


FIGURE 3 | Pointing error (Left) and latency (Right) in Experiment 1. Error bars are ± 1 SEM estimated from data within conditions. The letters above the bars identify the corresponding experimental conditions as defined in **Table 1**. Alignment and misalignment refer to the relation between the initial heading or the learning heading and the imagined heading (e.g., initial heading aligned means that the initial heading was aligned with the imagined heading; initial heading misaligned means that the initial heading was misaligned with the imagined heading).

Results and Discussion

Previous research suggested that gender differences may exist in spatial updating and path integration (Kelly et al., 2008; He et al., 2018), so we included gender in the preliminary analysis. However, gender effects were not observed in any of the experiment so we collapsed the data across gender in all of the experiments for brevity. Based on the results of He et al. (2018), we identified two key planned comparisons between conditions: I vs. M and L vs. M. These test the initial heading effect and learning heading effect, respectively, when the other variable is misaligned with the imagined heading (see **Table 1**). He et al. (2018) found that performance was equivalent when the initial heading, the learning heading, or both were aligned with the imagined heading (i.e., I ≡ L ≡ IL), and we had no reason to predict a different pattern in the current experiment. Planned comparisons used the contrast as the conceptual unit of error (i.e., no adjustment to nominal α). Unplanned comparisons were Bonferroni corrected.

Pointing error and latency were analyzed in 2 (alignment between the learning and imagined headings, referred to as learning-imagined) × 2 (alignment between the initial and imagined headings, referred to as initial-imagined) repeated ANOVAs (**Figure 3**). For pointing error (**Figure 3**, Left), neither the main effect of learning-imagined ($F_{(1,23)}$ = 3.48, MSE = 333.07, p = 0.07, η^2 = 0.13) nor the main effect of initial-imagined ($F_{(1,23)}$ = 4.26 MSE = 105.95, p = 0.051, η^2 = 0.15) was significant. However, the interaction between learning-imagined and initial-imagined was significant ($F_{(1,23)}$ = 4.64, MSE = 71.38, p = 0.042, η^2 = 0.17).

We followed up the significant interaction with planned pairwise comparisons (2): Pointing error was higher in the M condition than in the L and I conditions, $ts_{(23)} > 2.31$, ps < 0.03, suggesting that participants used both the learning and the initial headings to establish reference directions in the current task. In addition, the IL condition did not differ from the I or the L condition (unplanned; $ts_{(23)} < 0.92$, ps < 0.37, $\alpha_c = 0.025$).

For pointing latency (**Figure 3**, Right), only the main effect of learning-imagined was significant, $F_{(1,23)}$ = 8.66, MSE = 0.67, p = 0.007, η^2 = 0.27, suggesting that participants responded faster when the imagined heading was aligned with the learning heading.

In sum, the results from Experiment 1 replicated He et al.'s (2018) findings that during spatial updating without body-based cues, participants used both the learning heading and the initial heading to establish reference directions but did not benefit in this paradigm when the imagined heading was aligned with both headings relative to when it was aligned with only one (i.e., IL vs. L or I conditions, respectively). It is important to emphasize that the difference in performance between the M and the I conditions cannot be caused by the disparity between the imagined heading and the learning heading, as it was 90° in both conditions (see **Table 1**). This effect is also not likely to be caused by disparity between the imagined heading and the physical orientation of the participants, as the latter was equivalent to the learning heading in this paradigm.

EXPERIMENT 2

Experiment 2 was designed to determine whether geometry of the boundary might have influenced the pattern of results in Experiment 1. The initial heading in the I condition was parallel to the 90° ↔ −90° axis. It is possible that participants in Experiment 1 represented object-to-object spatial relations using reference directions parallel to the 0° ↔ 180° axis and the 90° ↔ −90° axis due to the geometry of the boundary (Shelton and McNamara, 2001; Mou and McNamara, 2002; but see Street and Wang, 2014, for a different interpretation). People are much less likely to represent the layout along the 90° ↔ −90° axis when

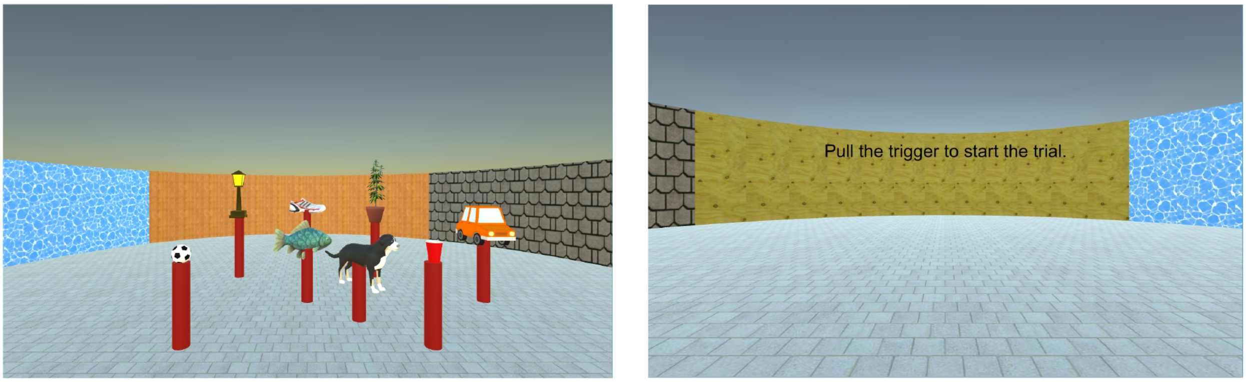


FIGURE 4 | Left. Participants' actual view in the learning phase in Experiment 2. Right. Participants' initial view (M condition) in the testing phase in Experiment 2. The walls would disappear when participants pulled the trigger to start the trial.

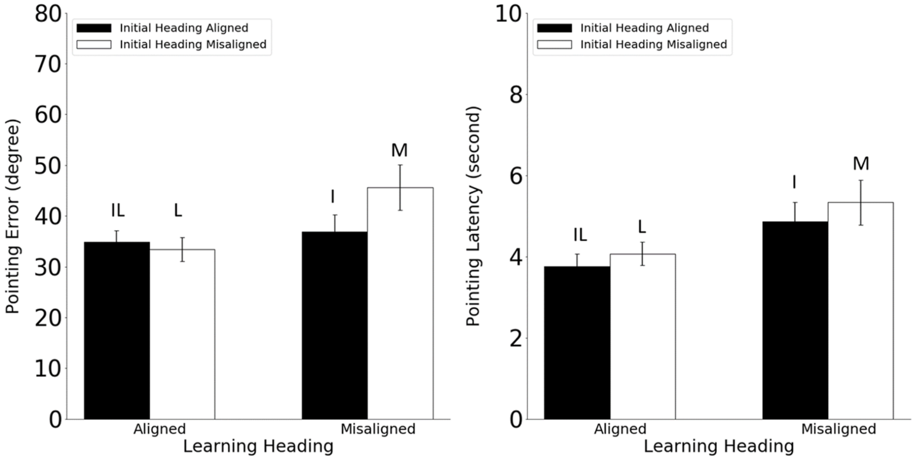


FIGURE 5 | Pointing error (Left) and latency (Right) in Experiment 2. Error bars are ± 1 SEM estimated from data within conditions. The letters above the bars stand for the corresponding experimental conditions as defined in **Table 1**. Alignment and misalignment refer to the relation between the initial heading or the learning heading and the imagined heading (e.g., initial heading aligned means that the initial heading was aligned with the imagined heading; initial heading misaligned means that the initial heading was misaligned with the imagined heading).

they learn it in a cylindrical room (Mou and McNamara, 2002; Experiment 3; Shelton and McNamara, 2001, Experiment 6). In Experiment 2, we changed the boundary to a circle and examined whether the initial heading effect still persisted.

Method

Participants

Twenty-four students (12 women) from Vanderbilt University and the Nashville community participated in this experiment in return for extra credit in psychology courses or monetary compensation.

Materials, Design and Procedure

The materials and design in Experiment 2 were similar to those in Experiment 1 except that the boundary was circular during learning and at the beginning of a test trial (**Figure 4**).

Results and Discussion

Pointing error and latency were analyzed in 2 (learning-imagined) × 2 (initial-imagined) repeated ANOVAs (**Figure 5**). For pointing error (**Figure 5**, Left), the main effect of learning-imagined was significant ($F_{(1,23)} = 6.97$, $MSE = 174.87$, $p = 0.015$, $\eta^2 = 0.23$), but the main effect of initial-imagined was not ($F_{(1,23)} = 2.63$, $MSE = 122.05$, $p = 0.12$, $\eta^2 = 0.10$. The interaction between learning-imagined and initial-imagined was significant ($F_{(1,23)} = 5.31$, $MSE = 117.08$, $p = 0.031$, $\eta^2 = 0.18$).

Planned pairwise comparisons (2) showed that pointing error was higher in the M condition than in the L and I conditions, $ts_{(23)} > 2.14$, $ps < 0.043$, indicating that participants used both the learning and the initial headings to establish reference directions in the current experiment. In addition, the IL condition did not differ from the I or the L condition (unplanned, $ts_{(23)} < 0.79$, $ps < 0.44$, $\alpha_c = 0.025$).

FIGURE 6 | Participants' initial view in the testing phase in Experiment 3.

For pointing latency (**Figure 5**, Right), only the main effect of learning-imagined was significant, $F_{(1,23)} = 17.04$, $MSE = 2.82$, $p < 0.001$, $\eta^2 = 0.42$, suggesting that participants responded faster when the imagined heading was aligned with the learning heading.

The pattern of results from Experiment 2 was almost identical to that in Experiment 1, suggesting that the initial heading effect was not tied to a geometry which had a limited number of axes of symmetry. In addition, the results from Experiment 2 also suggested that the reference frame defined by the initial heading was not formed in the learning phase, but rather in the testing phase.

EXPERIMENT 3

Experiment 2 suggested that the reference frame defined by the initial heading was formed in the navigation period. Experiment 3 tested He et al.'s (2018) conjecture that participants imagined the layout of objects at the beginning of the navigation trial and maintained this representation in working memory. To imagine the layout accurately, participants would need to know their allocentric orientation. In Experiment 3, we removed the room walls at the beginning of the test trial so that participants had no information about their location and orientation at the beginning of navigation.

Method

Participants

Thirty-eight students (20 women) from Vanderbilt University and the Nashville community participated in this experiment in return for extra credit in psychology courses or monetary compensation.

Materials, Design and Procedure

The materials and design of Experiment 3 were similar to those in Experiment 1 except that the room walls were absent throughout the test phase. In addition, the tiles on the floor in Experiment 1 were replaced by carpet (**Figure 6**), both in the training and testing phase. This change was made to prevent participants from using the orientation of the tiles to orient themselves at the beginning of a trial.

Results and Discussion

As described in the "Introduction" section, we decided to recruit 24 participants in all experiments based on the power analysis from He et al.'s (2018) data, but found that the results were not as conclusive in this experiment as in the previous experiments: Although the critical comparisons across the I, M, and L conditions were very similar to those observed in Experiments 1–2 and were significant (pointing error was higher in the M condition than in the other conditions, $ts_{(23)} > 2.32$, $ps < 0.029$), the interaction between learning-imagined and initial-imagined was only marginally significant ($F_{(1,23)} = 3.69$, $MSE = 150.86$, $p = 0.067$, $\eta^2 = 0.14$). To ensure that the initial heading effect was robust in this experiment, we ran a power analysis based on the data of the current experiment (using the observed effect size with $N = 24$), and found that a sample size of 38 participants was required to reach a power of 0.8 in the interaction. We therefore recruited 14 more participants and the following analyses were based on the data from 38 participants.

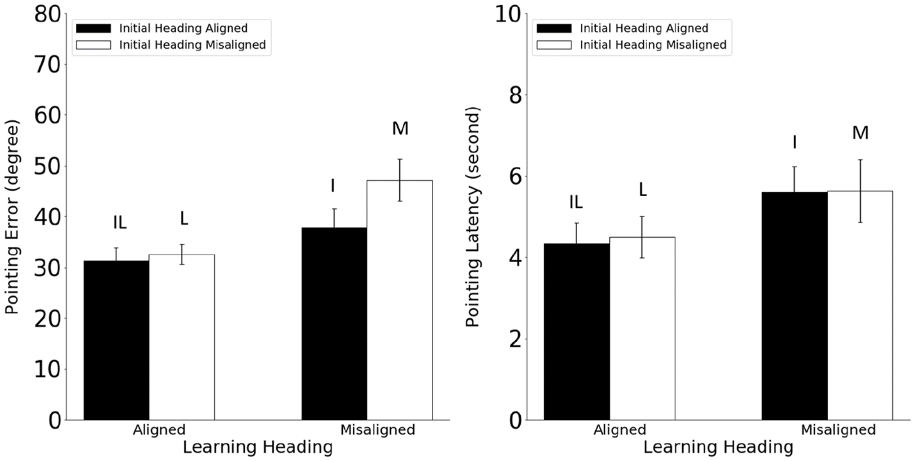


FIGURE 7 | Pointing error (Left) and latency (Right) in Experiment 3. Error bars are ± 1 SEM estimated from data within conditions. The letters above the bars stand for the corresponding experimental conditions as defined in **Table 1**. Alignment and misalignment refer to the relation between the initial heading or the learning heading and the imagined heading (e.g., initial heading aligned means that the initial heading was aligned with the imagined heading; initial heading misaligned means that the initial heading was misaligned with the imagined heading).

Pointing error and latency were analyzed in 2 (learning-imagined) × 2 (initial-imagined) repeated ANOVAs (**Figure 7**). For pointing error (**Figure 7**, Left), the main effect of learning-imagined and the main effect of initial-imagined were significant ($Fs_{(1,23)} > 6.22$, $p < 0.017$. Critically, the interaction between learning-imagined and initial-imagined was significant ($F_{(1,23)} = 5.36$, $MSE = 117.83$, $p = 0.026$, $\eta^2 = 0.13$).

Planned pairwise comparisons (2) showed that pointing error was higher in the M condition than in the L and I conditions, $ts_{(23)} > 2.59$, $ps < 0.013$, suggesting that participants used both the learning and the initial headings to establish reference directions in the current task. Unplanned pairwise comparisons ($\alpha_c = 0.025$) showed that the IL condition did not differ significantly from the I condition ($t_{(23)} = 2.04$, $p = 0.048$) or the L condition ($t_{(23)} = 0.87$, $p = 0.39$).

For pointing latency (**Figure 7**, Right), only the main effect of learning-imagined was significant, $F_{(1,23)} = 23.86$, $MSE = 2.32$, $p < 0.001$, $\eta^2 = 0.39$, suggesting that participants responded faster when the imagined heading was aligned with the learning heading.

The pattern of results from Experiment 3 was almost identical to those in Experiments 1–2. Given that participants did not know their location and orientation at the beginning of the navigation trial, they could not have imagined the layout of objects from the appropriate location and orientation. Note too that if participants were reconstructing in working memory the layout of objects from the initial heading in Experiments 1 and 2, then in Experiment 3, they would not be able to do this until they saw and were oriented toward the second object. The second leg of the path (e.g., plant → lamp or lamp → plant; see **Figure 1**) would function as the "initial heading" and the working memory representations should be equivalent in the I and the M conditions. Because participants did not have any allocentric orientation cues to specify the initial heading (i.e., whether they were facing north, south, east or west), the findings in Experiment 3 also suggested that the reference frame defined by the initial heading was egocentric rather than allocentric.

EXPERIMENT 4

Although we matched the path complexities during navigation across conditions, we could not rule out the possibility that the trial composition in the current study somehow made the M condition more difficult than the I condition. To rule out this possibility, we used the same layout and trial composition as in Experiments 1–3, but asked participants to perform a judgment of relative direction (JRD) task instead of navigation in Experiment 4. If the initial heading effect observed in Experiments 1–3 were due to the trial composition, then the pattern of results in Experiment 4 should be similar to those in the previous experiments. Otherwise, we should observe comparable performance between the I and M conditions.

Method

Participants

Twenty-four students (12 women) from Vanderbilt University and the Nashville community participated in this experiment in return for extra credit in psychology courses or monetary compensation.

Materials, Design and Procedure

The learning phase in Experiment 4 was identical to that in Experiment 1. In the testing phase, participants only saw text indicating the location and orientation they were to imagine occupying, instead of using the keyboard to navigate to objects. For example, they would see "Imagine you are standing at the ball, with the cup behind your back. Pull the trigger when you are ready". When participants pulled the trigger, they would see the name of the target object they needed to point to ("Please point to the fish".). The number of trials and trial composition

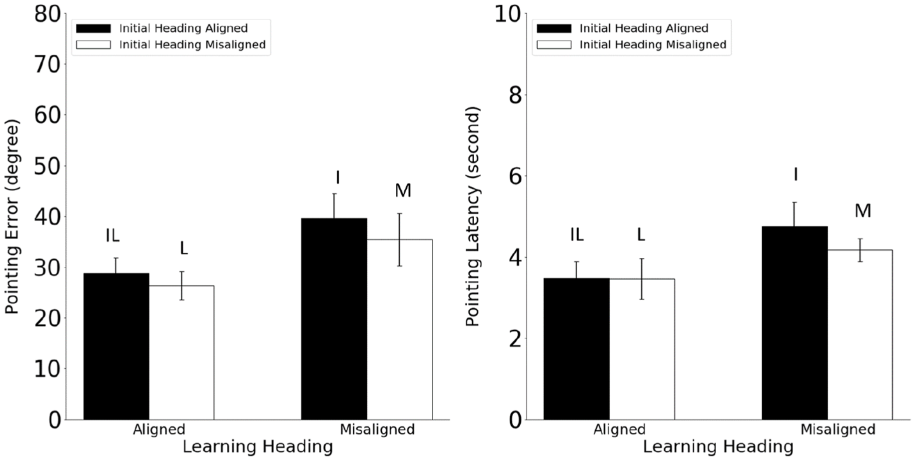


FIGURE 8 | Pointing error (Left) and latency (Right) in Experiment 4. Error bars are ± 1 SEM estimated from data within conditions. The letters above the bars stand for the corresponding experimental conditions as defined in **Table 1**. Alignment and misalignment refer to the relation between the initial heading or the learning heading and the imagined heading. In Experiment 4, alignment with the initial heading was a dummy variable as the initial heading was not defined in judgments of relative direction.

were identical to those in Experiments 1–3. For example, in one of the trials of the I condition in Experiment 1, participants would first navigate to plant and then to the lamp, and then point to the car (**Figure 1**). In the I condition in Experiment 4, participants would see "Imagine you are at the lamp, with the plant behind your back. Pull the trigger when you are ready", and then "Please point to the car".

The orientation time was defined as the elapsed time between the time at which participants saw the text specifying the imagined position in the VE and the time at which they pulled the trigger to see the target object. The pointing latency was defined as the elapsed time between the time at which the participants pulled the trigger to see the target object and the time at which the pointing response was detected.

Results and Discussion

Because no navigation or initial heading was involved, the initial-imagined variable was not defined in Experiment 4. However, to compare the results from this experiment with those of the others directly, data were assigned to the combinations of the two factors based on the assignment of trials in Experiments 1–3 and were analyzed in the same 2 (learning-imagined) × 2 (initial-imagined) repeated ANOVAs.

For pointing error (**Figure 8**, Left), the main effect of learning-imagined was significant ($F_{(1,23)} = 5.61$, $MSE = 417.26$, $p = 0.027$, $\eta^2 = 0.20$), but the main effect of initial-imagined ($F_{(1,23)} = 3.39$, $MSE = 76.43$, $p = 0.08$, $\eta^2 = 0.13$), and the interaction between learning-imagined and initial-imagined were not significant ($F_{(1,23)} = 0.16$, $MSE = 104.38$, $p = 0.69$, $\eta^2 = 0.007$). Critically, the performance in the I condition was no better than in the M condition (planned: $t_{(23)} = -1.23$). The performance in the L condition was significantly better than in the M condition (planned: $t_{(23)} = 2.10$, $p = 0.046$).

For orientation time, neither the main effects nor the interaction was significant (Fs < 1.16, ps > 0.29). For pointing latency (**Figure 8**, Right), only the main effect of learning-imagined was significant, $F_{(1,23)} = 18.88$, $MSE = 1.24$, $p < 0.001$, $\eta^2 = 0.45$, suggesting that participants responded faster when the imagined heading was aligned with the learning heading.

The pattern of results in pointing error from Experiment 4 was different from those in Experiments 1–3; in particular, performance in the I and the M conditions did not differ. This result indicates that the initial heading effect observed in the previous experiments could not be attributed to the trial composition, and the initial heading effect had to be induced by spatial updating. Because we also controlled the path complexities across conditions during navigation, we believe that the initial heading effect was caused by the alignment between the initial and imagined headings.

GENERAL DISCUSSION

The current project investigated the nature of the reference system used to represent the self-to-object spatial relations and the cognitive processes underlying reference frame selection in spatial updating when body-based cues were not available. In the first three experiments, participants first learned a layout of eight objects from a fixed perspective in a VE, and were placed in the same VE to navigate to two of the learned objects before pointing to a third object. The navigation was realized by keyboard and therefore the body-based cues were reduced to a minimum. Experiment 1 replicated the initial heading effect observed in He et al.'s (2018) study. Experiment 2 showed that the initial heading effect was not tied to rectilinear room geometry and further suggested that the reference frame defined by the initial heading was established during spatial updating. Experiment 3 showed that the initial heading effect was not caused by participants representing the layout of objects along the initial heading at the beginning of navigation. Experiment 4 showed that the initial heading effect observed in the previous experiments and in He et al. (2018) study was not caused by differences in the complexities of inter-object spatial relations in the critical M and I conditions.

Motivated by concerns about reproducibility in psychology (Open Science Collaboration, 2015), we first conducted an experiment to replicate the results in He et al. (2018). We manipulated the alignment between the learning and the imagined headings, and the alignment between the initial and the imagined headings. Because the effect of the learning heading is a well-established finding, we were primarily interested in whether the initial heading effect could be replicated. The patterns of results in Experiment 1 were very similar to those in He et al. (2018), and thus we concluded that the initial heading effect was reproducible (see also, Palij et al., 1984; Richardson et al., 1999; Wilson et al., 1999).

Because the initial heading in the VE was different from participants' physical heading (in all but the IL condition), the ability of participants to use the initial heading to establish a reference direction suggested that the "egocentric" heading in the VE could override (physical) egocentric front. Because the shape of the environment used in Experiment 1 and in He et al.'s (2018) study was square, participants could have used both the 0° ↔ 180° axis and the 90° ↔ −90° axis in the learning phase to establish reference directions to represent the object-to-object relations. Because the initial heading in the I condition, in particular, was parallel to the 90° ↔ −90° axis, the reference frame defined by the initial heading might have been formed during learning.

In Experiment 2, we discouraged participants from using the axis of the initial heading (90° ↔ −90°) to represent the object-to-object relations by rendering the environmental geometry as a circle. Previous studies have shown that people did not or were much less likely to use the 90° ↔ −90° axis as a reference direction when the room was cylindrical (Mou and McNamara, 2002, Experiment 3; Shelton and McNamara, 2001, Experiment 6). Based on these previous findings, we assumed that participants would not use the initial heading to encode object-to-object relations during learning in Experiment 2. The persisting initial heading effect suggested that the reference frame defined by the initial heading was established during spatial updating. A limitation of Experiment 2 is that we did not measure directly whether the 90° ↔ −90° axis was used as a reference direction during learning. It is possible, for example, that participants used the rectangular shape of the monitor screen to represent the object-to-object relations. An experiment that is similar to our Experiment 2 but is realized in immersive virtual reality and tests participant's reference direction(s) during learning could determine when the reference frame defined by the initial heading was established.

Experiment 3 was designed to test He et al.'s (2018) hypothesis that the initial heading effect was produced because participants imagined the layout of objects at the beginning of the navigation trial and maintained this representation in working memory. Imagining the layout from the appropriate allocentric heading would only be possible if participants knew their location and orientation at the beginning of the trial. In Experiment 3, we removed all orientation cues during the test phase. We observed that the initial heading effect still persisted. This finding indicates that the initial heading effect is produced by spatial updating and is egocentric.

Experiment 4 was designed to rule out the possibility that the poorer performance in the M condition than in the I condition was due to the differences in trial composition. Participants in Experiment 4 did not navigate to various waypoints but instead imagined themselves occupying the corresponding location and orientation. If the trial composition was the driving force behind the initial heading effect, then we should have observed similar patterns of results in Experiment 4 to those in Experiments 1–3. Instead, the equivalent performance between the I and M conditions in Experiment 4 suggested that spatial updating was necessary to induce the initial heading effect.

When people adopt a spatial perspective in imagination other than the perspective they physically occupy, their spatial reasoning performance is inferior (Rieser et al., 1986; Rieser, 1989; Presson and Montello, 1994; May, 2004; Mou et al., 2004). The performance cost has been attributed to interference from the online, egocentric representations of the immediate environment (Presson and Montello, 1994; May, 2004; Avraamides and Kelly, 2008), but this interference can also occur when people are in a remote environment (Kelly et al., 2007; May, 2007; Shelton and Marchette, 2010; Riecke and McNamara, 2017). We believe that the initial heading effect observed in our experiments is analogous.

Consider first the processes involved when participants can infer their location and orientation at the beginning of the navigation trial (Experiments 1 and 2 of the current project; Experiment 1 of He et al., 2018). At the beginning of the trial, participants establish a location and orientation in the VE. As they navigate, they update their virtual position with respect to this starting location and orientation. This is how participants stay oriented in the VE. At the end of the path, they must retrieve or infer the location of the target object. When the second leg of the path/final heading is parallel to the learning heading, participants recognize this, probably while navigating, and retrieve the location of the target from long-term memory. This explains why performance is equivalent in the IL and L conditions. When the second leg of the path/final heading is not parallel to the learning heading, they must infer the direction of the target object from their current virtual position (this relative direction is not likely to be encoded). These inferential processes have to be efficient in the I condition to account for the equivalent level of performance in the I, L and IL conditions. The cost in performance in the M condition relative to the I condition is analogous to the cost produced by a disparity between an imagined heading and a physical body heading. In our paradigm, the virtual heading at the end of the path is the imagined heading and the initial heading functions like the actual body heading. In essence, the virtual initial heading supplants physical egocentric front.

A crucial difference between spatial updating without body-based cues to self-motion and spatial updating with body-based cues to self-motion (e.g., locomotion in the real world) is that in the former situation the "actual" body heading defined by the initial heading must not be updated completely during navigation; if it were, then performance in the M condition would be equivalent to that in the I condition (and presumably equivalent to performance in the L and IL conditions), as in both conditions, the imagined heading is the same as the final heading at the end of navigation (Rieser, 1989; He et al., 2017). The magnitude of pointing error in the M condition indicates either that partial updating of the "actual" body heading/initial heading occurred in our paradigm or that navigators were able to compensate with inferential processes (or both). It is not clear why the disparity between the initial heading and the imagined heading did not produce a deficit in performance in the L condition. As suggested previously, it is possible that participants relied on long-term memory in the L condition to make their responses. Performance also may be determined by a race between parallel processes (e.g., Logan, 2002) in which the learning heading effect typically dominates.

To account for the findings of Experiment 3, we propose that the virtual position established at the beginning of the trial is not defined allocentrically; the location is left unspecified and the heading is given a default value (e.g., 0°). After navigating to the first object, the virtual location can be specified and the virtual heading is updated based on how much the participant has rotated from the initial default heading. When the second object appears, participants have sufficient information to infer their allocentric heading and can update the default initial heading with the correct value. The difference in performance between the M and the other conditions in Experiment 3 is produced by the same processes as in Experiments 1 and 2. The only difference between the two scenarios is the time at which the initial heading can be specified allocentrically.

The other consistent finding in Experiments 1–4 was the learning heading effect. Pointing performance was more accurate and faster when the imagined heading was parallel to the learning heading than when it was not. This result has been observed in dozens of published studies now and establishes orientation dependance as a fundamental property of spatial memory.

Although significant gender differences were found in He et al.'s (2018) study with men having a weaker initial heading effect, we did not observe such a trend in any of the experiments in the current project and we did not observe that men's performance was better than women's. The absence of gender differences implies that the strategy of mental rotation was not generally used in our task, as researchers have found that men consistently outperform women in mental rotation tests (Linn and Petersen, 1985; Casey, 2013).

To conclude, the results of the present experiments and those of He et al. (2018) indicate that when navigating in a VE without body-based cues to self-motion, the initial heading in the environment functions in a manner similar to the physical orientation of the body in real-world perspective taking tasks. To our knowledge, this finding is novel. An important difference between virtual navigation without body-based cues to self-motion and navigation (real or virtual) with body-based cues to self-motion is that the orientation of the body seems not to be fully updated in the former situation but certainly is in the latter. This finding may explain in part why spatial updating in desktop VEs is less efficient than spatial updating in VEs that afford body-based cues to self-motion (e.g., Ruddle and Lessels, 2006; Riecke et al., 2010; Ruddle et al., 2011). The correspondence between the virtual initial heading and the physical orientation of the body may provide evidence that despite its lower efficiency, spatial updating in desktop VEs may depend on similar cognitive and neural processes to those underlying spatial learning in the real world, where body-based cues are available (e.g., Chrastil, 2013). This, in turn, may provide some justification to use desktop VEs to investigate the neural mechanisms of human navigation (see Taube et al., 2013).

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Vanderbilt University Institutional Review Board and the protocol was approved by the Vanderbilt University IRB. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

QH and TM designed the experiments. QH conducted the experiments, analyzed the data and wrote the first draft of the manuscript. Both authors contributed to the final version of the manuscript.

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Adolescent Hippocampal and Prefrontal Brain Activation During Performance of the Virtual Morris Water Task

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The frontal cortex undergoes substantial structural and functional changes during adolescence and significant developmental changes also occur in the hippocampus. Both of these regions are notably vulnerable to alcohol and other substance use, which is typically initiated during adolescence. Identifying measures of brain function during adolescence, particularly before initiation of drug or alcohol use, is critical to understanding how such behaviors may affect brain development, especially in these vulnerable brain regions. While there is a substantial developmental literature on adolescent working memory, less is known about spatial memory. Thus, a virtual Morris water task (vMWT) was applied to probe function of the adolescent hippocampus. Multiband blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) data were acquired at 3T during task performance. Participants included 32 healthy, alcohol- and drug-naïve adolescents, 13–14 years old, examined at baseline of a 3-year longitudinal MRI study. Significantly greater BOLD activation was observed in the hippocampus and surrounding areas, and in prefrontal regions involved in executive function, during retrieval relative to motor performance. In contrast, significantly greater BOLD activation was observed in components of the default mode network, including frontal medial cortex, during the motor condition (when task demands were minimal) relative to the retrieval condition. Worse performance (longer path length) during retrieval was associated with greater activation of angular gyrus/supramarginal gyrus, whereas worse performance (longer path length/latency) during motor control was associated with less activation of frontal pole. Furthermore, while latency (time to complete task) was greater in females than in males, there were no sex differences in path length (accuracy), suggesting that females required more time to navigate the virtual environment, but did so as effectively as males. These findings demonstrate that performance of the vMWT elicits hippocampal and prefrontal activation patterns in early adolescence, similar to activation observed during spatial memory retrieval in adults. Given that this task is sensitive to hippocampal function, and that the adolescent hippocampus is notably

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vulnerable to the effects of alcohol and other substances, data acquired using this task during healthy adolescent development may provide a framework for understanding neurobiological impact of later initiation of use.

Keywords: adolescence, BOLD fMRI, Morris water task, spatial memory, hippocampus, prefrontal cortex

INTRODUCTION

While the frontal cortex undergoes substantial and rapid structural and functional changes during adolescence, significant developmental changes also occur in the medial temporal lobe, specifically the hippocampus, which is responsible for learning and memory (Spear, 2000; Paus, 2005; Mills et al., 2014). Neurodevelopmentally, dynamic integration of hippocampal and prefrontal circuitry is necessary to incorporate experience into behaviors that are ultimately adaptive for successful developmental transitions (Murty et al., 2016). These regions also are notably susceptible to alcohol, cannabis, and stimulant use (Conrad et al., 2016), the onset of which typically overlaps with this crucial period of adolescent brain development. Thus, identifying neurobiological precursors of use and vulnerabilities associated with early and escalating substance use during adolescence is critical (Casey and Jones, 2010).

The hippocampus is involved in the spatial layout and structural representation of an environment in both rodents (O'Keefe and Nadel, 1978; Sutherland et al., 1989; Jarrard, 1993) and humans (Maguire et al., 1999, 2000) and also serves spatial memory processing (O'Keefe and Nadel, 1978; Guderian et al., 2015). The Morris water task (MWT) (Morris, 1984) has been used extensively in animal research to probe spatial memory ability and related hippocampal circuitry. Virtual MWT (vMWT) versions also have been developed to assess spatial memory ability in humans (Hamilton et al., 2009), providing an important translational approach for bridging current knowledge of memory function across species. Several studies have confirmed that the hippocampus is essential for solving a spatial navigation challenge, e.g., using cues in an environment to successfully and efficiently navigate to a hidden platform (Astur et al., 2002, 2004; Bohbot et al., 2004; Hamilton et al., 2009; Sneider et al., 2015). Spatial memory paradigms have been paired with blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) to characterize neurocircuitry involved in task performance (Sneider et al., 2011, 2013; Dahmani and Bohbot, 2015; Woolley et al., 2015; Pu et al., 2017). On a version of the vMWT similar to the one used in the current study, there were no significant sex differences on behavioral measures, however, adult females exhibited greater left lateralized hippocampal activity compared to adult males that was specific to fMRI learning trials (not retrieval) (Sneider et al., 2011). In a study of chronic marijuana (MJ) users, the MJ group showed equivalent learning to that observed in non-users, yet demonstrated a deficit in memory retrieval performance that was accompanied by hypoactivation of right parahippocampal gyrus and cingulate gyrus (Sneider et al., 2013). There are only two other studies published to date that have employed a similar vMWT (all in adult cohorts), one that was paired with magnetoencephalography (MEG) and the other that was paired with resting state fMRI. In the MEG study, greater left hippocampal and parahippocampal theta activity was reported in healthy male adults during directional navigation relative to random navigating, findings interpreted as reflecting hippocampal place cell activity implicated in memory formation (Pu et al., 2017). In the resting state fMRI functional connectivity study, adult participants performing the vMWT demonstrated increased functional connectivity between left posterior hippocampus and left dorsal caudate that was specific to the learning session (i.e., pre- versus post-learning), with the magnitude of the increase being correlated with offline gains in performance (Woolley et al., 2015). Results of these vMWT studies are consistent with another type of spatial task used during fMRI – a virtual concurrent spatial discrimination learning task (12-arm radial maze) – in which BOLD activation was observed in hippocampus, prefrontal cortex, and caudate nucleus in healthy 18- to 35-year olds during navigation performance (Dahmani and Bohbot, 2015). Taken together, these studies underscore the involvement of hippocampus, and in some cases the coupling of hippocampus with executive function neurocircuitry, during spatial memory task performance across neuroimaging modalities and different types of tasks.

Not surprisingly, spatial memory ability and behavioral performance on the vMWT decline in the elderly (Etchamendy et al., 2012), and are impaired in individuals with hippocampal damage (Astur et al., 2002). While there have been substantial studies documenting normative development of working memory during adolescence (e.g., Squeglia et al., 2013; Andre et al., 2016; Montez et al., 2017), the literature on this type of vMWT spatial memory during adolescent development does not yet exist. To this end, the objective of the current study was to use the vMWT with BOLD fMRI to investigate hippocampal and executive function neurocircuitry during task performance in 13- to 14-year-old healthy adolescents. These results represent baseline data from an ongoing longitudinal study of adolescent brain development, for which participants were alcohol- and drug-naïve and who had no psychiatric diagnoses. Hippocampal and prefrontal activation have been observed during memory retrieval on this task in adults, therefore, it was hypothesized that significant hippocampal and prefrontal activation also would be observed in healthy adolescents. Furthermore, given that differences between males and females in spatial memory performance, on this task and others, have been well established (Astur et al., 2004; Newhouse et al., 2007; Andreano and Cahill, 2009; Woolley et al., 2010; Sneider et al., 2015; Voyer et al., 2017; Piber et al., 2018), sex differences in performance and BOLD fMRI data were examined. Examination of brain activation during performance of an established translational vMWT provides an important opportunity to characterize normative hippocampal and prefrontal contributions to memory retrieval in physically and psychologically healthy adolescents who were substance-naïve. Given that integration of these regions is important for enhancing decision-making skills during a crucial decade of brain development (Murty et al., 2016), and that alterations in hippocampal and prefrontal functioning have been implicated in substance use and other psychiatric disorders (e.g., Chambers et al., 2003; Bava and Tapert, 2010; Lichenstein et al., 2016; Silveri et al., 2016), data from this study establish an important baseline that may help elucidate neurobiological markers of risk for an early initiation of substance use, as well as manifestation of psychiatric symptoms (e.g., depression and anxiety) that tend to emerge during adolescence.

MATERIALS AND METHODS

Participants

The study sample consisted of 32 healthy adolescents (15 females) who completed the baseline visit of a 3-year longitudinal study of adolescent brain development. Demographic details are provided in **Table 1**. The clinical research protocol was approved by the Partners Healthcare Institutional Review Board of McLean Hospital. Participants were recruited through Boston Children Hospital's (BCH) Research Participant Registry (which involves recruitment of adolescent participants across local pediatrician clinics) and local advertisements. Interested participants were subsequently screened via an online eligibility survey and completed follow-up verification and scheduling via telephone. All participants and their parent(s) or guardian(s) provided written informed assent and consent, respectively, after they received a complete description of the study. Monetary compensation was provided to all participants for study completion.

TABLE 1 | Participant demographics and cognitive measures.

	Total sample ($n = 32$)
Age (years)	13.9 ± 0.7
Female/Male	15 (47%)/17 (53%)
Education (years)	7.7 ± 0.9
SES[a]	49.4 ± 9.4
Handedness	30R, 2L
Ethnicity[b]	97% Non-Hispanic
Race[c]	75% Caucasian
	12% Asian
	13% Other
WASI T-Scores	
IQ estimate (2-subtest, vocabulary/matrix)	114.3 ± 9.6
Vocabulary	59.4 ± 7.5
Matrix reasoning	56.8 ± 6.5
Block design	57.0 ± 9.0

Data represent means ± standard deviations. SES, socioeconomic status; WASI, Wechsler Abbreviated Scale of Intelligence. [a]SES (Hollingshead, 1975); [b]Ethnicity: Hispanic vs. Non-Hispanic; [c]"Other" included the following designations: Asian/Caucasian; African American/Caucasian; American Indian or Native Alaskan/Caucasian. There were no significant sex differences on any measure.

Participants completed urine screening prior to scanning to rule out current psychoactive substance use (Clarity Diagnostics Drugs of Abuse Panel, Boca Raton, FL, United States) and pregnancy (QuPID One-Step Pregnancy, Stanbio Laboratory, Inc., San Antonio, TX, United States). Participants had no prior head trauma with loss of consciousness, were free of radiologic brain abnormalities and MR scanning contraindications, and had no lifetime psychoactive substance use, including nicotine or alcohol, and had no previous or current diagnosis of any psychiatric condition.

Clinical and Cognitive Measures

Trained staff conducted diagnostic clinical interviews using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (Sheehan et al., 2010). The vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) were administered to obtain an estimate of general intelligence, and the block design subtest was administered to assess visuospatial processing (**Table 1**).

Virtual Morris Water Task (vMWT)

Participants completed offline vMWT training prior to performing the task in the MRI scanner. For additional details of the virtual vMWT, see the prior publications (Hamilton et al., 2009; Sneider et al., 2013, 2015). A laptop using a Windows operating system was used to administer vMWT both offline and during fMRI. The laptop displayed a first-person perspective of a virtual environment: a circular pool within a square room. A square platform was either hidden or visible according to trial design and was located in the southwest (SW) quadrant of the virtual pool environment for all trials.

Offline training consisted of learning/retrieval, probe and motor conditions (**Figure 1**). Participants first completed 12 learning/retrieval trials, where the platform was hidden below the surface of the water in a virtual environment featuring distinct spatial cues (pictures) on each of the four walls. Participants completed three blocks of four trials, in which each of the four trials began in a unique location, north, south, east or west (pseudorandom order). Participants had up to 60 s per trial to navigate to the hidden platform, at which point a "platform found" message was presented on the screen. If participants did not find the platform (unsuccessful), the platform becomes visible until they successfully navigate to it. The inter-trial interval was 1 s. The next trial was a single probe trial, in which the environment was the same as the prior 12 learning/retrieval trials, however, the platform was removed unbeknownst to participants, who search for 30 s before the trial ends. Participants then completed one block of four motor trials, which served as a motor performance control condition, where the platform was visible above the surface of the water in the same virtual environment but with no spatial cues on any of the four walls. Participants also had up to 60 s to complete the motor trials. Participants navigated through the virtual environment using laptop keyboard arrow keys (right, left, and forward) for offline training. For the learning/retrieval, probe and motor conditions, the virtual

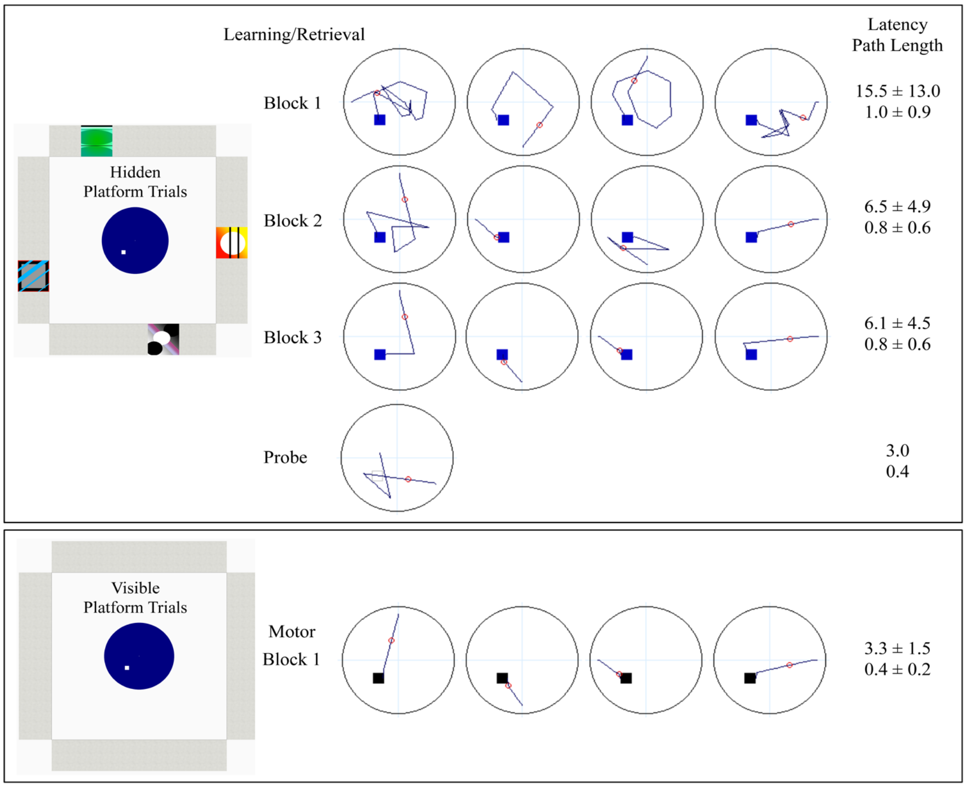

FIGURE 1 | Schematic denoting the layout of offline vMWT training for learning/retrieval, probe and motor control. Learning/retrieval consisted of three blocks of four hidden platform trials, each starting from a unique direction (in pseudorandom order). The probe was a single trial, with a start location of either NW or the SE (pseudorandom), which were equidistant from the platform location in the SW. Dark blue lines represent sample paths from a single study participant completed each condition. The small squares within the pool represent platform location (blue: hidden; gray open: probe; black: visible). The small red circle is used to calculate heading error (only calculated for the probe). Accompanying latency (seconds) and path lengths, averaged over block for sets of four trials, or for the single probe trial, are provided from the study participant. Decreased latency (speed of performance) and decreased path length (accuracy independent of speed) indicate successful learning.

environments, release points, platform location, layout of blocks and trials, and sample paths, latency and path lengths for one study participant are illustrated in **Figure 1**.

The fMRI vMWT paradigm (**Figure 2**) utilized a block design, consisting of pairs of alternating retrieval (left/orange) and motor (right/green) blocks (four of each, 36 s per block) (Shipman and Astur, 2008) separated by rest blocks (fixation cross, 21 s per block), and ending with a probe trial (36-s block). For retrieval and motor trials, participants completed as many trials as possible with fixed 36-s blocks. For the probe trial, in which the cues in

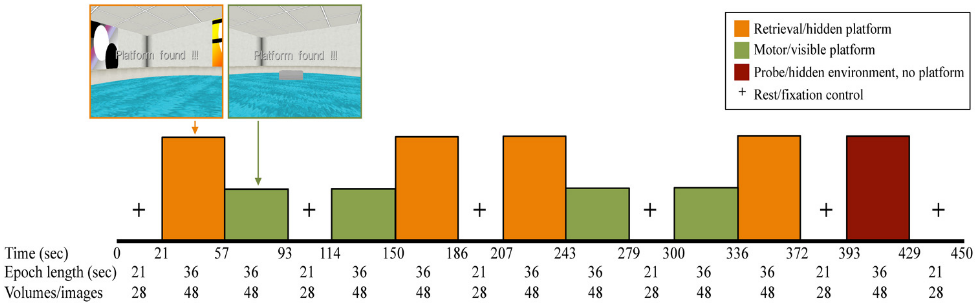

FIGURE 2 | fMRI paradigm in which all participants completed four retrieval (orange) and four motor conditions (green) (36-s epochs), interspersed with rest periods where participants viewed a fixation cross on the screen (21 s). The last performance block was a 36-s probe trial (maroon), in which the platform was removed from the pool unbeknownst to the participant.

the virtual environment were the same as in the retrieval trial only with the platform removed, participants navigated for the entire duration of the 36-s block. Navigation was controlled using an MRI-compatible fiber optic response pad (fORP) (diamond configuration) during BOLD fMRI acquisition.

For offline training and fMRI, vMWT performance measures included latency to reach the platform (time from first movement to reaching the platform, measured in seconds) and path length (distance traveled from release point to platform/end of trial, measured in arbitrary units). Significant decreases in latency and path lengths over trial blocks were interpreted as successful learning of the platform location. Sum of completed trials for retrieval and motor conditions during fMRI also were determined, indicating that all participants experienced successful navigation on both trial types. Data from one female subject was not available for offline training due to computer error during data acquisition.

For the offline probe trial, eight dependent measures were calculated: first move latency, latency to critical region, path length to critical region, % path length in critical region, latency to quadrant, path length to quadrant, % path length in quadrant, and heading error. "Quadrant" refers to the SW quadrant of the virtual space, which contains the platform (**Figures 1**, **3**), while "critical region" refers to a more circumscribed circular region (radius ∼12% of the pool diameter) centered around the platform. "Heading error" refers to the angular deviation of the participant's path from a direct path from the release point to the platform, calculated at the point where the cumulative path length first exceeds an amount equal to 25% of the pool diameter.

Independent raters blind to participant age and sex determined the navigation strategy utilized during performance of the offline probe trial: (1) a direct strategy, where participants navigated directly to the platform location from the starting location; or (2) a non-direct strategy, where participants navigated in a circuitous or random route that was not in the direction of the platform quadrant (NE) (Astur et al., 2004). Sample navigation paths are provided in **Figure 3**. Two coders (JS and MS), who independently viewed individual output files of navigation maps produced during the offline probe trial classify strategy, had complete agreement between rates, with an intraclass correlation coefficient for strategy coding of ICC = 1.00, $p < 0.001$. Given the shortened testing time of the probe trial during fMRI, and therefore a lack of comparability with offline probe performance, dependent measures from the fMRI probe trial are not presented in this report.

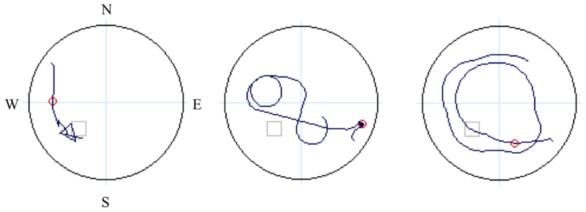

FIGURE 3 | Schematic denoting four quadrants (light blue lines: N, E, S, W), with dark blue lines representing sample paths from three study participants during navigation on the probe trial. The small gray open square is the location of the hidden platform and the small red circle is used to calculate heading error.

Functional Magnetic Resonance Imaging Acquisition and Preprocessing

Functional data were acquired on a Siemens TIM Trio 3 Tesla MRI system (Erlangen, Germany) with a 32-channel head coil. High-resolution structural images were collected using a T1-weighted multi-echo magnetization prepared rapid acquisition gradient echo (ME-MPRAGE) 3D sequence in four echoes (TE = 1.64/3.5/5.36/7.22 ms, TR = 2.1 s, TI = 1.1 s, FA = 12°, 176 slices, 1 mm × 1 mm × 1.3 mm voxel, acquisition time = 5 min) for registration of functional images into standard space. Whole-brain multiband gradient echo echo-planar imaging (EPI) with BOLD contrast was used to collect fMRI data in one 7.5 min run. Images were acquired in 54 interleaved oblique slices (TR/TE/FA = 750 ms/30 ms/52°, FOV = 220, voxel size: 2.8 mm × 2.8 mm × 2.8 mm, multiband = 6, GRAPPA = 2). A fieldmap was acquired at the same resolution and slice locations to allow for B0 unwarping (TR = 1000, TE = 10/12.46 ms, FA = 90°, 2:44 min).

Prior to statistical analyses, preprocessing was performed on raw functional images using the FMRIB Software Library (FSL) software v5.0.10 (Smith et al., 2004) (FMRIB, Oxford, United Kingdom), (Groves et al., 2009) including: motion correction, slice-timing correction, non-brain removal, spatial smoothing (FWHM 6 mm Gaussian kernel), and grand-mean intensity normalization of the 4D dataset by a single multiplicative factor. Ten volumes at the onset of the first rest block were removed to allow for signal equilibration. While data were initially acquired from 40 healthy adolescent subjects, eight subjects were removed from the analysis due to excessive motion in the scanner. Any subject with greater than 5 mm motion was excluded from further analysis. For the remaining 32 subjects, ICA AROMA, an independent component analysis-based denoising tool, was then used to remove motion-related components from the fMRI data (Pruim et al., 2015[1]). While ICA-AROMA identifies components related to motion, components related to respiration and other artifacts also were identified by visual inspection of ICA components, then all motion-related and artifacts removed from the fMRI data using fsl_regfilt. Denoised fMRI data were then temporally filtered using a Gaussian-weighted least-squares straight line fit with a high-pass cutoff = 100 s and underwent fieldmap based distortion correction. Functional MRI data were registered to MNI152 standard space by first registering the fMRI images to the high-resolution structural image using boundary-based registration (BBR) and then transforming into MNI stereotaxic space using the first registration step combined with the registration information from registering the high-resolution structural image to MNI152 standard space, which was done using FNIRT.

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[1] https://github.com/rhr-pruim/ICA-AROMA

Statistical Analyses

Analysis of the vMWT performance measures (first movement latency, total latency, and total path length) were conducted using repeated measures analysis of variance (ANOVA) for trial block (three blocks for offline and four blocks for fMRI), with sex included as an independent variable. Number of completed trials also was analyzed over retrieval and motor trial blocks during fMRI using repeated measures ANOVAs, with sex included as an independent variable. *Post hoc* analyses for ANOVAs were conducted using two sample *t*-tests (two-tailed) to determine sources of differences when main effects or interactions were statistically significant. For the probe trial, percentage of overall path length was tested relative to chance for region (5%) and quadrant (25%) using one sample *t*-tests. Qualitative evaluations of navigation paths (spatial strategy employed, e.g., direct vs. non-direct) were quantitatively analyzed using chi-square non-parametric analyses. All statistical analyses for non-imaging measures were conducted using SPSS 24.0 (SPSS, Chicago, IL, United States). Cohen's effect sizes (ES) were calculated for repeated measures ANOVAs with significant main effects or interactions (ES f), and for follow-up *post hoc t*-tests for dependent samples (ES dz) and for independent samples (ES d) using G*power (Version 3.1.9.2). The statistical threshold of significance was set to $\alpha = 0.05$.

FMRI Activation

FEAT v6.00 was used to conduct hierarchical voxel-wise general linear model (GLM) analyses for pre-processed fMRI data. First-level modeling was conducted for each participant. Trials with block types (retrieval, motor, and probe) and rest modeled as separate regressors, convolved with a gamma hemodynamic response function, while rest blocks were treated as a baseline. Temporal derivatives were also included in the model. Contrasts of parameter estimates (COPEs) were calculated between retrieval and motor conditions, retrieval and rest, and motor and rest. The probe condition was not examined in the current analysis due to a lack of specific hypotheses regarding brain activation for this condition. A group level GLM for each COPE was conducted with FLAME (FMRIB's Local Analysis of Mixed Effects) to assess the group average activation. In addition, separate two-group *t*-tests for each COPE were conducted to assess for sex differences. Four additional group-level GLM analyses were conducted to examine relationships between BOLD activation and performance measures; average total path length and latency to reach the platform in the retrieval condition were each examined as regressors in the higher-level model for the participant level retrieval COPE (retrieval versus rest), while these measures in the motor condition were examined as regressors in the higher-level model for the participant level motor COPE (motor versus rest). These variables were highly collinear in both retrieval and motor conditions, with a correlation of $r = 0.779$, $p < 0.000$ for path length and latency during retrieval and a correlation of $r = 0.949$, $p < 0.000$ for path length and latency during motor.

For all group level analyses, inference was done using Gaussian random field theory with cluster-based thresholding ($z = 3.1$) to control family-wise error, e.g., $p < 0.05$ corrected. Additionally, in order to understand specific increases or decreases relative to rest in frontal and hippocampal regions of interest during each condition, BOLD percent signal change was extracted from these regions for each contrast. Featquery was used with anatomical ROIs from the Harvard-Oxford Subcortical Structure Atlas to extract BOLD percent change for retrieval and motor conditions, from activated regions of the hippocampus, middle frontal gyrus (MFG), and anterior cingulate cortex (ACC) identified in the retrieval > motor contrast, and for activated regions of frontal medial cortex identified in the motor > retrieval contrast.

RESULTS

Offline vMWT Performance

There was a significant main effect of block for latency to reach the platform during Learning/retrieval trials [$F(2,58) = 9.24$, $p < 0.001$, ES f = 0.57], with shorter swim latencies observed by blocks 2 and 3 relative to block 1 [block 1 vs. 2: $t(30) = 2.34$, $p < 0.05$, ES dx = 0.42; block 1 vs. 3: $t(30) = 4.16$, $p < 0.001$, ES dx = 0.74] (**Figure 4A**, top left). No significant sex by block interaction effect was observed, however, there was a main effect of sex for latency during learning/retrieval trials [$F(1,29) = 8.72$, $p < 0.05$; ES f = 0.55], with adolescent males demonstrating a shorter latency relative to adolescent females. Similarly, for path length, there was a significant main effect of block [$F(2,58) = 6.03$, $p < 0.005$, ES f = 0.46], with a shorter path length observed by blocks 2 and 3 relative to block 1 [block 1 vs. 2: $t(30) = 2.96$, $p < 0.01$, ES dx = 0.52; block 1 vs. 3: $t(30) = 2.89$, $p < 0.001$, ES dx = 0.51] (**Figure 5A**, top left). There were no significant interactions or main effects for sex or block. For the single block of motor trials, there were no significant sex differences for latency to reach the platform or path length (**Figures 4B**, **5B**, bottom left).

On the probe trial (fixed time length of 30 s), there were significant main effects of sex for latency [$F(1,29) = 7.57$, $p < 0.05$; ES f = 0.51], latency in region [$F(1,29) = 10.74$, $p < 0.005$; ES f = 0.51] and a trend for latency in quadrant [$F(1,29) = 3.44$, $p = 0.07$; ES f = 0.34] effect sizes. However, there were no significant sex differences for path length or percent total path length in the target region, path length or percent total in the platform quadrant, or heading error (**Table 2**). Percentage of overall path length, however, was significantly different than chance for all participants for both the region (5%) and the quadrant (25%) analyses ($p = 0.000$, for both one sample *t*-tests). No significant strategy preference was observed on the probe trial: 62.5% ($n = 20$) of adolescents utilized a direct strategy and 37.5% ($n = 12$) of adolescents utilized a non-direct strategy to reach the platform [$\chi^2(1,32) = 2.00$, $p > 0.05$]. Sex differences for strategy utilization did not reach statistical significance. Of the 62.5% using a direct strategy, 55% were female and 45% were male [$\chi^2(1,20) = 0.20$, $p = 0.66$], whereas for the 37.5% using a non-direct strategy, 33% were female, and 67% were male [$\chi^2(1,12) = 1.33$, $p = 0.25$].

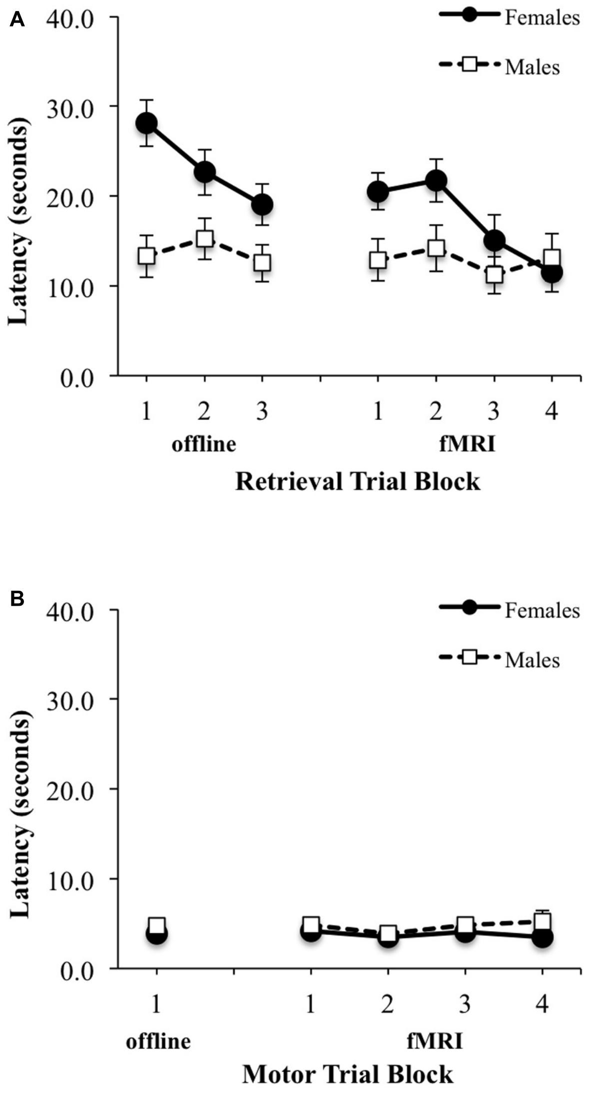

FIGURE 4 | Latency (seconds) to reach the platform during: **(A)** three offline (left) and four fMRI (right) retrieval/hidden trial blocks; **(B)** one offline (left) and four fMRI motor/visible trial blocks. Females are represented as filled black circles with solid lines and males are represented as open squares with dotted lines.

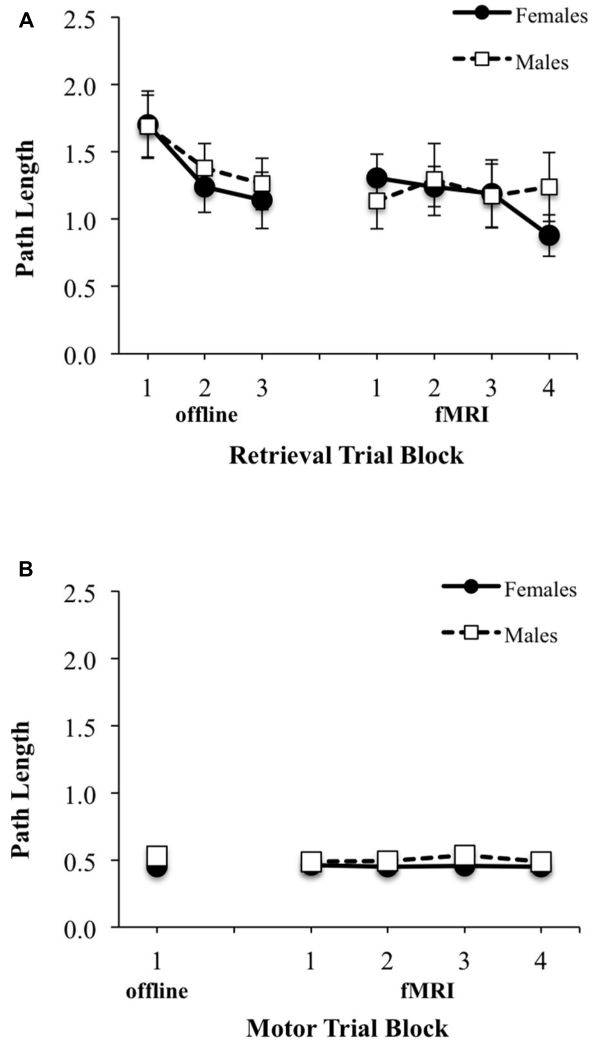

FIGURE 5 | Path length (arbitrary units) from starting location relative to pool diameter during: **(A)** three offline (left) and four fMRI (right) retrieval/hidden trial blocks; **(B)** one offline (left) and four fMRI motor/visible trial blocks. Females are represented as filled black circles with solid lines and males are represented as open squares with dotted lines.

fMRI vMWT Performance

No significant sex by block interaction was observed, however, there was a significant main effect of block for latency to reach the platform during retrieval fMRI trials [$F(3,90) = 3.16$, $p < 0.05$; ES $f = 0.32$], with shorter swim latencies observed only between block 2 and block 4 [$t(31) = 1.87$, $p < 0.05$; EF $dx = 0.41$] (**Figure 4A**, top right). There also was a trend for a sex difference was observed for latency [$F(1,30) = 4.15$, $p = 0.051$, ES $f = 0.37$], with adolescent males demonstrating a shorter overall latency relative to adolescent females. For path length during fMRI, there were no significant interactions or main effects of block or sex (**Figure 5B**, top right). There were also no significant interactions or main effects of block or sex, for latency or path length for motor trials (**Figures 4B**, **5B**, bottom right). There were significant sex differences only in the average number of completed retrieval trials [$F(1,30) = 6.11$, $p < 0.05$; ES $f = 0.45$; males: 7.82 ± 4.19; females: 4.87 ± 2.10], but not in the motor trials [$F(1,30) = 1.82$, $p = 0.19$; ES $f = 0.25$; males: 16.88 ± 2.96; females: 15.80 ± 1.01].

fMRI vMWT BOLD Activation

A contrast of the retrieval (hidden) versus motor (visible) condition revealed five spatially extended clusters comprised of multiple brain regions. Regions within these clusters included portions of hippocampus and surrounding medial temporal lobe structures, such as parahippocampal gyrus. Significant activation was also observed in frontal cortex regions, including bilateral superior frontal gyrus (SFG), bilateral MFG, ACC and

TABLE 2 | Offline probe performance data.

	Total sample ($N = 31^{a}$)	**Males ($N = 17$)**	**Females ($N = 14$)**	***p***
First move latency	4.0 ± 1.7	3.3 ± 1.3	4.8 ± 1.8	0.01*
Latency to critical region	8.7 ± 7.2	5.3 ± 2.8	12.7 ± 8.8	0.003**
Path length to critical region	0.61 ± 0.32	0.57 ± 0.29	0.67 ± 0.36	0.39
% Path length in critical region	22.6 ± 15.0	21.6 ± 12.6	23.8 ± 17.8	0.69
Latency to quadrant	6.4 ± 7.1	4.3 ± 2.8	8.9 ± 9.8	0.07
Path length to quadrant	0.48 ± 0.31	0.46 ± 0.28	0.50 ± 0.35	0.71
% Path length in quadrant	52.9 ± 24.0	52.2 ± 25.1	53.6 ± 23.5	0.87
Heading error (degree)	22.1° ± 24.1	22.7° ± 26.1	21.3° ± 22.5	0.88

Data represent mean ± standard deviation ($n = 31$). ^{a}Offline data from one female participant was not available. There were no significant sex differences on any measure.
$^{*}p < 0.05$, $^{**}p < 0.005$.

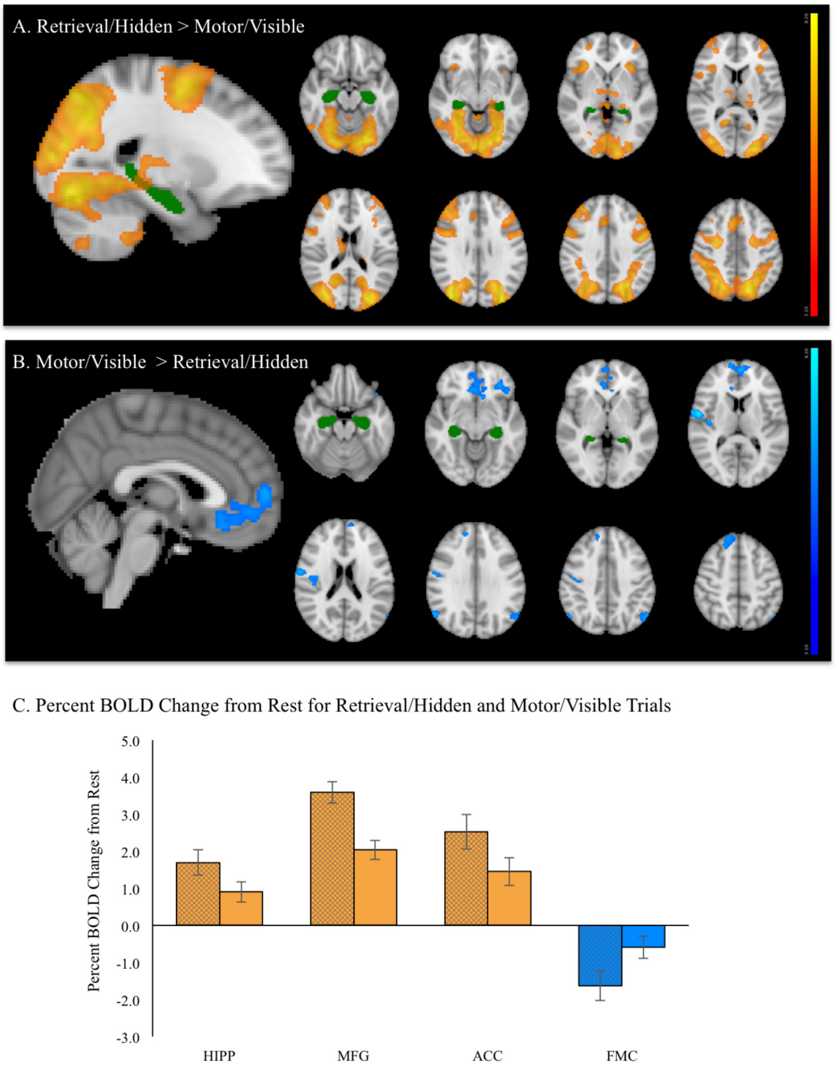

FIGURE 6 | During fMRI vMWT performance: **(A)** Regions showing significant increases in brain activation (red–yellow, $p < 0.05$ corrected) during retrieval/hidden trials (with room cues) relative to motor/visible trials (with no room cues). **(B)** Regions showing significantly greater activation (blue–light blue, $p < 0.05$ corrected) during motor/visible trials relative to retrieval (hidden platform) trials. For reference, the hippocampus region of interest from the Harvard-Oxford Subcortical Structure Atlas threshold at 30% is shown in green. **(C)** Mean % BOLD signal change for retrieval/hidden > rest (solid bars with black cross hatch) and motor/visible > rest (solid bars) extracted from hippocampus (HIPP), middle frontal gyrus (MFG), anterior cingulate cortex (ACC), and frontal medial cortex (FMC). Orange indicates increased BOLD signal, blue indicates decreased BOLD signal.

paracingulate gyrus and bilateral precentral gyrus. In addition to medial temporal and frontal areas, extensive activation was observed in visual processing areas such as bilateral fusiform gyrus and large bilateral areas of superior lateral occipital cortex. Activation also included the portions of posterior cingulate gyrus, thalamus, cerebellum, and brainstem (**Figure 6A**). A summary of the anatomical locations of local maxima for the clusters is provided in **Table 3**. In each region, mean activation was greater than rest in both retrieval/hidden and motor/visible blocks. This increased hippocampal activation relative to rest, however, as shown in the whole-brain analysis, was significantly greater for retrieval/hidden than motor/visible (**Figure 6C**, orange).

A contrast of motor > retrieval revealed seven clusters, many of which comprised multiple brain regions (**Figure 6B**). The largest of these clusters included bilateral frontal medial cortex, with activation extending into bilateral subcallosal cortex, frontal pole, ACC and paracingulate gyrus. Other frontal areas of activation included dorsal medial regions of right SFG and left frontal orbital cortex, with the latter cluster extending into left temporal pole. Significant activation also was observed in a right-lateralized cluster comprising pre- and postcentral gyrus, right insular cortex and right central opercular cortex. Other significantly activated regions for this contrast included portions of left and right superior lateral occipital cortex and right cerebellum, but not hippocampus. A summary of the anatomical locations of local maxima for the clusters is provided in **Table 4**. Notably, while retrieval > rest and motor > rest showed deactivation, the magnitude of deactivation was larger for retrieval than for motor (**Figure 6C**, blue), which contributed to the difference observed for the motor > retrieval contrast (**Figure 6B**).

There were no significant sex differences for any COPE. Regression analyses conducted to examine relationships between BOLD activation and performance measures revealed that, in the retrieval condition, longer path lengths were significantly associated with greater activation of the angular gyrus/supramarginal gyrus (retrieval > rest, **Figure 7A**). In the motor condition, both longer latencies and path lengths were associated with less activation of the frontal pole (motor > rest, **Figure 7B**).

DISCUSSION

This study demonstrates fMRI evidence that a vMWT, modeled after the classic Morris task, elicits activation of the hippocampus

TABLE 3 | Local maxima of activation: Retrieval/Hidden > Motor/Visible Contrast.

Region	Side	Volume (mm^3)	z-max $df = 31$	MNI coordinates		
				x	*y*	*z*
Extended region including:		28304				
Fusiform gyrus	L		7.04	−24	−80	−14
Superior lateral occipital cortex	R		7.03	38	−70	24
	L		6.96	−32	−86	26
	L		6.85	−30	−82	24
	R		6.85	38	−86	30
	R		6.78	38	−82	28
Extended region including:		11659				
SFG	R		6.74	22	−2	58
SFG/MFG	R		6.72	26	−2	58
Precentral gyrus/MFG	L		6.41	−32	−8	56
SFG/MFG	L		6.29	−24	−2	58
Precentral gyrus	R		6.29	24	−8	48
SFG	L		6.23	−22	−6	54
Extended region including:		271				
Cerebellum	L		5.21	−30	−72	−56
	L		5.1	−30	−70	−50
	L		3.95	−18	−76	−50
Extended region including:		150				
Cerebellum	R		4.69	26	−72	−50
	R		4.16	36	−72	−52
	R		4.06	32	−70	−46
Extended region including:		146				
Brainstem			4.6	4	−32	0
Hippocampus/PCG	L		4.04	−4	−44	4
Thalamus	R		3.69	12	−32	−4

Superior Frontal Gyrus (SFG); Middle Frontal Gyrus (MFG); Posterior Cingulate Gyrus (PCG).

TABLE 4 | Local maxima of activation: Motor/Visible > Retrieval/Hidden Contrast.

Region	Side	Volume (mm^3)	z-max $df = 31$	MNI coordinates		
				x	*y*	*z*
Extended region including:		1261				
Frontal pole, paracingulate gyrus	L		4.62	−4	58	6
Subcallosal cortex, FMC	L, R		4.45	0	30	−16
Frontal pole	R		4.2	12	64	8
Anterior subcallosal cortex	R		4.19	8	30	−10
ACC	R		4.15	10	34	4
Cingulate cortex/paracingulate gyrus	R		4.11	6	38	−2
Extended region including:		666				
Central opercular cortex	R		5.69	56	−2	10
	R		5.07	64	−2	6
Precentral gyrus	R		4.58	60	−2	16
Central opercular cortex/insular cortex	R		4.43	42	−14	14
Precentral gyrus	R		4.41	62	−4	20
Post-central gyrus/precentral gyrus	R		4.1	56	−8	28
Extended region including:		334				
Superior lateral occipital cortex	L		4.24	−56	−64	40
	L		4.09	−52	−66	42
	L		4.05	−50	−68	46
	L		4.03	−56	−66	34
	L		3.68	−60	−64	22
Extended region including:		286				
Frontal pole, SFG	R		4.3	16	42	44
Frontal pole	R		3.94	14	48	30
SFG, frontal pole	R		3.68	20	34	52
SFG	R		3.67	18	30	50
Frontal pole/SFG	R		3.48	8	44	48
Extended region including:		284				
Frontal orbital cortex	L		4.97	−44	28	−14
Frontal orbital cortex/frontal pole	L		4.02	−32	36	−10
Frontal pole	L		3.95	−36	40	−14
Temporal pole	L		3.77	−46	24	−22
Extended region including:		189				
Cerebellum	R		4.74	32	−82	−40
	R		3.61	46	−70	−38
Extended region including:		144				
Superior lateral occipital cortex	R		4.7	58	−64	34
	R		4.06	54	−66	42
	R		3.71	56	−60	46

FMC, frontal medial cortex; ACC, anterior cingulate cortex; SFG, superior frontal gyrus.

and frontal lobe regions during memory retrieval in healthy adolescents. Importantly, this version of the vMWT reliably and rigorously measures spatial memory retrieval. Behavioral performance data confirm that participants could successfully perform and learn the task, based on decreased task latencies and increased number of trials completed during fMRI (reflecting speed of performance), and decreased path lengths to reach the platform location (indicative of better accuracy, independent of speed). Despite an extensive literature documenting robust sex differences in behavioral spatial memory performance (Astur et al., 2004; Andreano and Cahill, 2009; Voyer et al., 2017), only minimal sex differences were observed in the present study. In this healthy adolescent sample, males consistently demonstrated shorter latencies to reach the platform than females during both offline learning trials (Newhouse et al., 2007; Woolley et al., 2010; Sneider et al., 2015; Piber et al., 2018) and fMRI retrieval trials, which resulted in males also completing more retrieval/hidden fMRI trials. However, path lengths to reach the platform (offline learning and probe, and during fMRI) did not differ significantly between sexes, which is consistent with prior adolescent results (Sneider et al., 2015), but not with prior data reported from in prepubertal children (Newhouse et al., 2007) or in adults (Piber et al., 2018), in which males displayed significantly shorter path lengths than females when performing

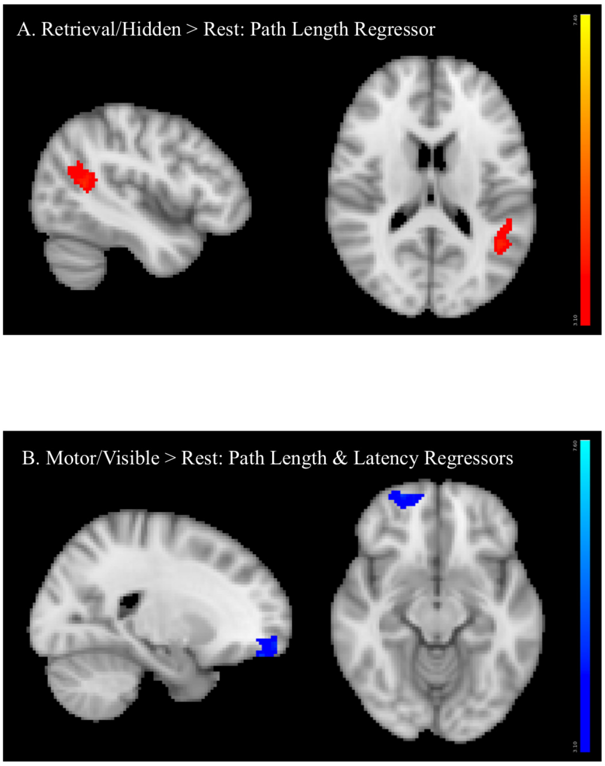

FIGURE 7 | Regression analyses between BOLD activation and performance measures showing that **(A)** longer path length (orange) was associated with greater angular gyrus/supramarginal gyrus activation (retrieval > rest) and **(B)** longer latency (dark blue) and longer path length (lighter blue) (conducted in two separate analyses, activation superimposed in the same image) were associated with less frontal pole activation (motor > rest).

a vMWT. Nonetheless, these data provide subtle behavioral evidence consistent with a male advantage on the vMWT, in that females displayed the same accuracy as males (based on path lengths and probe performance), but at the expense of taking significantly longer to complete the trial. Stronger sex differences in retrieval may emerge beyond this particular age of adolescence (13–14 years old) with changes in pubertal status, as the proportion of males employing a more efficient strategy (direct spatial strategy) for reaching the platform location is greater than in females (Astur et al., 2002), and increases with age (Sneider et al., 2015).

Significant activation was observed in left hippocampus and posterior cingulate gyrus, as well as frontal executive regions that included bilateral SFG, bilateral MFG, and ACC. Importantly, hippocampal activation was observed during the retrieval > motor contrast, but not for motor > retrieval. Moreover, when retrieval and motor conditions were independently examined relative to rest, hippocampus was activated to a greater degree during retrieval than during motor. This pattern also was observed for frontal lobe regions including the MFG and ACC, again suggesting that these regions are active during processing of spatial information to a greater extent when memory retrieval is occurring as compared to motor performance alone. These findings are consistent with regional activation reported in middle-aged adults in our previous study that used a similar version of the vMWT, although acquired using a less efficient, non-multiband fMRI paradigm (Sneider et al., 2011). The lack of sex differences in brain activation is not consistent with adult findings; however, it is possible that either brain activation did not differ due to the similarities in path lengths (accuracy) on the task, or because the sample size was too small to detect sex differences in brain activation. Although to date there are no adolescent studies to compare the current results, overall, the regions of brain activation observed are similar to those observed during navigation of a familiar environment in adults, including bilateral hippocampus, posterior cingulate, MFG, and precuneus (Hirshhorn et al., 2012), and in adults during performance of a spatial discrimination learning task who exhibited significant hippocampal BOLD activation (Dahmani and Bohbot, 2015).

Analyses conducted to examine fMRI correlates of spatial memory performance showed that worse performance, measured as longer path lengths, was significantly associated with greater recruitment of the angular gyrus/supramarginal gyrus. In contrast, worse performance on motor trials, as evidenced as longer path lengths and longer latencies, was associated with reduced recruitment of the frontal pole. The regions of activation identified in these brain/performance associations in whole brain analyses were unique from regions activated in individual task contrasts (without performance regressors). Furthermore, no significant relationships were observed for performance measures and for brain activation from specific regions of interest (hippocampus, MFG, or ACC). Nonetheless, these brain-behavior relationships are not surprising, as the activated regions associated with performance measures have been implicated in spatial cognition and memory retrieval, including angular gyrus (Seghier, 2013), and for planning action sequences, mediated by the frontal pole (Okuda et al., 2003)). The angular gyrus, including the supramarginal gyrus, also plays a role in shifting of attention toward stimuli with high salience (toward task-relevant information, i.e., environmental cues in the vMWT) and particularly to retrieved memories (Ciaramelli et al., 2008). The angular gyrus also has been implicated in a multitude of functions involving distributed subsystems with brain regions that are involved in memory, attention, action and semantics (Seghier, 2013). Thus, greater activation of the angular gyrus might be present in worse navigators who make more errors, whereas less activation of the frontal pole might be present in worse navigators who are less effective in planning their navigation path. Notably, the current cohort consisted of healthy adolescents, examined within a narrow age range, who learned to perform the spatial and non-spatial tasks well and displayed little variability in task performance. These characteristics of the behavioral data could be one reason that specific regions of interest activated during retrieval (hippocampus, MFG, or ACC) were not significantly associated with performance.

A limitation of this study was the modest sample size of 32 adolescent participants, although this sample size is relatively typical for fMRI studies, and participants were healthy, well characterized and within a narrow age range. It is acknowledged that WASI IQ estimates were ∼1.5 standard deviations above the mean, which may not reflect the general population, and accordingly, could impact learning and memory measures, as well as BOLD signal. Preliminary sex differences were evident for some behavioral measures, but not for BOLD activation. A lack of BOLD differences could be due to a sample size that did not provide enough power to permit a full investigation of sex differences. Hence, sex differences reported, or lack thereof, should be interpreted with caution. A second study limitation was motion during the fMRI acquisition. However, participants with greater than 5 mm movement at any time point were excluded, after standard motion correction of remaining data, ICA-AROMA was applied to denoise motion effects from the fMRI data to further mitigate the impact of motion. Group level maps reflect clearly delineated brain regions that resemble well-known brain networks, thus the strategy used for motion reduction was successful. Finally, as the current vMWT paradigm acquired BOLD fMRI data during retrieval rather than during encoding (learning), it was necessary to establish that adolescent participants could successfully complete the task during fMRI (successfully retrieve the memory of the platform location), otherwise BOLD fMRI may have reflected navigation, rather than a longer-term memory process such as retrieval. Acquiring BOLD signal during learning could be accomplished, however, given the required efficiency of the block design and the relatively short, fixed length of hidden platform trials, it may have been more difficult for adolescents to learn the task for the first time while in the scanner. It also is plausible that participants continued to encode spatial information during fMRI, especially adolescent females who appeared to continue to show decreased latency over retrieval trials. These limitations should be addressed in future investigations.

CONCLUSION

Data from this study demonstrate hippocampal activation when adolescents learned to use cues to navigate successfully in a virtual environment (retrieval memory). Activation during retrieval also was observed in several key frontal lobes critical for executive functioning, including planning, organizing, error monitoring, and decision-making. Thus, this translational task successfully targets neurocircuitry relevant for memory function in adolescents, which provides feasibility of this rigorous vMWT application for tracking developmental changes in integrated hippocampal and prefrontal neural activation and resource utilization (Murty et al., 2016). To this end, these adolescents are completing two additional annual neuroimaging assessments, along with assessments of perception of risk for alcohol and drug use, cognition, changes in mental health (e.g., depression and anxiety), and other behaviors particularly relevant to adolescent (e.g., risk taking, sensation seeking, impulsivity and delay discounting). As quarterly follow-up surveys and yearly visits reveal new alcohol and other drug use in particular, which is common during this passage of adolescence, the current data provide an important baseline for interpreting the impact of later initiation on the developmental maturation of hippocampal and frontal circuitry on the vMWT. Such examination of youth prior to behaviors that are maladaptive, e.g., alcohol and drug initiation, may also help establish a neurobiological signature that predicts who is at heightened risk for onset and continued use, and emerging issues with mental health (increased depressive and anxiety symptoms), which could concomitantly interfere with the incorporation of experience into adaptive behaviors required for transitioning through adolescence (Murty et al., 2016).

AUTHOR CONTRIBUTIONS

JS and MS were involved in all aspects of the research, including conception and design of the fMRI paradigm and study, analysis, interpretation, and writing the manuscript. DH was involved in task programming and data processing. JC-G was involved in the analysis, interpretation, and writing the manuscript. ES, NG, EO, and AS were involved in recruitment, study coordination, acquisition of all study data, and administration of the vMWT during fMRI. MR was involved in development of the multiband fMRI protocol on the 3T scanner. SH recruited participants and contributed to the concept and design of the study, interpretation of data, and review of the manuscript. LN provided training and oversight of all fMRI processing and data analysis. All authors read and approved the final manuscript.

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The Complex Nature of Hippocampal-Striatal Interactions in Spatial Navigation

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Decades of research have established the importance of the hippocampus for episodic and spatial memory. In spatial navigation tasks, the role of the hippocampus has been classically juxtaposed with the role of the dorsal striatum, the latter of which has been characterized as a system important for implementing stimulus-response and action-outcome associations. In many neuroimaging paradigms, this has been explored through contrasting way finding and route-following behavior. The distinction between the contributions of the hippocampus and striatum to spatial navigation has been supported by extensive literature. Convergent research has also underscored the fact that these different memory systems can interact in dynamic ways and contribute to a broad range of navigational scenarios. For example, although familiar routes may often be navigable based on stimulus-response associations, hippocampal episodic memory mechanisms can also contribute to egocentric route-oriented memory, enabling recall of context-dependent sequences of landmarks or the actions to be made at decision points. Additionally, the literature has stressed the importance of *subdividing* the striatum into functional gradients—with more ventral and medial components being important for the behavioral expression of hippocampal-dependent spatial memories. More research is needed to reveal how networks involving these regions process and respond to dynamic changes in memory and control demands over the course of navigational events. In this Perspective article, we suggest that a critical direction for navigation research is to further characterize how hippocampal and striatal subdivisions interact in different navigational contexts.

Keywords: hippocampus, caudate, striatum, navigation, planning, strategies

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INTRODUCTION

In our daily lives, we are continually faced with decisions about where to go next and how to get there. Making these decisions can rely on a map-like representation of the overall spatial environment which we occupy, as well as retrieval of memories for routes that connect different locations. Flexible selection between learned routes to our destinations often involves disambiguating memory traces for similar, or even physically overlapping, locations. Alternative routes can introduce computational demands on declarative memory and response selection circuitry, which can vary depending on how ambiguous the current context is and how well-learned the behaviors are. As we navigate branches between overlapping routes (**Figure 1**) or attempt to retrieve different memories of the same location, we may need to rely on neural systems

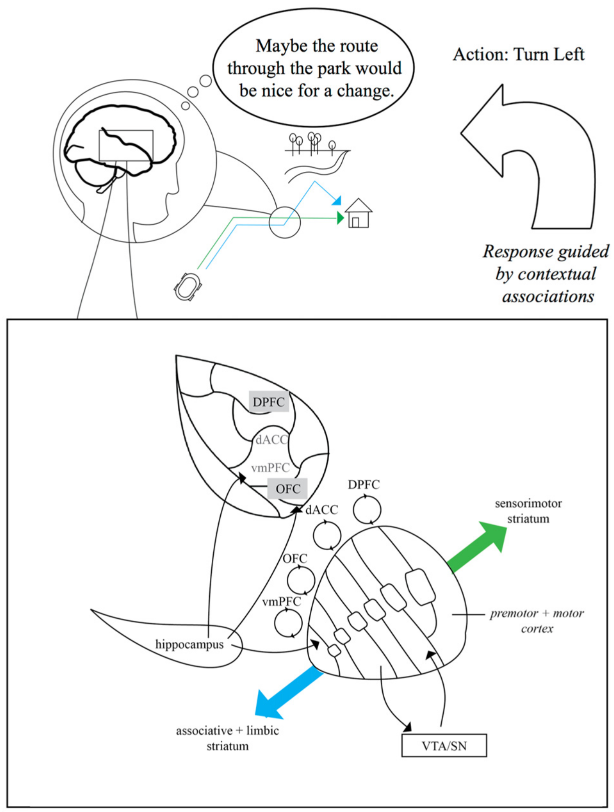

FIGURE 1 | Schematic of striatal anatomy and hippocampal-dorsal striatal contributions to navigational route flexibility. Inset box: coronal view of the striatum and some relevant connections. The striatum receives dopaminergic input from ventral tegmental area (VTA) and the substantia nigra (SN). Primate dorsomedial striatum (DMS) is characterized by partially-overlapping reciprocal connectivity with ventral striatum (VS) and ventromedial prefrontal cortex (PFC) (vmPFC), orbitofrontal cortex (OFC), dorsal anterior cingulate cortex (dACC) and dorsal prefrontal areas (DPFC). Striatum-PFC connectivity is a continuum that changes as we move dorsal and lateral from "limbic" and "associative" striatum (DMS) towards the "sensorimotor" striatum (DLS). DMS function can interface with hippocampal function via hippocampal inputs to VS and to shared prefrontal targets (particularly vmPFC and OFC). Upper figure: conceptual example of the balance between model-free and model-based navigation. Model-free navigation (e.g., green "habitual" route) may be governed by DLS. When goals change (e.g., blue alternative route), mnemonic input from the hippocampus to VS and PFC enables contextual traces (e.g., goal states and event memory cues) to guide model-based action selection and updating via DMS-frontostriatial loops. In this example, the navigator might disengage from an overlearned route home (green route), suppressing a "straight" action in favor of a goal-directed left-turn into the park (blue route). Gray text boxes on PFC indicate subdivisions on the lateral surface.

that: (a) enable behavioral flexibility and cognitive control; and (b) enable context-dependent retrieval of episodes. The striatum and hippocampus, respectively, are parts of these systems, and are functionally linked via the prefrontal cortex (PFC). This Perspective article, highlights research indicating that the functions of these structures may interact to enable the types of flexible navigational decisions we often make in our daily lives.

Our perspective article is focused on two overlapping literatures, which we briefly survey below and then elaborate on in separate sections. Building on the famous discovery of "place cells" and on landmark case studies involving patient H.M., research has established the importance of the hippocampus for both spatial and episodic memory (Scoville and Milner, 1957; O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978; O'Keefe et al., 1998; Eichenbaum et al., 2007; Squire et al., 2007; Harand et al., 2012; Corkin, 2013; Squire and Dede, 2015). Critically, space is a core component within the definition of episodic memory (Tulving, 1972). Findings in rodents and humans: (a) demonstrate context-dependent coding of space in the hippocampus; and (b) indicate that the hippocampus is important for disambiguation and episodic retrieval of overlapping navigational memories (Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Lee et al., 2006; Smith and Mizumori, 2006; Brown et al., 2010, 2012; Brown and Stern, 2014; Brown et al., 2014; Chanales et al., 2017).

Navigational route disambiguation provides an important example of the link between navigation and episodic memory mechanisms (Hasselmo and Eichenbaum, 2005), because seminal fMRI studies have emphasized preferential engagement of the hippocampus for map-based over egocentric landmark or route-based navigation (Hartley et al., 2003; Iaria et al., 2003; Doeller et al., 2008; Marchette et al., 2011). Such work has been critical for establishing functional links between the human hippocampus and "map-like" representations of environments that could be supported by place cells observed in rodents and recently humans (O'Keefe and Nadel, 1978; Thompson and Best, 1989; O'Keefe et al., 1998; Eichenbaum et al., 1999; Eichenbaum, 2000; Ekstrom et al., 2003). However, retrieval of navigational routes can be framed as retrieval of sequential, spatio-temporal events that may draw upon episodic memory mechanisms (particularly when overlap between routes increases contextual-dependency of behavior).

Indeed, the rodent literature demonstrates that place cells fire in sequences and along routes, potentially helping link specific sequences of turns and landmarks to eventual rewards and goals (Johnson and Redish, 2007; Wikenheiser and Redish, 2015). Therefore, particularly in cases when stimulus-response associations may be inadequate for overcoming multiple possible actions for a location, hippocampal-dependent memory for sequences can enable accurate goal-directed behavior. Paralleling data from neural recordings in rodents (Wikenheiser and Redish, 2015), we have recently demonstrated evidence in humans for the hippocampus supporting such a retrieval mechanism in a highly familiar environment (Brown et al., 2016). These data illustrate the broader point, which we revisit in the next section, that in some circumstances the medial temporal lobe (MTL) declarative memory system may cooperate with components of the striatum to retrieve memories (Scimeca and Badre, 2012) and navigate decision points along routes (Johnson et al., 2007).

Our Perspective article also focuses on the role of the dorsal striatum in navigation. As noted above, a classic distinction has been made between the functioning of the dorsal striatum and the hippocampus (Packard and McGaugh, 1996; Hartley et al., 2003; Iaria et al., 2003; Doeller et al., 2008; Marchette et al., 2011). Importantly, it is well-known that the dorsal striatum is not a functionally-uniform region. It can be *subdivided* into functional gradients, with more ventral and medial components being important for the behavioral acquisition and expression of hippocampal-dependent memories and alternate behaviors in maze environments (Devan and White, 1999; Ragozzino, 2002; DeCoteau et al., 2007; Thorn et al., 2010). Indeed, recent research in both humans and rodents has emphasized that although one function of the striatum is the formation and execution of inflexible stimulus-response associations ("habits"; Yin and Knowlton, 2006), frontostriatal loops may also enable us to flexibly update prepotent navigational responses and leverage mnemonic signals from the hippocampus to drive context-dependent spatial decision-making and responding (Brown et al., 2012; Brown and Stern, 2014; Ferbinteanu, 2016; **Figure 1**).

The distinct hippocampal and dorsal striatal systems may dynamically interact to enable us to fluidly transition between more rigid and flexible navigational behaviors, and to translate declarative memory into guidance of ongoing actions. The literature suggests these interactions between dorsal striatum and hippocampal regions may be mediated by PFC and ventral striatum (VS).

HIPPOCAMPAL MECHANISMS FOR SPATIAL MAPPING AND ROUTE LEARNING

As noted above, much imaging research has focused on the role of the hippocampus in retrieving "map-like" declarative knowledge of spatial environments. Such hippocampal-dependent knowledge is putatively built upon underlying spatial mapping mechanisms in the MTL (place and grid cells, Buzsáki and Moser, 2013) and the broader network supporting allocentric reference frames in navigation (Ekstrom et al., 2014). In some conceptual frameworks, hippocampal function has been explicitly linked with path integration (Wolbers et al., 2007; Sherrill et al., 2013; Chrastil et al., 2015). By contrast, egocentric landmark or route-oriented navigation has been attributed to striatal-dependent motor associations for environmental cues (Hartley et al., 2003; Iaria et al., 2003; Doeller et al., 2008; Marchette et al., 2011).

In a recent critical review of the literature, Ekstrom et al. (2014) argued that the study of the cognitive basis of allocentric memory has been complicated by the fact that many imaging studies may involve a blending of allocentric and egocentric representations in some form. Consequently, they argue that attributing signals to one reference frame or the other may be challenging (for broader discussion, see also Wolbers and Wiener, 2014). Indeed, the same hippocampal cell can encode place information when an animal engages in place-based strategies, and sequential state information during route-based navigation (Cabral et al., 2014). Ekstrom et al. (2014) argue that allocentric memory need not emerge from a singular type of representation in one region (such as the hippocampus), but could arise from a convergence of partially-overlapping computations in a broad network of areas that have been attributed to either allocentric and egocentric reference frames in various experiments. Here, we emphasize complementary evidence linking hippocampal function to route-based navigation. The rodent hippocampus has been explicitly linked to egocentric route navigation by demonstrating that mice lacking CA1 NMDA receptors were impaired in acquisition of both egocentric and allocentric memory for navigation (Rondi-Reig et al., 2006). This group has recently extended this to humans, with evidence the hippocampal association with route-based navigation may be left lateralized (Iglói et al., 2010).

One bridge between allocentric and egocentric navigational memory is to consider hippocampal representations of location as a mechanism underlying the ability to associate stimuli and experiences across space and time (Eichenbaum and Cohen, 2014). In the real-world, episodic memories encompass the "who, what, when and where" of an experience and, thus, require the ability to embed non-spatial information (e.g., faces and objects) in memory for environments (e.g., Burgess et al., 2001; reviewed in Burgess et al., 2002; Bird and Burgess, 2008). The early discovery of "place cells" in the hippocampus (O'Keefe and Dostrovsky, 1971; O'Keefe, 1976) lent critical neurobiological support to the concept of a "cognitive map" (Tolman, 1948; O'Keefe and Nadel, 1978). Since then this spatial mapping framework has been extended by evidence that place cell activity during route navigation exhibits hallmarks of episodic memory: the ability to fire in sequences, and in a context-dependent manner (Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Lee et al., 2006; Smith and Mizumori, 2006; Johnson and Redish, 2007; Wikenheiser and Redish, 2015; Ólafsdóttir et al., 2015). Although relatively sparse, complementary work in humans has shown that hippocampal gray matter volume and function similarly support context-dependent route navigation (Brown et al., 2010, 2012, 2014; Brown and Stern, 2014; Chanales et al., 2017). The role of the human hippocampus in route-based navigation (Iglói et al., 2010) includes specific computations relevant to goal-directed decision-making, such as encoding path length of routes to goals (Howard et al., 2014).

Indeed, it is important to note that access to a spatial representation does not necessarily lead to a map-based strategy, as in the case of place-recognition triggered response strategies (Trullier et al., 1997). It is also important to consider how sequential firing for navigational routes could facilitate mechanisms of memory formation, retrieval, and even planning. Sequential firing potentially helps link specific turns and landmarks to memories for specific events and to eventual rewards and goals, and continued experience with routes may ultimately give rise to more "semanticized" map-level representations (Buzsáki, 2005; Buzsáki and Moser, 2013). During rest periods, sequential place cell firing could reflect the hippocampus "practicing" encoded route memories in service of consolidation—enabling long-term spatial memory (Wilson and McNaughton, 1994; McKenzie and Eichenbaum, 2011). Indeed, replay following new spatial learning predicts subsequent memory performance (Dupret et al., 2010) and post-encoding disruption of hippocampal sharp-wave ripples impairs subsequent spatial memory (Girardeau et al., 2009). Likewise, triggering place cell activity during sleep influences waking spatial behavior (De Lavilléon et al., 2015).

Similarly, sequential place expression may give rise to mnemonic signals important for *planning* routes (Ólafsdóttir et al., 2018). Specifically, place coding associated with cognitive mapping can also contribute to order sequencing of goal-oriented spatio-behavioral events (Howard et al., 2014). This includes prospective replay of navigational routes in both rodents and humans (Johnson and Redish, 2007; Foster and Knierim, 2012; Wikenheiser and Redish, 2015; Brown et al., 2016), as well as coding of goal and path distances (Sherrill et al., 2013; Howard et al., 2014; Spiers et al., 2017). Such evidence from rodent and human spatial navigation literature is suggestive of mechanistic links between hippocampal memory and prospective planning and motor selection processes.

These scenarios present interesting opportunities for future research. For example, overlapping routes present situations in which the brain may dynamically shift between stimulus-response and hippocampal-dependent associations as the navigator traverses more and less automated decision points. This shift may be associated with engagement of prefrontal cognitive control and evaluation processes (Brown et al., 2012). How these dynamics are mediated, and how the brain detects a need for high control in some states vs. an opportunity to release cognitive resources in others (e.g., when behavior can return to a more habitual state), is an area ripe for additional research (we return to this idea in the next section). There is also a need for research testing models of how route navigation can be solved by either: (a) an initial retrieval of the sequence that is maintained in working memory until critical decision points (Zilli and Hasselmo, 2008a); or (b) retrieval of necessary information for critical decisions that are cued at the decision points themselves (Zilli and Hasselmo, 2008b). What network dynamics determine when and how route-oriented navigation is guided by prospective or retrospective hippocampal processes?

One takeaway from the above literature is that a distinction between hippocampal and striatal function in navigation may be better framed according to the computational process, rather than the type of information (e.g., place-oriented). In particular some researchers have advocated characterizing navigation within a reinforcement learning perspective of behavior (for review and recent fMRI work, see Khamassi and Humphries, 2012; Simon and Daw, 2011), with the contributions of the hippocampus and different striatal subdivisions attributed to model-based or model-free mechanisms. As framed by this line of work, the hippocampus (and components of the striatum discussed further in the "Striatal Subdivisions and the Translation of Memory Into Behavior" section) may contribute to goal-directed, model-based behavior. Independent of perspective (allocentric or egocentric) or information type (explicitly spatial or not), this circuitry is theorized to enable construction and updating of a world/task model.

One important point is that despite its central role in spatial navigation, the hippocampus is not anatomically positioned to directly control motor behavior. However, hippocampal regions have direct connections with PFC and frontostriatal loops (by proxy) (Alexander et al., 1986; Cavada et al., 2000; Middleton and Strick, 2002; Haber et al., 2006; Roberts et al., 2007; **Figure 1**). Moreover, the hippocampus sends direct projections to the VS (Thierry et al., 2000), which can provide an explicit link between hippocampal memory output and striatal reward signals that strongly influence goal-directed behavior (Khamassi and Humphries, 2012). These hippocampal-prefrontal-striatal connections could enable flexible decision-making and behavioral updating (Brown et al., 2012, 2016; Brown and Stern, 2014; Ferbinteanu, 2016) based on the goal-directed output from the hippocampus during planning and navigation. Models of navigation have proposed that spatially-diffuse firing of place cells in the subiculum of the hippocampus may support coding of goals (Burgess and O'Keefe, 1996). Such signals could reflect interactions with PFC and reward circuitry. Babayan et al. (2017) showed that the hippocampus, VS and dorsomedial striatum (DMS) operate as a network in service of route navigation. In their study, the hippocampus served as network node involved in learning a sequential egocentric strategy, and as a network hub when sustaining sequence-based navigation. Therefore, although hippocampal and striatal forms of memory may differ in fundamental ways (White and McDonald, 2002; Graybiel and Grafton, 2015), our ability to engage in model-based navigation in real-world settings may draw on subdivisions of both regions. More generally, integration of MTL and frontostriatal computations may be important for memory and memory-guided behavior in many scenarios as a function of their combined relevance to current task demands (Moses et al., 2010; Ben-Yakov and Dudai, 2011; Ross et al., 2011; Sadeh et al., 2011). Below, we further outline the potential complementary roles of dorsal striatal in real-life navigational contexts.

STRIATAL SUBDIVISIONS AND THE TRANSLATION OF MEMORY INTO BEHAVIOR

The striatum is a large, heterogeneous region of the brain that can broadly be divided into ventral, dorsomedial and dorsolateral subregions, although this organization may be best viewed as a gradient of anatomical connections with different prefrontal divisions and with a different functional emphasis within regions (Haber and Knutson, 2010). The striatum is a principal interface in the motor/reward/addiction circuit that receives glutamatergic inputs from the amygdala, thalamus, hippocampus and cortex; and dopaminergic inputs from the ventral tegmental area (VTA) and the substantia nigra (SN; Haber and Knutson, 2010; Yager et al., 2015). Although the striatum is a component of the "reward" circuit, it also interacts with memory, emotion, and cognitive planning areas of the MTL and PFC to contribute flexibility to responses and decision making (Haber and Knutson, 2010; Brown et al., 2012; Scimeca and Badre, 2012; Yager et al., 2015; Ferbinteanu, 2016).

In spatial navigation research, a classic dichotomy between hippocampal-dependent and dorsal striatal-dependent memory emerged with Packard and McGaugh's (1996) demonstration that hippocampal function supported a "navigate-to-place" strategy, as opposed to a dorsal striatum-dependent response-learning strategy. In this classic experiment, inactivation of the hippocampus resulted in a blockade of place learning, whereas inactivation of the caudate (a component of the dorsal striatum) resulted in a blockade of response learning. As discussed above, this classic dissociation has found extensive parallels in human navigation research (Hartley et al., 2003; Iaria et al., 2003; Doeller et al., 2008; Marchette et al., 2011). Indeed, gray matter volume in the hippocampus and caudate nucleus differentially correlate with the predisposition of a person to rely on spatial knowledge or response-based strategies to solve navigational problems (Bohbot et al., 2007; Konishi and Bohbot, 2013).

Early work in rodents (Devan and White, 1999) also prompted attention to functional subdivisions of the striatum. Devan and White's (1999) findings indicated that DMS, in contrast to dorsolateral striatum (DLS), might be important for promoting flexible, hippocampally-dependent navigation behavior. They demonstrated that lesions to medial caudate-putamen resulted in a preference for cue-guided responses, whereas lesions to the lateral caudate-putamen resulted in a preference for spatial responses. This finding contributed to the emergent idea that through parallel pathways, which can interact via the hippocampal-prefrontal-striatal connectivity described above (**Figure 1**), mnemonic signals and decision-making processes could regulate action selection and "downstream" processing in DLS and motor cortex (Brown et al., 2012).

Adopting a reinforcement-learning perspective of model-based and model-free navigation may be advantageous over attributing striatal function to response vs. place strategies (Simon and Daw, 2011; Khamassi and Humphries, 2012). Specifically, in conjunction with the hippocampus, the DMS may support behavior based on an inner representation of world or task space and model-based processing, whereas model-free response learning can underlie "habits" and may be attributable to the DLS (Daw et al., 2005; Khamassi and Humphries, 2012). The tightly reward-related VS may play a key role in the model building process for model-based action. Model-based control is predictive, based on action-outcome contingencies that can quickly incorporate changes in goal-relevant information (reward) throughout a world model. This gives rise to a system that can support goal-directed changes in behavior and contrasts with model-free responses emerging from gradually-learned independent action-state representations (Simon and Daw, 2011; Khamassi and Humphries, 2012). taxonomy of striatal subdivision mechanisms offers a view of how this system enables transitions from flexible to relatively automated navigational behavior, without attributing a specific information type to simple state-response information (model-free) or predictive action-outcome based processing (model-based).

One aspect of our view is that the dorsal striatum functions as a prepotent motor response regulating structure. That is, the striatum collectively enables habitual motor control, but increasingly medial and ventral components interface with dorsolateral, medial and ventral/orbital PFC to help govern *flexible* suppression, selection and updating of responses (Yin and Knowlton, 2004, 2006; Haber et al., 2006; Haber and Knutson, 2010). Through a pattern of partially-overlapping reciprocal connections (**Figure 1**), reward and goal-oriented processing in PFC and its associated VS and DMS subdivisions can exert control over behavior that could otherwise be governed by response associations. Having a "habit" system is very adaptive, and its utility can be exemplified by navigational scenarios in which responses based on stimulus-response associations can free up cognition for, e.g., holding conversations, monitoring for threats (Schwabe and Wolf, 2013), or planning how to achieve unrelated goals. However, the functional continuum in the dorsal striatum, grounded in differential connectivity with prefrontal subdivisions (Yin and Knowlton, 2006; Haber and Knutson, 2010) gives rise to an elegant system that can also re-engage with such ongoing behavior to exert cognitive control over, or update, our motor response program when it's adaptive to do so. Studies targeting how this system can learn and implement stimulus-control state associations in spatial environments will be of substantial impact for theories of when and how navigational behaviors are executed in more or less automated manners. It has been proposed that this depends on function of the caudate and its interactions with the hippocampus in humans (Jiang et al., 2015; Chiu et al., 2017).

Although surprisingly under-studied in human navigation, the view that the caudate is involved in flexible behavior is not novel. Research has long associated striatal function with set-shifting, cognitive flexibility, and rule learning (Alexander et al., 1986; Middleton and Strick, 2000; Seger and Cincotta, 2005; Graham et al., 2009; Vaghi et al., 2017). One extension of the human navigation literature addressing this point (e.g., Brown et al., 2012) is evidence that indirect connectivity between the hippocampus and caudate may enable these distinct memory systems to compensate for one another and preserve navigation ability when one system starts to fail. This has been observed with hippocampal compensation for route-based navigation in patients with Huntington's Disease (Voermans et al., 2004).

In keeping with Khamassi and Humphries's (2012) theoretical perspective, the DMS contributes to non-habitual route-based navigation in part through interactions with hippocampus. The DMS supports the ability of rodents to learn and execute alternative behaviors in environments (Ragozzino, 2002; DeCoteau et al., 2007; Ragozzino et al., 2009; Baker and Ragozzino, 2014). Specifically, the DMS is a key network node alongside the VS and hippocampus for egocentric route-based navigation (Babayan et al., 2017), and DeCoteau et al. (2007) demonstrated that hippocampal and DMS theta oscillations are tightly coupled during critical choice periods in T-mazes. Such functional connectivity data indicate that these two systems actively interact in service of goal-directed route navigation. This work has been mirrored in recent fMRI research in humans (Brown et al., 2010, 2012), and has revealed parallel, dynamic changes in the hippocampus and DMS that track learning, suggesting both structures contribute to the ability of humans to learn new alternative, memory-dependent responses (Brown and Stern, 2014). Looking forward, an especially open area for future imaging research is testing whether different learning dynamics which have been observed in rodent dorsal striatal subdivisions (Thorn et al., 2010) underlie development of model-based and model-free navigational behavior in humans. An important recent discovery suggests that even a distinction between DMS and DLS for comparatively flexible and inflexible navigation may be insufficient (Ferbinteanu, 2016). They found that the contributions of dorsal striatal subdivisions to memory-guided behavior are also influenced by training history. DMS was found to support both response-based and spatial (hippocampal-dependent) navigational strategies, consistent with a role for this region in translating mnemonic content into ongoing behavior. However, they also found that the DLS and hippocampus could support their respective alternative place- and response-based navigational strategies if the animal was concurrently trained to solve the task based on both types of cues. This work suggests that the entirety of the dorsal striatum can contribute, in some circumstances (see also Miyoshi et al., 2012), to navigational behaviors which also draw upon spatial mapping mechanisms.

FUTURE DIRECTIONS

The data reviewed above suggest that a particularly fruitful direction for navigation research is systematic examination of: (1) the contributions of different striatal subdivisions in navigation under different learning conditions; and (2) how interactions between these subregions with spatial and non-spatial contextual information from the hippocampus (putatively mediated via the PFC and VS) drives flexible decision-making behavior. Prior work juxtaposing reward, action, and route representations in VS, dorsal striatum and hippocampus (van der Meer et al., 2010) sets the stage for examining differences within dorsal striatal subregions in a similar manner.

Another critical direction for future work converges with active research into the hierarchical organization of the PFC (Desrochers and Badre, 2012). Given evidence that dorsal striatal function may be organized according to its reciprocal connections with prefrontal subdivisions (Haber et al., 2006; Haber and Knutson, 2010), future work should target striatal contributions to navigation through the lens of associated prefrontal functional subdivisions, with attention to how these hierarchies may enable us to juggle "habitual" impulses to landmark cues with contextual guidance from the declarative memory system. Studies targeting how networks incorporating the hippocampus and subdivisions along the ventromedial-dorsolateral extent of the striatum learn, detect and implement shifts from more model-based to model-free action dynamically as control demands change (Jiang et al., 2015; Chiu et al., 2017) will be of substantial impact. Future imaging research could also more explicitly focus on how "value" is assigned to locations, particularly from a reinforcement learning perspective (Simon and Daw, 2011; Khamassi and Humphries, 2012). Such work could advance our understanding behavioral flexibility in navigation, and potentially inform interventions that leverage incentives to improve learning in rehabilitation settings.

AUTHOR CONTRIBUTIONS

SG, JS and TB wrote and reviewed all aspects of the manuscript. SG generated the figure.

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Tracing a Route and Finding a Shortcut: The Working Memory, Motivational, and Personality Factors Involved

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Wayfinding (WF) is the ability to move around efficiently and find the way from a starting point to a destination. It is a component of spatial navigation, a coordinate and goal-directed movement of one's self through the environment. In the present study, the relationship between WF tasks (route tracing and shortcut finding) and individual factors were explored with the hypothesis that WF tasks would be predicted by different types of cognitive, affective, motivational variables, and personality factors. A group of 116 university students (88 F.) were conducted along a route in a virtual environment and then asked first to trace the same route again, and then to find a shortcut between the start and end points. Several instruments assessing visuospatial working memory, mental rotation ability, self-efficacy, spatial anxiety, positive attitude to exploring, and personality traits were administered. The results showed that a latent spatial ability factor (measured with the visuospatial working memory and mental rotations tests) – controlled for gender – predicted route-tracing performance, while self-report measures of anxiety, efficacy, and pleasure in exploring, and some personality traits were more likely to predict shortcut-finding performance. We concluded that both personality and cognitive abilities affect WF performance, but differently, depending on the requirements of the task.

Keywords: virtual exploration, wayfinding, visuospatial working memory, mental rotation, personality traits, pleasure in exploring, spatial anxiety, self-efficacy

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INTRODUCTION

Wayfinding: Multiple Abilities and Processes

Wayfinding (WF) is generally defined as the ability to move around efficiently and find the way from a starting point to a destination (Montello, 2005).

It is widely acknowledged that WF is a multicomponent ability (Hegarty et al., 2006; Wolbers and Hegarty, 2010) susceptible to broad individual differences (Hegarty and Waller, 2005), ranging from individuals who suffer from severe orientation deficits from childhood onward (Iaria et al., 2009; Iaria and Burles, 2016; Piccardi et al., 2017) to people with excellent orientation skills (Verde et al., 2015). It has been largely established that various mechanisms and processes are implicated in WF (Wolbers and Hegarty, 2010), and served by a complex network of neural substrates (Wegman et al., 2014).

The direct involvement of different working memory (WM) components has been demonstrated by using dual task paradigms in experiments in which participants were asked to perform WF tasks while concurrently performing secondary tasks assumed to load different WM components (Garden et al., 2002; Labate et al., 2014; Meilinger et al., 2008). On the whole, these studies proved that visuospatial working memory (VSWM) is implicated in the performance of spatial navigation tasks. These results converge with those of other studies using structural equation modeling that found a role for VSWM in the performance of spatial navigation tasks (Allen et al., 1996; Meneghetti et al., 2016). Correlational and structural equation modeling studies likewise found relationships between scores obtained in tests on spatial abilities [mainly involving mental rotation tasks (MRT)] and in WF tasks (Hegarty et al., 2006; Muffato et al., 2017).

There is also evidence of stress and/or anxiety harming WF performance (Hund and Minarik, 2006; Walkowiak et al., 2015), particularly in difficult tasks (Srinivas, 2011). Spatial anxiety, i.e., the degree of anxiety experienced when performing spatial tasks, is related to a worse performance in navigation tasks (e.g., Lawton, 1994, 2010; Schmitz, 1997). It may act as a mediator in gender-related differences, and be associated with particular spatial representation strategies (Lawton and Kallai, 2002). Schmitz (1997) found that spatial anxiety slowed WF performance in a virtual environment (VE); and Lawton (1994) showed that it correlated with route WF strategy use, and that more spatial anxiety was associated with less spatial competence.

As for the positive emotions, it was found that individuals who take pleasure in exploring places tend to have a good sense of direction (De Beni et al., 2014), and perform better in spatial tasks (Meneghetti et al., 2014; Muffato et al., 2016, 2017). In the same vein, Pazzaglia et al. (2017) showed that a significant part of the variability in the performance of a shortcut-finding task was explained by an aggregate measure of pleasure in exploring and spatial self-efficacy. Interestingly, the strength of the relationship between subjective measures and WF tasks seems to depend on how difficult the task is: the tougher the task, the stronger the relationship (Weisberg et al., 2014; Pazzaglia et al., 2017)

The study by Pazzaglia et al. (2017) suggests that self-efficacy, as well as anxiety, may affect WF behavior. Bandura (1997) described self-efficacy (a motivational factor traditionally defined from a socio-cognitive perspective) as a person's belief in their ability to accomplish a task. Its influence has been demonstrated in a number of domains, including: cognitive development (Bandura, 1993); self-regulated learning and academic motivation (Schunk and Di Benedetto, 2014); and performance in sports (Moritz et al., 2000).

Other factors relating to spatial task performance have been explored from a socio-cognitive perspective too. For instance, stereotype threat (Maass and Cadinu, 2003), and gender identification (Yang and Merrill, 2016) revealed a role in determining performance in mental rotation tasks: young women did worse in the MRT when under stereotype threat than in a non-stereotyped control condition (Moè and Pazzaglia, 2006); and gender identification seemed to interact with stereotype threat in worsening MRT performance (Nori et al., 2009). Taken together, the literature reviewed above suggests that emotions and motivation can play a part in spatial learning, and these factors need to be further explored in the specific case of WF.

Another order of variables that might influence WF ability regards personality. Already Tolman (1938) introduced personality variables among the factors prone to affect navigation behavior in rats. Bryant (1982) subsequently found that personality measures correlated with self-reports of Sense of Direction (SOD, flexibility, worrying about becoming lost, dominance, capacity for status, sociability, social presence, self-acceptance, well-being, and intellectual efficiency), and pointing errors (capacity for status, sociability, social presence, and self-acceptance), and concluded that personality dispositions are important to the acquisition and accuracy of mental representations of the environment.

In line with these assumptions the literature supports a relationship between certain personality traits and performance in spatial and WF tasks. Extroversion is one of the personality traits most often studied, and findings indicate that extroverts are more likely to have an exploratory behavior (Wyllie and Smith, 1996), and to score higher for self-reported SOD (Condon et al., 2015), a measure that predicts performance in environment tasks (Hegarty et al., 2006). Wyllie and Smith (1996) found that adolescents scoring high in extroversion were more likely to explore the environment and spend their leisure time in places farther from home than their less extrovert counterparts. Condon et al. (2015) found a correlation between scores for extroversion and self-reported SOD, and also with other personality traits, such as conscientiousness, intellect, and emotional stability.

More recently, Walkowiak et al. (2015) explored the relationship between three major personality traits and the time taken, the mistakes made, and the length of the path covered in a WF task in a VE, which involved retracing a route just learned. They found moderate correlations between psychoticism (i.e., less emotional stability) and the variables considered, high scores for psychoticism being associated with a worse spatial performance. They explained these results as being due to participants scoring high on psychoticism being more erratic and exploratory in their WF. The same study revealed moderate correlations between WF variables and WF anxiety, as measured on the Wayfinding Anxiety Scale (Lawton and Kallai, 2002). Another study supporting a relationship between personality traits and self-reported WF competence was conducted by Yang and Merrill (2016), who found that more feminine personality characteristics (described, among others, as being affectionate and gentle) predicted a worse self-reported WF competence.

The above-mentioned studies generally corroborate the idea of a connection between personality and spatial competence, but some aspects remain unexplored. First of all, we need to establish more precisely which specific mechanisms link some personality traits with performance in spatial tasks, and the role of potential mediators (as discussed in Bryant, 1982). Second, personality has so far been considered mainly with reference to subjective measures of spatial navigation, such as SOD (Condon et al., 2015; Yang and Merrill, 2016), or spatial worrying (Bryant, 1982), or to spatial tasks other than navigation, such as pointing (Bryant, 1982), and mental rotation (Nori et al., 2009). Only one of the studies reviewed here analyzed the influence of personality using a WF task (Walkowiak et al., 2015). More work is needed to see whether and how certain personality traits relate to specific WF tasks. It is important to recognize that several distinctions can be drawn between different WF tasks, and they need to be taken into account in order for us to investigate the relationship between personality traits and WF ability in more depth. In this regard, it is worth noting that the general concept of WF actually involves numerous tasks that differ considerably in their features and complexity, and presumably also in the abilities required, and the cognitive processes involved.

Several attempts have been made to classify spatial navigation (Allen, 1999; Montello, 2005; Wiener et al., 2009). In empirical research, spatial learning and navigation are studied using numerous tasks and learning conditions, with distinctive implications for perception, attention, and memory. A psychologically relevant distinction is drawn between tasks that involve tracing a known route and those that entail finding a novel way to reach a destination, such as shortcut-finding tasks. The present study focuses on this distinction between route tracing and shortcut finding.

The aim of this study was to explore the influence of various individual factors on performance in two different WF tasks: route tracing and shortcut finding.

MATERIALS AND METHODS

Participants

A total of 116 undergraduates (88 females) voluntarily took part in the study (age *M* = 21.07, *SD* = 3.97). Exclusion criteria were not adopted. All participants had adequate performances in the VSWM and MR tests, allowing us to exclude the presence of visuospatial disorders. This experiment was carried out in accordance with the recommendations of the Italian Association of Psychology (AIP) and of the Ethics Committee for Psychological Research (CERP) of University. All procedures were approved by CERP. Participants provided written consent.

Materials

Pleasure in Exploring, Self-Efficacy, and Spatial Anxiety Measures

Attitude to Spatial Exploration Questionnaire (Attitude, revised from Pazzaglia et al., 2004) tool is designed to assess attitude to orientation tasks and pleasure in exploring. It comprises 10 statements that describe feelings, attitudes, and preferences in situations involving environmental orientation (e.g., "I love exploring different places that I still don't know well, and finding new ways to get to places"; "I would like to play a sport like orienteering, where people have to move very fast in unknown places"). For each statement, respondents indicate their agreement on a 5-point scale from 1 (not at all) to 5 (very much), and the total score is obtained from the sum of each item rating. Internal consistency was acceptable (α = 0.68, calculated on the study sample). For the present study, we considered the total score for items 3, 6, 9, 10, which are the items specifically mentioning WF tasks (α = 0.50, calculated on the present sample). Maximum score: 20.

Wayfinding Self-Efficacy Questionnaire (Efficacy, revised from Mitolo et al., 2015) tool investigates how confident individuals feel about their ability to perform typical spatial tasks. It consists of 8 items that describe precise tasks (e.g., "Finding the car in a large parking lot"; "Visiting friends who live in an unfamiliar neighborhood"), scored on a 6-point scale from 1 (not at all) to 6 (very much) in response to the prompt: "Indicate how well you think you would cope in the situations described", and the total score is given by the sum of each item rating. Internal consistency was good (α = 0.81, calculated on the present sample).

Spatial Anxiety Questionnaire (Anxiety, adapted from Lawton, 1994) tool investigates the levels of anxiety experienced while performing everyday spatial tasks. The items used in this scale are the same as those in the Wayfinding Self-Efficacy Questionnaire, and respondents are asked to indicate the level of anxiety experienced in the situations described. The 8 items are scored on a 6-point scale: from 1 (not at all) to 6 (very much). The final score is calculated by adding together the scores for each item. Example item: "Indicate the level of anxiety you experience in the situation described: Reaching an appointment venue in an unfamiliar part of a town." Internal consistency was good (α = 0.82, calculated on the present sample).

In the analyses described below, for both Efficacy and Anxiety we considered the total score calculated on items 1, 2, 4, 5, 8, which refer to WF tasks in outdoor environments (Efficacy α = 0.77; Anxiety α = 0.73 calculated on the present sample). Maximum score: 30 (both for Efficacy and Anxiety scales)

Personality Measure

Big Five Personality Questionnaire (BFQ; Italian version by Caprara et al., 2008) is one of the most often used instruments for assessing personality. It comprises 134 statements that refer to 5 traits, and 2 "facets" for each trait (for a total of 10 facets, with 12 items for each facet), plus a social desirability scale measuring the respondents' desire to give a very positive impression of themselves. For each statement, respondents indicate the extent to which they agree or disagree on a 5-point scale from 1 (very false for me) to 5 (very true for me).

The Energy trait is the level of activity, vigor, sociability, and competitiveness, in which one facet is Dynamism (activity and enthusiasm), and the other is Dominance (assertiveness and self-confidence). The Agreeableness trait refers to concern and sensitivity expressed toward others and their needs, with one facet concerning Cooperativeness (altruism and trust), and the other Politeness (kindness and civility). The Conscientiousness trait relates to self-regulation in both its proactive and its inhibitory aspects, one facet being Scrupulousness (orderliness and precision), and the other Perseverance (tenacity and persistence). The Emotional Stability trait concerns the ability to control one's affect and emotional reactions, and one facet of this is Emotion Control (ability to handle anxiety and feelings of despondency), and the other is Impulse Control (ability to maintain control over one's behavior). The Openness trait concerns the breadth of an individual's cultural interests and willingness to explore and seek novelty; one facet is Openness to Culture (intellectual curiosity, interest in knowledge), and the other is Openness to Experience (interest shown toward different values and lifestyles). In a large normative population, the reliability of the five factors ranged from 0.73 to 0.90, and the reliability of the facets from 0.60 to 0.86 (Caprara et al., 2008). Maximum score for each factor: 120.

Visuospatial Working Memory and Spatial Ability Measures

Corsi Blocks Task (CBT, Corsi, 1972) is designed to test spatial WM. The apparatus used in the CBT consists of 9 identical blocks randomly placed on a board. The experimenter points to a sequence of blocks at a rate of one block per second and then asks the respondent to point at the same blocks in the same order. The length of each sequence of blocks to recall ranged from 2 to 9 blocks, and two trials were used for each sequence length. The procedure stopped when a participant was unable to reproduce both the sequences of a given length. The number of blocks in the longest sequence for which at least one of the two trials was recalled correctly was taken as the measure of the respondent's visuospatial span. Maximum score: 8.

Pathway Span Task (PST, Mammarella et al., 2008) is designed to test spatial WM. Participants are asked to mentally visualize a path followed by a little man moving on a blank matrix. After the experimenter has given a set of statements regarding the directions he takes (i.e., forward, backward, to the left or right), participants are asked to indicate the man's final position on the matrix. The complexity of the task can vary, depending on the size of the matrix (from 2×2 to 6×6) and the length of the path covered. The final score is obtained from the number of moves correctly recalled in at least two matrices out of three. Maximum score: 10.

Mental Rotations Test (MRT, from Vandenberg and Kuse, 1978) comprises 20 items, each consisting of one target and four alternative figures (made up of assembled cubes). The task consists in identifying which two of the four alternative figures correspond to a rotated view of the target figure. Respondents had 8 min to accomplish the task, and they scored one point when they identified both of the correct alternatives. The total score corresponded to the sum of the scores obtained for the single items. Maximum score: 20.

Virtual Environment

The VE was programmed in Superscape 5.61 and adapted from Pazzaglia and Taylor (2007). It consisted of a typical urban environment where we selected a specific route, some 300 meters long, comprising 12 segments and a variety of landmarks. A second VE was used for practice. The VE was presented in desktop system mode on a 17-inch screen placed 50 cm away from the participant. We opted to use a VE because it enables a greater control over the characteristics of the environment than in a real environment, and the mechanisms involved in learning a VE are much the same as in the real world (e.g., Ruddle et al., 1997; Weisberg et al., 2014).

Recall Tasks

Route-tracing task is involved tracing a previously learned route from a starting point to an end point, using a joystick to move forward, backward, right or left.

Shortcut-finding task is entailed using a joystick to move freely in the VE and finding the shortest path between the starting and end points of the previously learned route.

Both tasks began at the starting point used in the learning phase. The program recorded how many wrong turns were taken throughout the route in the tracing task (errors), and the length of the path covered in meters in the shortcut-finding task, which were used as dependent variables.

Procedure

Participants were individually tested during a single session lasting about 90 min. They completed the following questionnaires in the following order: Anxiety, Attitude (pleasure in exploring), and Efficacy, plus two other questionnaires not considered in the present study. Then, the route learning phase started. Participants were told that their task was to memorize a path through a VE and then perform a number of spatial tasks. They were first familiarized with the use of the joystick and the virtual reality apparatus in a sample VE for 3 min before starting the experimental task. Participants watched an avatar walk for about 3 min from the starting point to the end point of the path. Immediately afterward, they were returned to the starting point and asked to use the joystick to trace the same route as they had just seen (route-tracing task). They were told that, if they took a wrong turn, the program would take them back to the previous intersection. If participant took three wrong turns at the same intersection, the experimenter told them which way to go (e.g., "You have to turn left here"). The program recorded how many wrong turns each participant took along the way. Then they were returned to the starting point again and asked to find the shortest way to reach the destination (shortcut-finding task). Participants were allowed to navigate the environment freely (for up to 10 min) until they reached the destination, and the route they covered was recorded. The task finished when the end point was reached, or when 10 min had passed. The dependent variables were the errors in the first task, and the length of the shortcut in the second. After the two navigation tasks, the Corsi Blocks Task and the Pathway Span Task were administered, followed by the Big Five Questionnaire, which concluded the experimental session. The order of administration of all measures (questionnaires and tasks) was the same for each participant.

RESULTS

Rationale for Analyses

We conducted our analyses in four steps. First, we examined participants' route-tracing and shortcut-finding performance to check for any broad individual differences (Hegarty and Waller, 2005). We then correlated the study variables in a second step, and used confirmatory factor analyses (CFAs) to test the relationship between the observed and latent variables in a third.

This process was recommended by Schreiber (2008) to derive the best indicators of latent variables before testing a structural model. Fourth, a structural equation model (SEM) was generated using spatial ability, emotion/motivation, and personality as latent variables, and route tracing and shortcut finding as the observed variables.

Measurements and structural analyses were done using the LISREL 8.7 statistical package (Jöreskog and Sörbom, 2004). Among the various fit indexes, we adopted the root-mean-square error of approximation (RMSEA, below 0.05), the non-normed fit index (NNFI, above 0.97), the comparative fit index (CFI, above 0.97), the standardized root mean square residual (SRMR, below 0.05), and a non-significant chi-square. The issue of normality was considered too: the observed data indicated a non-significant departure from normality, as shown by Mardia's measure of relative multivariate kurtosis (MK) obtained with the PRELIS program (Jöreskog and Sörbom, 2004): MK = 1.02 ($-1.96 < z < 1.96$).

We expected to find VSWM and spatial ability crucial to learning a path and forming a spatial mental representation of the urban environment, as suggested by a number of past studies (Garden et al., 2002; Meilinger et al., 2008; Labate et al., 2014). Once the path had been learned, however, then motivation, attitude to spatial tasks, and personality traits might be even more important to success in finding a shortcut to the same destination. Although the involvement of non-cognitive factors (personality, emotion, motivation) in WF has already been suggested (in the past studies reviewed above, for instance), our study is the first to examine a wide range of variables with reference to different WF tasks. This enabled us to see whether different groups of variables (cognitive, affective/motivational, personality) were more or less important in relation to the two tasks. Our hypotheses were tested by using path modeling, after a confirmatory factor analysis had validated our distinction of the variables in three groups: spatial ability (measured with VSWM tasks and MRT), affective/motivational factors (spatial self-efficacy, pleasure in exploring, and spatial anxiety), and several personality traits. We expected to see different patterns of relationships between the predictive variables on the one hand, and route tracing and shortcut finding on the other. Gender was inserted as an initial variable to control for its effect on all the other relationships (given its role on spatial performance; e.g., Lawton, 2010).

Based on the above-reviewed literature, we expected spatial ability to predict performance in both navigation tasks, while the affective/motivational and personality variables were expected to predict performance only in the shortcut-finding task. As for which specific personality traits might correlate with performance in the latter task, we took an exploratory stance because past research had identified different factors, from extraversion to psychoticism and dominance. Given that previous evidence showed that route tracing and shortcut finding could demand a different involvement of visuospatial competences (Labate et al., 2014; Muffato et al., 2016), the last two dependent variables were kept separate on the assumption that spatial abilities, spatial self-reports, and personality traits could affect route-tracing and shortcut-finding performance differently.

Step 1: Individual Differences in Route-Tracing and Shortcut-Finding Performance

Route tracing

Although the task was quite easy (54% of participants made no or only 1 error), we found that the 25% of the sample made 5 or more errors, with a maximum of 9 errors in one case. These data confirm reports in the literature of a marked variability in the performance of navigation tasks (Hegarty and Waller, 2005).

Shortcut finding

This task revealed a broad range of individual differences too. A total of 50 of the 116 participants (43%) actually found one of the two shortest routes from the starting point to the destination (the VE, the path learned, and the two shortcuts are illustrated in **Figure 1**). Another 23 participants traced a slightly longer route, 13 covered the route they had learned previously, or one only slightly shorter (n. 11), and 18 covered much longer routes than the one they had learned, using no apparent strategy. The shortcut-finding task thus revealed individual differences that were possibly even more marked than those seen in the retracing task.

Step 2: Correlations

Table 1 shows descriptive statistics and correlations between all variables, revealing a distinct pattern of correlations between the measures of individual differences, and between these and the two WF tasks. As expected, the two WM tests, the Corsi Blocks Task and the Pathway Span Task, correlated moderately with each other, such as the Corsi Blocks Task and the MRT. Significantly, all these WM and spatial abilities measures showed specific correlations with the number of errors in the route-tracing task. On the other hand, the measures of pleasure in exploring, self-efficacy, and spatial anxiety correlated strongly with each other,

FIGURE 1 | The virtual environment with the original route learned (in white) and the two shortcuts (in blue and orange) correctly identified by 50 (43%) participants.

TABLE 1 | Correlation matrix and descriptive statistics [Means (M) and Standard Deviations (*SD*)] for the measures of interest.

	M (SD)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1. Gender[a]		–																		
2. Spatial anxiety	2.85 (0.80)	0.13																		
3. Pleasure in exploring	2.56 (0.64)	−0.09	−0.41***																	
4. Self-efficacy	3.74 (0.71)	−0.13	−0.60***	0.48***																
5. BFQ – Dynamism	3.38 (0.55)	0.17	−0.29**	0.22*	0.08															
6. BFQ – Dominance	3.03 (0.51)	−0.09	−0.17	0.19*	0.23*	0.37***														
7. BFQ – Cooperativeness	3.63 (0.41)	0.23*	0.15	−0.07	−0.15	0.22*	−0.20*													
8. BFQ – Politeness	3.22 (0.52)	0.09	0.09	−0.12	−0.19*	0.25**	−0.25**	0.53***												
9. BFQ – Scrupulousness	3.23 (0.66)	0.08	0.19*	−0.12	−0.02	−0.13	−0.06	0.01	−0.14											
10. BFQ – Perseverance	3.70 (0.46)	0.18	−0.03	0.22*	0.16	0.40***	0.41***	0.22*	0.08	0.24*										
11. BFQ – Emotion Control	2.63 (0.70)	−0.21*	−0.37***	0.03	0.29**	−0.03	0.01	−0.13	0.04	−0.10	−0.07									
12. BFQ – Impulse Control	2.70 (0.63)	−0.15	−0.01	−0.17	0.06	−0.27**	−0.34***	0.09	0.32***	0.01	−0.23*	0.51***								
13. BFQ – Openness to Culture	3.46 (0.46)	−0.08	−0.07	0.05	0.15	0.24**	0.18	0.11	−0.02	0.20*	0.19*	−0.18	−0.24*							
14. BFQ – Openness to Experience	3.62 (0.47)	−0.05	−0.28**	0.21*	0.25**	0.46***	0.15	0.36***	0.25**	−0.06	0.23*	−0.03	−0.06	0.46***						
15. BFQ – Lie	1.79 /0.46)	0.01	−0.03	−0.08	0.02	−0.03	−0.01	−0.23*	0.01	−0.01	−0.18	0.31**	0.25**	−0.16	0.19*					
16. Mental Rotations Test	5.30 (3.84)	−0.47***	−0.16	0.02	0.16	0.05	0.04	−0.02	0.14	−0.17	−0.19*	0.18	0.13	0.06	0.10	0.11				
17. Corsi Blocks Task	6.25 (1.29)	−0.21*	−0.06	0.05	0.14	0.12	0.05	−0.07	0.02	−0.14	−0.06	0.11	0.02	−0.06	−0.04	0.12	0.32***			
18. Pathway Span Task	8.81 (1.50)	−0.05	−0.04	0.04	0.03	0.02	−0.02	−0.11	−0.06	−0.04	−0.09	−0.04	−0.10	0.04	0.12	0.11	0.14	0.21*		
19. Route-tracing task (Errors)[b]	2.05 (2.47)	0.26**	0.06	−0.04	−0.02	0.08	−0.03	0.05	0.09	0.07	0.18	−0.01	−0.01	0.04	0.06	−0.12	−0.34***	−0.30**	−0.22*	
20. Shortcut-finding task (Length)[b]	163.12 (78.92)	0.06	0.19*	−0.23*	0.22*	0.01	−0.15	0.15	0.21*	0.05	0.01	−0.01	0.19*	−0.03	0.01	0.15	−0.10	−0.01	−0.04	0.15

*N = 116; ***$p < 0.001$; **$p < 0.01$, *$p < 0.05$. [a]The negative value of the correlations between Route tracing and Shortcut finding had a positive meaning, i.e., fewer errors and shorter lengths were associated with greater accuracy in objective measures or higher scores in subjective measures (except for spatial anxiety, where higher values had a negative meaning). [b]Gender was a dichotomous variable (1 = male, 2 = female).*

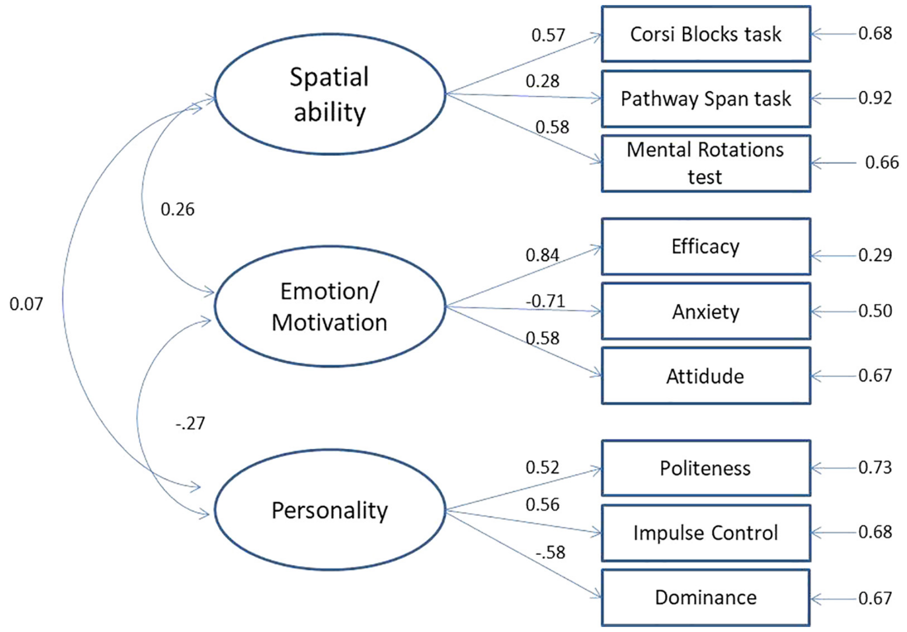

FIGURE 2 | Measurement model including spatial ability, emotion/motivation self-reports, and facets of personality traits. The values reported are standardized β, all significant ($z = 2.33$ $p < 0.05$ to $z = 7.28$ $p < 0.001$) except for the correlation between spatial ability and facets of personality traits ($z = 0.29$).

and all showed significant correlations with the shortcut-finding task: better performance correlated with less anxiety and more self-efficacy and pleasure in exploring. Shortcut-finding performance also correlated with the personality facets Politeness and Impulse Control, referring, respectively, to the factors Agreeableness and Emotional Stability: a better performance was associated with lower scores for Politeness and Impulse Control.

Step 3: Confirmatory Factor Analyses

Factor compositions

In the light of previous evidence to indicate that spatial abilities constitute a single factor grouping mental rotation and VSWM (Allen et al., 1996; Hegarty et al., 2006), and that they can be distinguished by self-reported spatial measures (Hegarty et al., 2006), we tested the existence of two latent factors: spatial abilities (using the Corsi Blocks Task, the Pathway Span Task, and the MRT), and motivation/emotion (anxiety, pleasure in exploring, and self-efficacy). We also identified a third personality latent factor consisting of Politeness, Impulse Control, and Dominance, which – within each personality factor – were the facets showing the strongest correlation with the shortcut-finding task (see **Table 1**). This measurement model, based on the three factors of interest, showed good fit indices, $\chi^2 = 24.19$, $df = 24$ $p = 0.45$, $CFI = 1.00$, $NNFI = 1.00$, $SRMR = 0.05$, $RMSEA = 0.008$. The standardized β values are shown in **Figure 2**. The three latent variables, i.e., spatial ability, motivation/emotion, and personality, were retained in the subsequent analyses.

Step 4: Structural Models

In a first model, we considered all the relationships between the three latent variables and the two navigation tasks (route tracing and shortcut finding). The model showed satisfactory fit indices, $\chi^2 = 46.64$, $df = 46$ $p = 0.45$, $CFI = 1.00$, $NNFI = 1.00$, $SRMR = 0.07$, $RMSEA = 0.01$, but some relations were not significant ($z = -0.68$ to $z = 1.44$), i.e., gender and emotion/motivation; gender and personality; gender and route-tracing task, gender and shortcut-finding task; emotion/motivation and route tracing; personality and route tracing; route tracing and shortcut finding. We therefore tested a second model in which these relations were removed. The final model, shown in **Figure 3**, was satisfactory, $\chi^2 = 54.88$, $df = 53$ $p = 0.40$, $CFI = 0.99$, $NNFI = 0.99$, $SRMR = 0.08$, $RMSEA = 0.02$, and explained 24% of the variance for route tracing ($R^2 = 0.24$), and 14% of the variance for shortcut finding ($R^2 = 0.14$). Route-tracing performance was predicted by the spatial ability latent variable, which mediated the relationship between gender and route tracing (indirect effect: $\beta = 0.28$, $z = 4.21$ $p \leq 0.001$). A different pattern emerged for shortcut finding, which was predicted by emotion/motivation and personality latent variables: high scores for self-efficacy and pleasure in exploring, and low scores for spatial anxiety were associated with a good performance. Personality predicted shortcut-finding performance too: low scores for Politeness (a facet of Agreeableness), and Impulse Control (a facet of Emotional Stability), and high scores for Dominance (a facet of Energy) were associated with a good performance.

DISCUSSION

Overall, the results of the study confirmed our expectations.

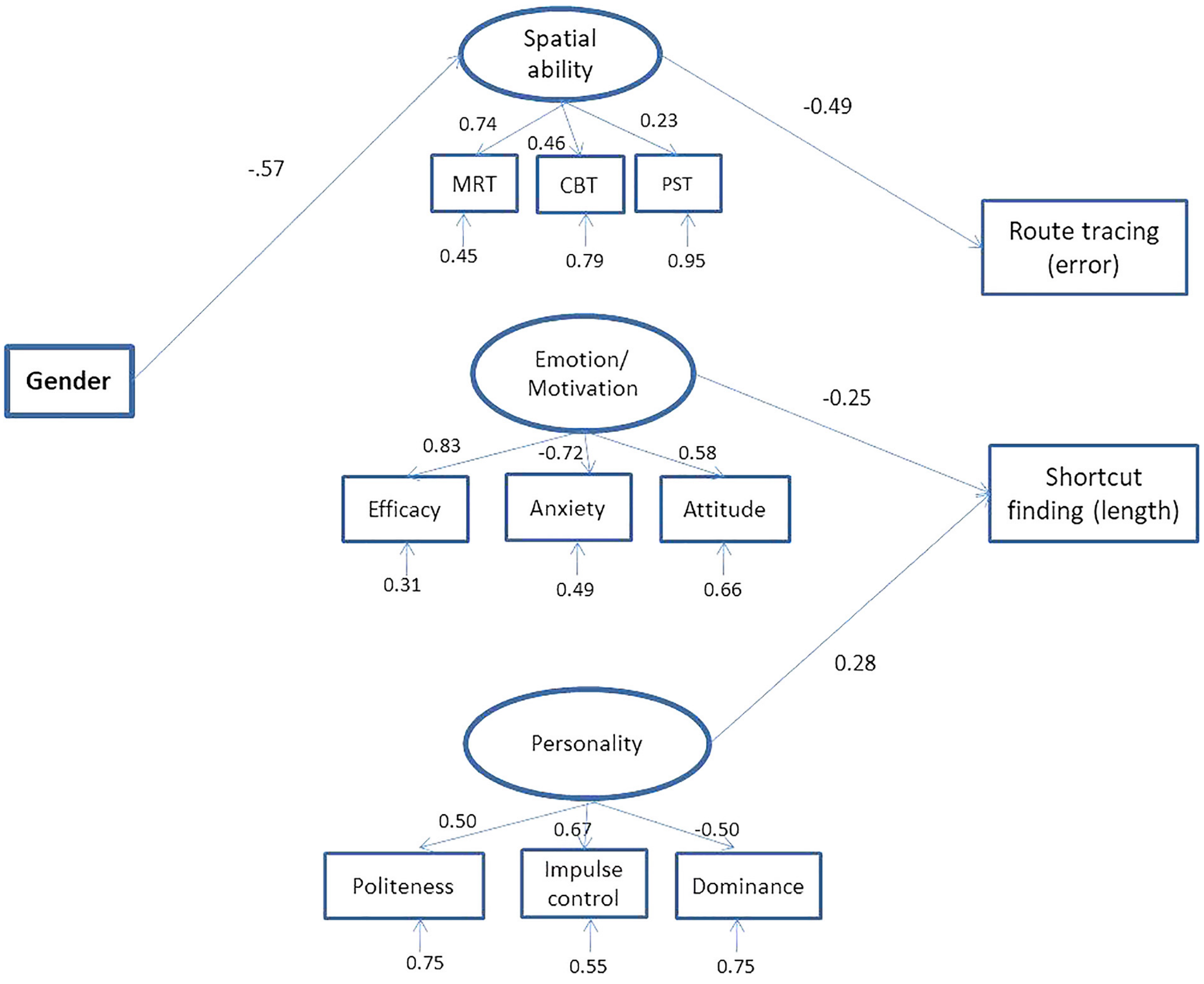

FIGURE 3 | Final structural model. The standardized solutions (β) are presented for each path (all significant, $z = -1.97$ $p < 0.05$ to $z = -0.3.76$ $p < 0.001$).

The preliminary analysis on participants' performance in the two navigation tasks (route tracing and shortcut finding) revealed wide individual differences. These preliminary results confirmed previous reports of marked individual differences in performance in spatial navigation and orientation tasks (e.g., Hegarty and Waller, 2005; Hegarty et al., 2006; Weisberg et al., 2014; see also Iaria and Burles, 2016, on specific developmental deficits in topographical orientation).

The subsequent analyses aimed to test distinctive patterns of relationships between cognitive abilities, emotion/motivation, and personality traits on the one hand, and navigation task performance on the other. The correlation analyses showed that route tracing and shortcut finding related differently to the other variables: route-tracing performance correlated with the MRT and two VSWM tasks, which revealed no significant correlations with the shortcut-finding task; the latter task correlated instead with spatial anxiety and pleasure in exploring and self-efficacy. As for personality, it is worth noting that Perseverance (a facet of Conscientiousness), correlated with route-tracing performance, whereas it was Politeness and Impulse Control (facets of Agreeableness and Emotional Stability, respectively) that correlated significantly with shortcut-finding performance.

We also found interesting correlations between the predictive variables. As expected, the two VSWM tasks correlated with one another, and one of them (the Corsi Blocks Task) showed a moderate correlation with the MRT. This latter result supports the conviction that VSWM is implicated in the performance of figural spatial tasks (Allen et al., 1996; Hegarty et al., 2006; Muffato et al., 2016). All the measures of emotions and self-efficacy relating to spatial tasks showed reciprocal correlations: higher scores for spatial anxiety corresponded to lower scores for self-efficacy in spatial tasks and for pleasure in exploring. This supports the existence of reciprocal relationships between affective and motivational factors in the spatial performance domain, as already seen in other domains (e.g., Bandura, 1997). It also confirms and extends the report from Bryant (1982) of participants who admitted that they feared getting lost also reporting a lack of self-confidence. It is worth noting that spatial anxiety also correlated with some personality facets, suggesting a complex relationship between a general difficulty in controlling negative emotions (Emotion Control) and anxiety in spatial navigation tasks (on this point, see also Kallai et al., 2007). Interestingly, individuals with high levels of spatial anxiety were also less open to novel experiences, whereas no such relationship emerged between spatial anxiety and openness to culture.

Based on the above-described correlations, we tested a model grouping the variables into three latent factors: a spatial ability factor (grouping the MRT and the VSWM tasks), an emotion/motivation factor (with spatial anxiety, pleasure in exploring, and self-efficacy), and a personality factor (including the facets correlating the most with the shortcut-finding task). The model showed good fit indices and enabled us to test the predictive value of the three factors vis-à-vis route-tracing and shortcut-finding performance with a structural equation model. The main outcome of this last analysis was that performance in the two navigation tasks was predicted by a distinct order of variables. Spatial ability predicted route-tracing performance, confirming the results of previous studies showing that VSWM is implicated in navigation tasks (Allen et al., 1996; Garden et al., 2002; Meilinger et al., 2008; Labate et al., 2014), but not shortcut-finding performance. The latter result seems to contradict previous reports. For instance, Labate et al. (2014) found that a concurrent WM task impaired performance in shortcut-finding tasks in a real environment. This apparent discrepancy could be due to differences between the two studies: our study was conducted in a virtual outdoor urban environment with wide streets and numerous landmarks visible from a distance; the study by Labate et al. (2014) was conducted inside a real building on a university campus, with rooms connected by corridors and staircases, the routes to learn involved moving from one floor to another, and the landmarks were not visible from a distance. It may be that finding a shortcut in such an indoor environment demanded the ability to retain a mental representation of movements, locations of landmarks, and layouts of rooms, which would involve the use of VSWM. On the other hand, participants in our study could refer to landmarks some distance away to pinpoint their destination, and head toward it using navigation strategies that would be less demanding in terms of VSWM, but require a greater degree of confidence in participants' ability to orient themselves, a positive attitude to exploring, and low levels of spatial anxiety. This view is also supported by our findings concerning the role of the personality latent factor comprising Politeness, Impulse Control, and Dominance in predicting shortcut-finding performance. In other words, an individual who is more likely to take the initiative (more dominant) and be impulsive (low impulse control), and less likely to consider other people's requirements (less polite), is probably more inclined to embark on a totally new route, relying on a landmark in the distance. Taken together, all the above elements could explain why personality and emotional/motivational factors proved much more important than cognitive factors in explaining shortcut-finding performance. The route-tracing task, on the other hand, involved repeating a known route. To do so, participants needed to encode and maintain a sequential order of changes of direction and landmarks, and their spatial abilities (comprising VSWM and MRT) had a major part to play.

Some inconsistencies emerged when we compared our results with those of previous studies on the influence of personality traits on spatial task performance. Walkowiak et al. (2015) found high scores for psychoticism associated with a worse performance in a WF task, an outcome partially contradicted by our results, in which high scores for impulse control and politeness were associated with a worse performance in the shortcut-finding task. Here again, the difference is probably due to differences between the tasks involved. In the study by Walkowiak et al. (2015), participants had to retrace their steps, returning from the destination to the starting point of a previously memorized route, whereas our tasks involved repeating a route (going in the same direction as in the learning phase), and finding a shortcut. The environment used in the former study only allowed for participants to refer to local (not more remote) landmarks, and it was probably important for them to control their anxiety and fear of getting lost in order to reach their destination. In our route-tracing task, it was less important to control any negative emotions because participants traced the same route again [instead of going in the opposite direction, as in Walkowiak et al.'s (2015) study] and, more importantly, if they made three mistakes at the same intersection, they were told which way to go, so any fear of getting lost or spatial anxiety would naturally have been more limited. It would be interesting to manipulate such environmental features and procedural variables in the same study to clarify their influence on performance, and importance as predictive variables. To give an example, Pazzaglia et al. (2017) compared two conditions, with and without landmarks, in the same VE, and found that self-efficacy and pleasure in exploring became more important when the task was more difficult (in the no landmarks condition). Srinivas (2011) also found that spatial anxiety has a more harmful effect in difficult than in easy tasks.

CONCLUSION

Overall, the results of the present study confirm that the type of environment, the type of task, and internal factors interact in contributing to WF performance (Pazzaglia and Meneghetti, 2017), but the whole picture is much more complex. Apparently trivial features of the task and environment can have a major impact, not only on performance, but also on the abilities required. A number of accurate classifications of WF tasks have been proposed in the past (e.g., Allen, 1999; Montello, 2005; Wiener et al., 2009), and proved very useful, but to understand the complex interaction between individual factors, environment and task, we probably need to draw finer distinctions. It is also important to bear in mind that, although many studies have examined individual differences in spatial navigation, they have focused largely on cognitive variables (WM, spatial ability). The present study underscores the importance of systematically considering other types of variable and referring to current models of emotions and their effect on cognition and motivation (Mischel and Shoda, 1995). How they affect the spatial domain needs to be further explored, also considering the same issues in samples at different level age (e.g., older than the age group considered in the presents research). The present study paves the way to research into how these factors influence performance in different WF tasks, and in the presence of different environmental features.

AUTHOR CONTRIBUTIONS

FP and CM conceived of the research and designed the experiment. CM and LR analyzed the data. FP drafted the manuscript. CM and LR provided the critical manuscript revisions.

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Ventral—Dorsal Functional Contribution of the Posterior Cingulate Cortex in Human Spatial Orientation: A Meta-Analysis

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The retrosplenial cortex has long been implicated in human spatial orientation and navigation. However, neural activity peaks labeled "retrosplenial cortex" in human neuroimaging studies investigating spatial orientation often lie significantly outside of the retrosplenial cortex proper. This has led to a large and anatomically heterogenous region being ascribed numerous roles in spatial orientation and navigation. Here, we performed a meta-analysis of functional Magnetic Resonance Imaging (fMRI) investigations of spatial orientation and navigation and have identified a ventral-dorsal functional specialization within the posterior cingulate for *spatial encoding* vs. *spatial recall*. Generally, ventral portions of the posterior cingulate cortex were more likely to be activated by *spatial encoding*, i.e., passive viewing of scenes or active navigation without a demand to respond, perform a spatial computation, or localize oneself in the environment. Conversely, dorsal portions of the posterior cingulate cortex were more likely to be activated by cognitive demands to recall spatial information or to produce judgments of distance or direction to non-visible locations or landmarks. The greatly varying resting-state functional connectivity profiles of the ventral (centroids at MNI −22, −60, 6 and 20, −56, 6) and dorsal (centroid at MNI 4, −60, 28) posterior cingulate regions identified in the meta-analysis supported the conclusion that these regions, which would commonly be labeled as "retrosplenial cortex," should be more appropriately referred to as distinct subregions of the posterior cingulate cortex. We suggest that future studies investigating the role of the retrosplenial and posterior cingulate cortex in spatial tasks carefully localize activity in the context of these identifiable subregions.

Keywords: hippocampus, navigation, retrosplenial, spatial memory, cognitive map

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INTRODUCTION

Over a century ago, Korbinian Brodmann published an exhaustive cytological parcellation of the human cerebral cortex (Brodmann, 2006); as a testament to his work, this parcellation is still commonly used across all neurological disciplines. Of particular interest in Brodmann's parcellation is the retrosplenial cortex (Brodmann's areas 26, 29, and 30), a small, enigmatic region in the human brain that Brodmann was only able to identify after delineating this region in lower animals, in which it is relatively larger and more easily identifiable (Brodmann, 2006, 124). In humans, the retrosplenial cortex occupies the small portion of the cingulate cortex that is immediately posterior to the most posterior region of the corpus callosum (i.e., the splenium). While at the time Brodmann was unsure of the significance of the retrosplenial cortex (and neighboring posterior cingulate areas 23 and 31; Brodmann, 2006, 123), more recently, this tiny region has been ascribed important functions involving emotion processing (Maddock, 1999) and episodic memory (Spreng et al., 2009), with substantial literature reporting its critical role in spatial orientation and navigation (Aguirre and D'Esposito, 1999; Maguire, 2001; Vann et al., 2009; Epstein et al., 2017).

Despite a precise localization of the retrosplenial cortex in the human brain, the vast majority of functional Magnetic Resonance Imaging (fMRI) studies investigating the role of this region in spatial cognition do not report results in the retrosplenial cortex proper. This is partially due to the fact that the retrosplenial cortex, as delineated by Vogt et al. (2001; **Figure 1C**) is effectively too small to be studied with common fMRI voxel sizes (e.g., 3 mm isotropic) used for whole-brain imaging, resulting in many fMRI peaks labeled as "retrosplenial cortex" lying in the posterior cingulate cortex (Vogt et al., 2000). Therefore, while the anatomically-defined region retrosplenial cortex is quite small, the manner in which the label "retrosplenial cortex" is used spans a very large region of the posterior medial cortex with variable cytology (Maguire, 2001; Vogt et al., 2001, 2006) and functional connectivity (Bzdok et al., 2015). This includes the functionally-defined, scene-sensitive "retrosplenial complex" (Epstein, 2008).

Although the mislocalization of the retrosplenial cortex is somewhat egregious, it is not without precedence. Brodmann himself, in fact, intentionally overrepresented the size of the retrosplenial cortex in his original figures (**Figure 1A**), and he noted this inaccuracy 16 pages after the figures (as it appears in the English translation by Gary). This large representation of the retrosplenial cortex also appeared in the Talairach atlas (Talairach and Tournoux, 1988), with the posterior border of the retrosplenial cortex reaching as far as the junction of the parietal-occipital fissure and the calcarine sulcus. This is in stark contrast to more modern cytological studies, which frequently confirm Brodmann's original localization (but not depiction) of the retrosplenial cortex as largely contained within the callosal sulcus and without the generous representation on the gyral surface (**Figure 1**; Morris et al., 2000; Vogt et al., 2001; Fatterpekar et al., 2002).

While it is possible that a slight misrepresentation of an anatomically-defined region provides a more accurate representation of a functionally-defined region involved in spatial orientation and navigation, the "retrosplenial cortex" label has been used in human spatial cognition research far too liberally, including many areas of the posterior medial cortex far beyond the anatomical border of the retrosplenial cortex proper (Nasr et al., 2011; Marchette et al., 2014; Silson et al., 2016). Considering the wide variety of spatial orientation and navigation tasks producing activity in this large area of the human brain, it is likely it could be more accurately described as a collection of relatively distinct subregions, performing slightly different functions within the spatial cognition domain.

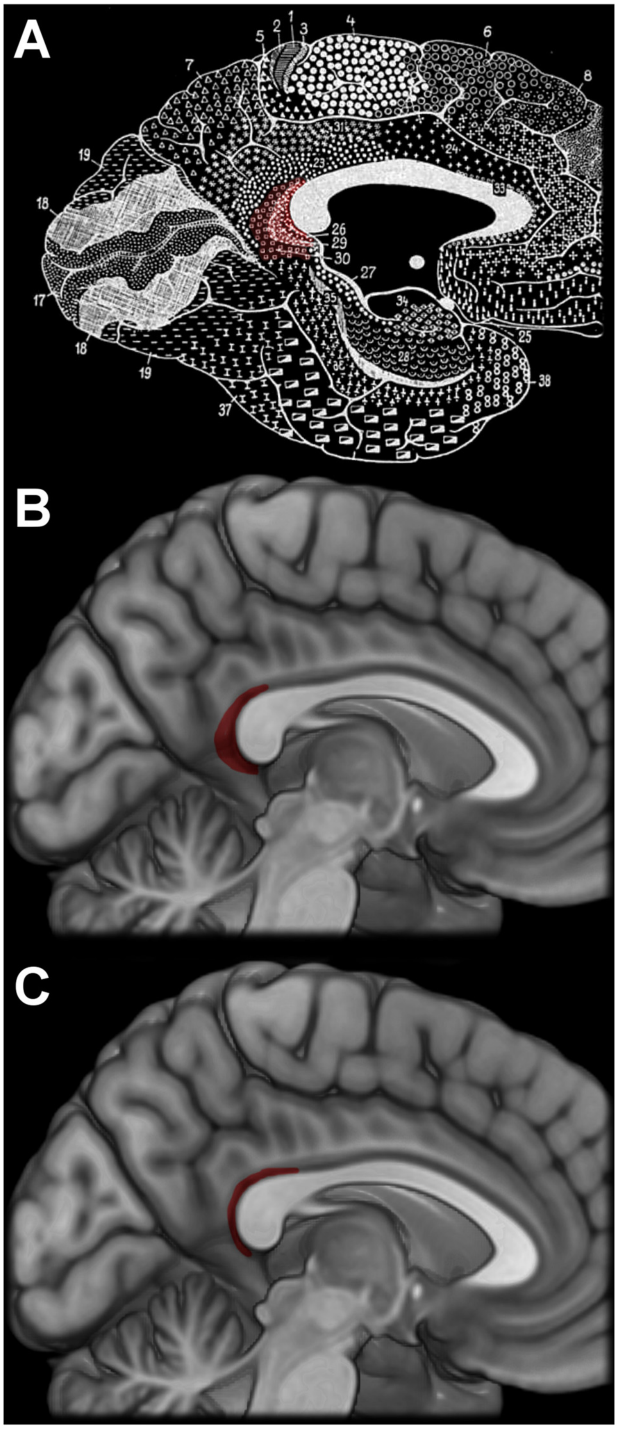

FIGURE 1 | Brodmann's original depiction of the retrosplenial cortex **(A)**, which was intentionally overrepresented (Brodmann, 2006). More modern illustrations based off the work by Morris et al. (2000) and Vogt et al. (2001) in panels **(B,C)**, respectively, depict a substantially humbler region. Brodmann's figures, originally published in 1910, are in the public domain.

Consistent with this assumption, we have recently identified a differential engagement of the ventral and dorsal portions of the posterior cingulate cortex while individuals performed a spatial memory task (Burles et al., 2017); we had identified that ventral regions were more involved in updating a mental representation of the environment, and more dorsal regions were involved in recalling the positions of unseen objects from that mental representation. These findings provided initial evidence of a simple encoding-recall specialization along the ventral-dorsal axis of the posterior cingulate and "retrosplenial cortex." Here, we performed a meta-analysis of relevant fMRI studies to provide further evidence of a ventral-dorsal functional specialization of the posterior cingulate and neighboring cortex supporting the processes of encoding and recalling spatial information.

MATERIALS AND METHODS

Literature Search

To identify relevant neuroimaging studies, we performed a literature search in PubMed identifying fMRI studies with human subjects investigating spatial orientation and mentioning retrosplenial or nearby regions in the posterior medial cortex. We ran the following conjunctive search:

1. retrosplenial OR (posterior cingulate) OR precuneus OR (medial parietal cortex) OR (posterior parietal cortex) OR ((parieto-occipital OR parietooccipital) and (sulcus OR fissure)) OR ((Brodmann Area OR BA) and (23 OR 26 OR 29 OR 30 OR 31))

AND

2. ((spatial OR topographical OR place OR path OR scene) and (navigation OR memory OR recognition OR learning OR integration OR construction OR imagination OR orientation)) OR path integration OR dead reckoning OR cognitive map OR mental representation OR spatial configuration OR perspective taking

AND

3. fMRI OR functional magnetic resonance imaging OR functional neuroimaging OR BOLD OR blood oxygen level dependent

This conjunctive search produced 297 articles, which were subsequently filtered to only include the 61 research articles with healthy, adult subjects performing a spatial task while fMRI data were collected, with coordinates reported in the manuscript or supplementary materials. The references in five relevant review articles included in search results were mined, resulting in an additional 23 articles meeting these criteria included from 497 references. Finally, an additional seven articles known to the authors through personal communications with other researchers were included. The total sample of articles passing filtering was comprised of 91 articles. This search strategy was not intended to be exhaustive, but rather generate a sample that is adequately representative of the state of the cognitive neuroscience literature investigating human spatial orientation and navigation.

For each of these 91 articles, we attempted to classify BOLD contrasts as either *spatial encoding* or *spatial recall*. Contrasts classified as *spatial encoding* were principally characterized by relatively more bottom-up or stimulus-driven BOLD activity. These included cases where participants were viewing or imagining visual stimuli, such as landmarks or scenes, or performing active navigation in a novel environment, without an explicit demand to perform a spatial computation or localize unseen landmarks in the environment. For instance, a functional localizer, contrasting BOLD activity while participants viewed scenes over BOLD activity while participants viewed faces or objects (Johnson et al., 2007; Sung et al., 2008) was classified as *spatial encoding*. These contrasts are commonly used to identify scene-sensitive retrosplenial and/or parahippocampal cortex and represent an easily classifiable contrast as the detected BOLD activity relates specifically to encoding scenes and has no demand to recall any spatial or navigational information. This category also included contrasts such as the one performed by Aguirre et al. (1996), subtracting BOLD activity while participants followed an endless, looping corridor from the activity evoked while participants were freely exploring a maze, and presumably encoding the locations of landmarks for a future navigation task.

Conversely, the BOLD contrasts identified as *spatial recall* were generally complementary to the *spatial encoding* category, in a manner similar to a classic encoding—recall dichotomy. For example, in the aforementioned study by Aguirre et al. (1996), free exploration in a maze over a control condition was classified as *spatial encoding*; a complementary contrast of a spatial navigation task (i.e., participants locating a target landmark using the shortest route possible) over a control task, would be classified as *spatial recall*. However, this category also included contrasts weighted more heavily towards spatial representations or judgments in addition to recall *per se*. For instance, Rosenbaum et al. (2004) asked participants to perform proximity judgments between familiar landmarks in downtown Toronto. In this study, landmarks were presented to participants via text, resulting in participants relying strongly on their capacity to recall complex, well-learned, spatial information, and use it to perform a spatial computation, i.e., the proximity judgment.

From the 91 articles passed on to classification, we classified 38 contrasts as *spatial encoding*, and 76 contrasts as *spatial recall* (Supplementary Table S1). We did not classify multiple non-orthogonal contrasts from a single study, and instead selected the contrast most representative of either *spatial encoding* or *spatial recall*, leaving non-orthogonal contrasts unclassified. We then passed all coordinates from classified contrasts to a Multilevel Kernel Density Analysis (MKDA; Wager et al., 2007).

Multilevel Kernel Density Analysis (MKDA)

We first converted all peak coordinates reported in Talairach space to MNI space (Lancaster et al., 2007), and imported

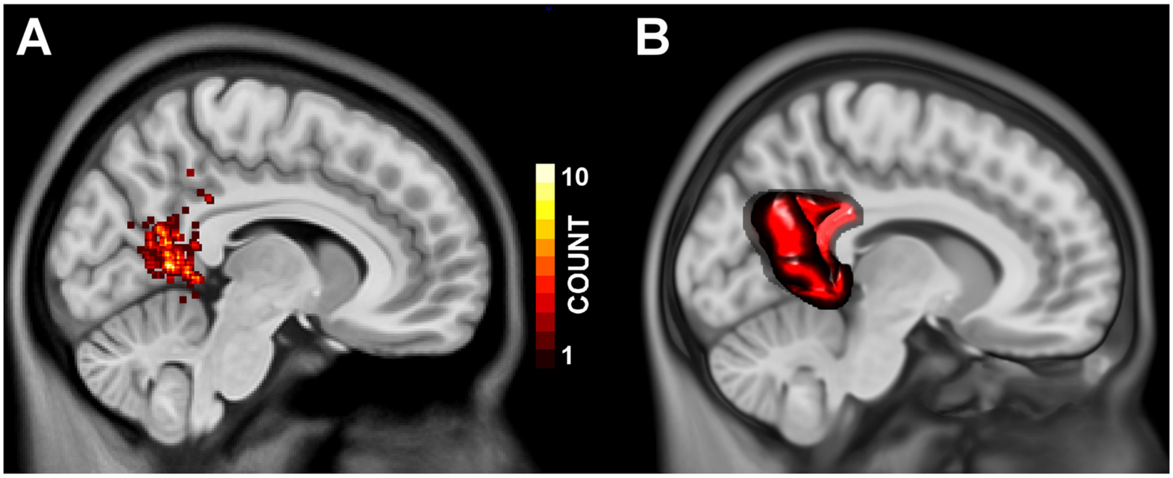

FIGURE 2 | Panel **(A)** depicts the frequency at which a coordinate label included "Retrosplenial Cortex" appeared within 2 mm of any given MNI Y, Z position, projected onto an MNI standard brain at $x = 8$ mm. Panel **(B)** depicts the volume of interest generated to encompass the brain tissue commonly referred to as "retrosplenial cortex" in the spatial cognition literature.

them into NeuroElf[1] to perform an MKDA. The coordinates were then smoothed using a 12-mm Gaussian kernel and combined to form a single map for each classified contrast, ensuring that contrasts reporting more coordinates (from utilizing more liberal statistical thresholds, for instance) were not overrepresented. These maps were weighted by the square root of the sample size reported in the study. We then compared the z-transformed proportion of voxels differentially and commonly involved in *spatial encoding* and *spatial recall*. To detect differential engagement, we compared the contrast of *spatial encoding vs. spatial recall* against an empirical null distribution generated from label permutation. To detect common engagement, we performed a conjunction from independent activations of *spatial encoding* and *spatial recall* each compared against a spatial scrambling null distribution. In all cases 5000 simulation iterations were performed within an 8385 voxel retrosplenial and posterior cingulate mask, with a 2 mm resolution. The resulting statistical map was thresholded at $p < 0.001$.

Subregion Functional Connectivity Characterization

To characterize the differences between subregions identified in the MKDA, we contrasted the resting-state functional connectivity profile of regions more likely to be activated by *spatial encoding* contrasts vs. *spatial recall* contrasts and vice-versa. We utilized preprocessed resting state functional connectivity data from 38 unrelated, young adult participants of the Human Connectome Project (Van Essen et al., 2012; Glasser et al., 2013). We performed additional preprocessing on our resting state data using the CONN toolbox (v17.f[2]), modeling head motion with 24 parameters, and regressing out signal from white matter and cerebrospinal fluid (Behzadi et al., 2007), and temporally bandpass filtering between 0.008 Hz and 0.09 Hz. We generated seed regions of equivalent spatial extent from the thresholded results of the MKDA, eroding large clusters of equivalent values by smoothing and re-thresholding. Then, we calculated the difference in functional connectivity displayed by these two subregions by calculating the difference in seed-to-ROI temporal correlation coefficients for 131 ROIs included in CONN's default atlas, using a statistical threshold of $p_{\mathrm{fdr}} < 0.001$. For the connectivity analyses, Fisher-transformed correlation coefficient values were used for comparison, and the reverse transform was applied to return connectivity coefficients to r values for ease of interpretation. This research study was approved by the local research ethics board (CHREB-22848).

RESULTS

The Retrosplenial Cortex

From all 91 articles passing initial filtering, we identified 143 coordinates from 32 articles with a label including "retrosplenial cortex." **Figure 2A** depicts a histogram of coordinate locations projected into the sagittal plane. Approximately 10% of reported coordinates lie within the callosal sulcus, i.e., the retrosplenial cortex as defined by Vogt et al. (2001).

Multilevel Kernel Density Analysis

We performed an MKDA to identify regions within the retrosplenial cortex and posterior cingulate (**Figure 2B**) that are preferentially involved in *spatial encoding* and *spatial recall*. Contrasts classified as *spatial encoding* were generally characterized by stimulus-driven activity in which participants viewed scenes or explored virtual environments, with no explicit

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[1] neuroelf.net/

[2] nitrc.org/projects/conn

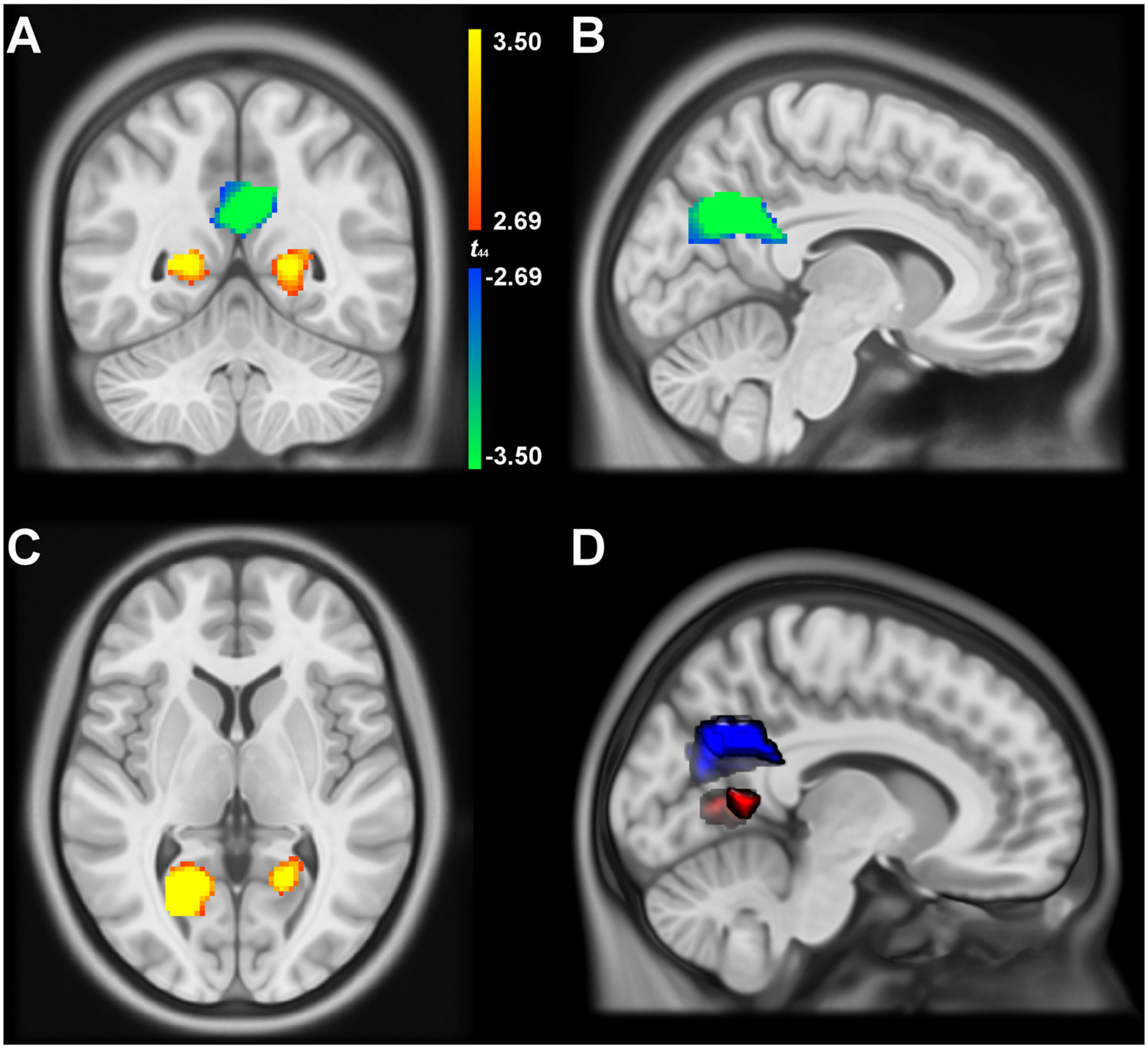

FIGURE 3 | Multilevel kernel density analysis (MKDA) results depicting regions more likely to be activated by *spatial encoding* (red/yellow) and *spatial recall* (blue/green). Panels **(A–C)** are displayed at MNI 8, −53, 5, color range bounds represent uncorrected thresholds of $p < 0.01$ at $t_{(44)} = 2.69$ and $p < 0.001$ at $t_{(44)} = 3.50$ in an 8385-voxel region of interest (**Figure 2B**). Panel **(D)** displays a volumetric depiction of the significant clusters at $p < 0.001$.

demand to localize themselves or unseen landmarks. Contrasts classified as *spatial recall* included those with demands to recall the location of, or route to, landmarks in familiar environments, as well as contrasts that track environmental properties or knowledge (e.g., parametric contrasts with navigational performance or goal proximity). As shown in **Figure 3**, the MKDA with a threshold of $p < 0.001$ revealed that *spatial encoding* was more likely to activate ventrolateral portions of the posterior cingulate (MNI centroids at −22, −60, 6; 333 voxels, and 20, −56, 6; 70 voxels), whereas *spatial recall* was more likely to activate dorsomedial portions of the posterior cingulate (MNI centroid 4, −60, 28; 847 voxels). These findings closely parallel the results reported in our previous study (Burles et al., 2017). A conjunction analysis did not detect any voxels engaged in both *spatial encoding* and *spatial recall* (peak $t_{(14)} = 3.719$, $p = 0.002062$ at MNI −14, −60, 14).

Subregion Functional Connectivity Characterization

From the results of the MKDA, we selected the ventro-lateral clusters totaling 403-voxels more likely to be activated by *spatial encoding*, and a dorso-medial cluster of 408 voxels more likely to be activated by *spatial recall* as seeds for a resting state functional connectivity analysis. Contrasting the functional connectivity profiles of these regions revealed significant differences across the brain, detailed in Supplementary Table S2. Across the 132 brain regions tested, the ventro-lateral and dorso-medial posterior cingulate seeds displayed significantly ($p_{fdr} < 0.001$) different connectivity patterns with 69 regions (i.e., 52% of tested regions). The ventro-lateral *spatial encoding* seed displayed significantly more positive functional connectivity with numerous occipital, lateral parietal, and ventral temporal regions. The dorso-medial *spatial recall* seed, on the other hand, was more positively

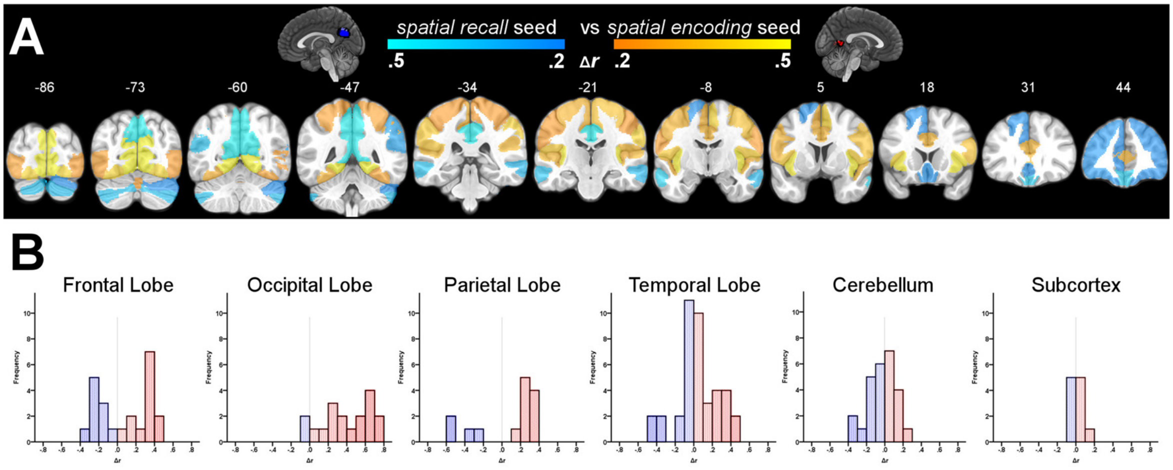

FIGURE 4 | Panel **(A)** depicts the difference in functional connectivity between the ventro-lateral posterior cingulate seeds more associated with *spatial encoding*, and the dorso-medial posterior cingulate seed more associated with *spatial recall*. Highlighted regions display significantly different functional connectivity profiles at $p_{fdr} < 0.001$. $N = 38$. Panel **(B)** displays grouped histograms of the differences in functional connectivity; red highlighting for more positive functional connectivity with the *spatial encoding* seeds, and blue for more positive functional connectivity with the *spatial recall* seed.

functionally connected to the posterior cingulate, as well as the frontal pole and dorsomedial prefrontal cortex (see **Figure 4**).

DISCUSSION

In the spatial cognition literature, the "retrosplenial cortex" label is used quite liberally for brain regions lying posterior to the splenium of the corpus callosum. Even by Brodmann's original, overdrawn depiction, a substantial number of MRI peaks labeled "retrosplenial cortex" drawn from the spatial orientation literature lie unequivocally outside of this anatomical region. It is likely that some of the "leaking" of the retrosplenial cortex into the posterior cingulate is not simply due to the rather large representation of the retrosplenial cortex in Brodmann's work, or the Talairach atlas (Talairach and Tournoux, 1988), but also due to the long history of spatial orientation research in rodents. Rodents lack a clear homologous region to the human posterior cingulate (i.e., BA 23 and 31), and instead boast an expansive retrosplenial cortex (Vogt and Peters, 1981). The human retrosplenial cortex label is applied in a manner that is potentially justifiable as functionally homologous to the rodent retrosplenial cortex, if not anatomically homologous.

While this could be shrugged off as a simple case of difference in nomenclature, we would argue that the lack of specificity in the use of the "retrosplenial cortex" label actively impedes generating a clear and precise understanding of how this region supports the cognitive processes involved in spatial orientation and navigation in humans. In the present study, we provided evidence that the large region that is commonly labeled "retrosplenial cortex" displays a relevant subregion specialization. We classified 114 contrasts from 91 articles as either *spatial encoding* or *spatial recall* and identified that within the "retrosplenial cortex" (more appropriately labeled as the posterior cingulate), ventral portions were more likely to be activated by *spatial encoding*, and dorsal portions more likely to be activated by *spatial recall*.

These findings are supported by a wide variety of previous research that have identified differences in cytology, as well as differences in functional and structural connectivity within this area (Vogt et al., 2006; Hagmann et al., 2008; Zhang and Li, 2012; Bzdok et al., 2015; Silson et al., 2016; Burles et al., 2017), supporting the interpretation that the identified regions are involved in somewhat different cognitive processes. Indeed, we detected markedly different resting state functional connectivity profiles between the ventro-lateral, *spatial encoding*, cluster and the dorso-medial, *spatial recall*, cluster. The *spatial encoding* seeds were centered upon lateral portions of the anterior bank of the common trunk of the parietal-occipital fissure and calcarine sulcus, immediately ventral to where they join. This region displayed more positive functional connectivity coefficients with many ventral-stream, "spatial context" regions, such as the fusiform and lingual gyri (Milner and Goodale, 2008), solidifying its characterization a relatively more involved in bottom-up or lower level perceptual processing and passive updating. In contrast, the *spatial recall* seed was centered 2 cm dorsal to the *spatial encoding* seeds, and displayed relatively greater resting state functional connectivity with regions commonly implicated in spatial manipulation, as well as spatial and episodic memory, such as the posterior cingulate, precuneus and frontal pole (Maddock et al., 2001; Okuda et al., 2003; Ridderinkhof et al., 2004; Wagner et al., 2005; Cavanna and Trimble, 2006; Addis et al., 2009).

While the ventral—dorsal distinction between these subregions was distinct, the *spatial encoding* clusters occupied a relatively more lateral position, deeply tucked within the parietal-occipital fissure. This localization is consistent with previous work by Silson et al. (2016), who localized the scene-sensitive region of the medial parietal cortex as within the parietal-occipital fissure, immediately dorsal to the junction with the calcarine sulcus. This region was characterized by a strong contralateral visual field bias, a property shared with other scene-sensitive cortex (i.e., the occipital and parahippocampal place areas). However, Silson et al. (2016) also described a region immediately anterior and medial to the functionally-localized scene-selective cortex, and noted this region was relatively less scene-sensitive and displayed relatively lower functional connectivity with the posterior parahippocampal place area and occipital place area, but relatively greater functional connectivity with the precuneus, superior frontal, and orbitofrontal cortex. The authors suggest that these regions may constitute partially different scene-processing networks, as proposed by Baldassano et al. (2016). In this paradigm, more lateral scene-sensitive would be relatively more involved in processing visual features, whereas more medial and anterior cortex, approaching or including the retrosplenial cortex proper, appear to be more strongly integrated with the hippocampus and potentially involved in navigation or more general episodic memory processes. Notably, the present meta-analysis did not appear to be sensitive to this region, but this may explain why the *spatial encoding* clusters were sequestered to the lateral portions of the parieto-occipital fissure, as more medial and anterior regions may be involved in processes that are poorly characterized by the *spatial encoding* and *spatial recall* paradigm we adopted.

In conclusion, we believe that the identification of detectable subregions within the posterior cingulate warrants a more precise and nuanced manner in which we discuss and report the results of neuroimaging findings in this region. While the number and location of the particular clusters identified in this meta-analysis likely do not represent *the* relevant subregions of this brain area, we do feel that some simple considerations can be taken into account to reduce the ambiguity of the retrosplenial cortex's position and role in cognition. First, we would suggest reserving the label "retrosplenial cortex" for peaks which reside within the callosal sulcus, or at least are closer to the callosal sulcus than the parietal-occipital fissure, especially at MNI z positions above +10 mm. Further, for the peaks in the posterior cingulate but in the vicinity of the retrosplenial cortex proper, it may be valuable to begin making the distinction between more ventral and dorsal regions; using the point at which the calcarine sulcus joins with the parietal-occipital fissure as an easily-identifiable landmark for differentiation, or at least reference, as our findings would indicate that regions ventral and significantly dorsal to this point may not be functionally homogenous.

AUTHOR CONTRIBUTIONS

FB and GI conceived and designed the study. FB, AU, LHM and KP collected and analyzed the data. All authors contributed to and have approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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Neural Codes for One's Own Position and Direction in a Real-World "Vista" Environment

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Humans, like animals, rely on an accurate knowledge of one's spatial position and facing direction to keep orientated in the surrounding space. Although previous neuroimaging studies demonstrated that scene-selective regions (the parahippocampal place area or PPA, the occipital place area or OPA and the retrosplenial complex or RSC), and the hippocampus (HC) are implicated in coding position and facing direction within small-(room-sized) and large-scale navigational environments, little is known about how these regions represent these spatial quantities in a large open-field environment. Here, we used functional magnetic resonance imaging (fMRI) in humans to explore the neural codes of these navigationally-relevant information while participants viewed images which varied for position and facing direction within a familiar, real-world circular square. We observed neural adaptation for repeated directions in the HC, even if no navigational task was required. Further, we found that the amount of knowledge of the environment interacts with the PPA selectivity in encoding positions: individuals who needed more time to memorize positions in the square during a preliminary training task showed less neural attenuation in this scene-selective region. We also observed adaptation effects, which reflect the real distances between consecutive positions, in scene-selective regions but not in the HC. When examining the multi-voxel patterns of activity we observed that scene-responsive regions and the HC encoded both spatial information and that the RSC classification accuracy for positions was higher in individuals scoring higher to a self-reported questionnaire of spatial abilities. Our findings provide new insight into how the human brain represents a real, large-scale "vista" space, demonstrating the presence of neural codes for position and direction in both scene-selective and hippocampal regions, and revealing the existence, in the former regions, of a map-like spatial representation reflecting real-world distance between consecutive positions.

Keywords: spatial representation, individual differences, hippocampus, retrosplenial complex, parahippocampal place area, occipital place area, fMRI adaptation, multi-voxel pattern analysis

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INTRODUCTION

In everyday life, our ability to keep oriented in the world depends on the accurate estimation of two spatial features: one's own location and facing direction. Neurophysiological evidence on freely moving animals reveals the existence of specific cells that encode these spatial information: place cells in the hippocampus (HC), which fire as a function of the spatial position independently of the animal's facing direction (O'Keefe and Dostrovsky, 1971), and head-direction cells in Papez circuit structures, which fire on the basis of the facing direction independently of the animal's location (Chen et al., 1994; Taube, 1998).

Recent neuroimaging evidence revealed that a similar navigational system is implemented in humans. By combing different analyses approaches (adaptation and multi-voxel pattern analyses) on functional magnetic resonance imaging (fMRI) data, we recently demonstrated that scene-selective regions such as the parahippocampal place area (PPA) and the retrosplenial complex (RSC) automatically encode one's own position and direction within a familiar virtual room and that these spatial quantities are organized as a map: similar activity patterns were observed for locations closer in physical space (Sulpizio et al., 2014). A quite different organization was instead observed in a previous study exploring the neural coding of position and direction within a large-scale, real-world environment (Vass and Epstein, 2013). The authors, by taking advantage of multi-voxel pattern analysis to explore the selectivity towards location and heading direction within a large-scale, real-world environment, found that the pattern of activity in RSC contains information about location but not about facing direction. Additionally, the authors failed in finding a relationship between real-world distances between locations and the activity patterns of PPA, RSC and any other brain regions. However, by using the same environment (the Pennsylvania University campus), Morgan et al. (2011) revealed a map-like spatial organization in the human HC. When participants viewed images of familiar campus buildings, the hippocampal activity response to each building scaled with the distance between that building and the building shown on the immediately preceding trial. Similar results were also obtained when requiring individuals to navigate through a complex real-world space such as a city district with many interconnected streets. For example, Howard et al. (2014) reported that the posterior hippocampal activity was sensitive to the path distance to the goal during navigation within the London's Soho district and that this distance-related effect was abolished when travel was guided by external cues. Map-like codes in the human HC have also been identified after learning spatio-temporal trajectories in a large-scale space. Specifically, Deuker et al. (2016) demonstrated that neural similarities in the hippocampal patterns reflected the remembered proximity of events within large-scale virtual city in both time and space.

Insight into the existence of a distance-dependent representation comes from behavioral and imaging studies exploring spatial memory through table-top or virtual room-sized displays. Performance decreased linearly with the amount of viewpoint rotation when asking participants to recall the object-to-object spatial relationship on a table (Diwadkar and McNamara, 1997), and to retrieve target locations across different perspectives in a familiar virtual room (Sulpizio et al., 2013, 2015, 2016b). Imaging evidence also reported orientation-dependent effects in scene-selective regions. For example, PPA and RSC showed an increase of activation as a function of the amount of experienced view change (Schmidt et al., 2007; Sulpizio et al., 2013), although only the RSC activity scaled with the size of viewpoint changes in the environmental frame (Sulpizio et al., 2013).

To summarize, previous works suggested that the human brain automatically encodes the recovered position and facing direction within the environment, although the existence of a map-like representation of these spatial codes is not consistent across these studies. It is possible that differences in the experimental settings may account for such a discrepancy. For example, some studies have used small-scale room-sized virtual environments (Schmidt et al., 2007; Sulpizio et al., 2013, 2014, 2015, 2016b) or table-top displays in real environments (Diwadkar and McNamara, 1997) in order to tightly control exposure to specific directions. In such situations, the observer could apprehend discrete locations from a single standpoint without remarkable locomotion ("vista" space). Other studies have used large-scale real environments (Morgan et al., 2011; Vass and Epstein, 2013; Howard et al., 2014) or large virtual spaces (Marchette et al., 2014), in which target locations, being beyond the sensory horizon, could only be represented after integrating multiple views acquired during locomotion ("environmental" space). Thus, disentangling between "vista" and "environmental" spaces seems to be essential, especially in the context of navigation (Montello, 1993; Wolbers and Wiener, 2014). However, the impact of different spatial scales on spatial representations of one's own position and direction has been rarely considered. The available imaging evidence speaks in favor of a significant impact of the spatial scale on these spatial quantities, with a metric, map-like spatial organization mainly observed in the HC during passive viewing of familiar buildings or during navigation within large-scale environments (Howard et al., 2014; Deuker et al., 2016), and in PPA and RSC during the mere exposure to small-scale room-sized, virtual environment (Sulpizio et al., 2014) or during object memory tasks within it (Schmidt et al., 2007; Sulpizio et al., 2013, 2016b).

However, although the "vista" vs. "environmental" distinction is crucial in the context of navigation, "vista" and "environmental" spaces are not necessarily different in terms of scale of space. For example, a single room or a space with multiple corridors may be equivalent in terms of spatial scale but different in terms of target visibility. Thus, since the small- vs. large-scale distinction does not necessarily coincide with the "vista" vs. "environmental" dichotomy, in the present study we sought to clarify the impact of the scale of space on spatial representations after controlling for this aspect. To do this, we focused on the neural representation elicited by the "vista" space so as to indirectly test the effect of spatial scale on position- and direction-dependent representations by exploring whether the neural code for one's own position and direction within a large open-field ("vista") space, such as a real town square, reveals the same organization previously observed in a smaller room-sized "vista" environment (Sulpizio et al., 2014). Although we recently reported behavioral priming for repeated positions and directions within that environment, with priming effects scaling with the real-word distances between these spatial quantities (Sulpizio et al., 2017), it remains unclear how such a space is represented in the human brain.

We asked participants to observe consecutive images, which varied for position and facing direction within a familiar real-world circular square. We hypothesized that both position and facing direction within such a "vista" space is represented in the HC and in scene-selective regions. To test this hypothesis, we combine functional magnetic imaging adaptation effects (Grill-Spector et al., 2006) elicited by repetition of any of the two spatial quantities across consecutive pictures, and multivariate pattern analysis (MVPA) to determine which information elicit patterns that are distinguishable (Morgan et al., 2011; Epstein and Morgan, 2012). Following Drucker and Aguirre (2009) hypothesis, these two techniques should explore different aspects, with the former reflecting clustering at a coarser spatial scale while the latter revealing tuning of individual neurons. We hypothesize that all the above-mentioned regions should be clustered according to the (implicitly) encoded spatial information, thus permitting decoding of both positions and directions using multi-voxel patterns. This approach identifies neural patterns which are consistently associated with one position/direction over time, i.e., neural "signatures" of long-term memory traces. On the other side, since univariate analysis of adaptation effects would be instead sensitive to the relationship between consecutive trials, thus reflecting the effect of "being in the same place as before" vs. "being in a different place", but irrespective of the absolute spatial location, we expected to find a more specific involvement of the explored regions in the dynamic process of updating these spatial information.

Beyond PPA and RSC, we also explored the role of the occipital place area (OPA). Although little is known about its function, recent work suggests that OPA supports navigation guided by visual cues and representation of local elements in the immediately visible scene, such as obstacles (Kamps et al., 2016), as well as the encoding of navigationally-relevant information such as environmental boundaries (Julian et al., 2016) and local navigational affordances (Bonner and Epstein, 2017). Additionally, inspired by previous evidence of a map-like representations for positions and facing directions (Sulpizio et al., 2014, 2017), we further explored whether hippocampal and scene-selective regions support this metric code even in a real-world "vista" space. We tested this hypothesis, by analyzing neural adaptation effects as a function of real-world distances between the covered positions/directions in consecutive images.

Another important aspect to be considered in the context of navigation is the individual experiential level: in some of the above-described studies participants learned a new environment (Schmidt et al., 2007; Sulpizio et al., 2013, 2014, 2015, 2016b; Marchette et al., 2014), typically through a limited number of exposures, while in other studies (Morgan et al., 2011; Vass and Epstein, 2013; Howard et al., 2014) they were very familiar with the experimental layout which was learned over extended time periods (typically years). One possibility is that the degree of familiarity with the environment affects the organization of position- and direction-dependent representations, and thus account for the reported discrepancy in the literature. We tested this hypothesis by controlling for the individual *a priori* and global knowledge of the environment, by using a series of questionnaires and training tests.

Finally, corollary to these aims, we further explored the impact of individual differences, in terms of navigational ability, on the neural representation of position and direction in both hippocampal and in scene-selective regions. Previous imaging studies have demonstrated that poor navigators showed a lower accuracy at identifying the most stable landmarks in the scene, and exhibited reduced responses in RSC, as compared to good navigators (Auger et al., 2012). To test this hypothesis we administered a self-reported questionnaire of navigational ability, the Santa Barbara Sense of Direction (SBSOD) questionnaire (Hegarty et al., 2002) that has been shown to be a reliable instrument to predict performance on objective tasks requiring to update one's location and direction in the environment (Kozhevnikov and Hegarty, 2001). Specifically, we expected that the individual differences in navigational abilities interact with the RSC function of encoding spatial information.

MATERIALS AND METHODS

Participants

Eighteen neurologically normal volunteers (9 females, mean age 27 s.d. 2.54) participated in the study. Sample size was determined based on previous fMRI experiments on the same topic (for a meta-analysis, see Boccia et al., 2014). One participant was excluded because he took part only to one of the two fMRI sessions. All participants were right handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971) and had normal or corrected-to-normal vision. All volunteers gave their written informed consent to participate in this study, which was approved by the local research ethics committee of the IRCCS Fondazione Santa Lucia in Rome, according to the Declaration of Helsinki.

Stimuli and Task

We used the same stimuli used in Sulpizio et al. (2017). We acquired each stimulus, consisting of a digitized color photograph (1024 × 768 pixel resolution), from one out of six different locations within Rome Kings' Square (*Piazza dei Re di Roma*) in Rome and orientated toward one of the different equidistributed directions starting from the square. Rome Kings' Square is a large (130 m of diameter), radial-arm maze-like round square situated in the Appio Latino neighborhood, distant 750 m from the Archbasilica of St. John in the Lateran (**Figure 1A**). Each photograph describes a specific position and facing direction within the square. Each location (A–F, **Figure 1A**) corresponds to one of the six wedges in which the square can be ideally subdivided. Within each wedge, we acquired photographs from two different positions (1–2) located at the distance of 32 m and 64 m from the center of the square, respectively. Each facing direction (A–F, **Figure 1A**) corresponds to one of the six streets (*Appia*—St. John direction, *Aosta*, *Pinerolo*, *Appia—Pontelungo* direction, *Albalonga* and *Cerveteri*) originating from the square. We thus acquired a total of 72 images (6 locations × 2 distances × 6 directions).

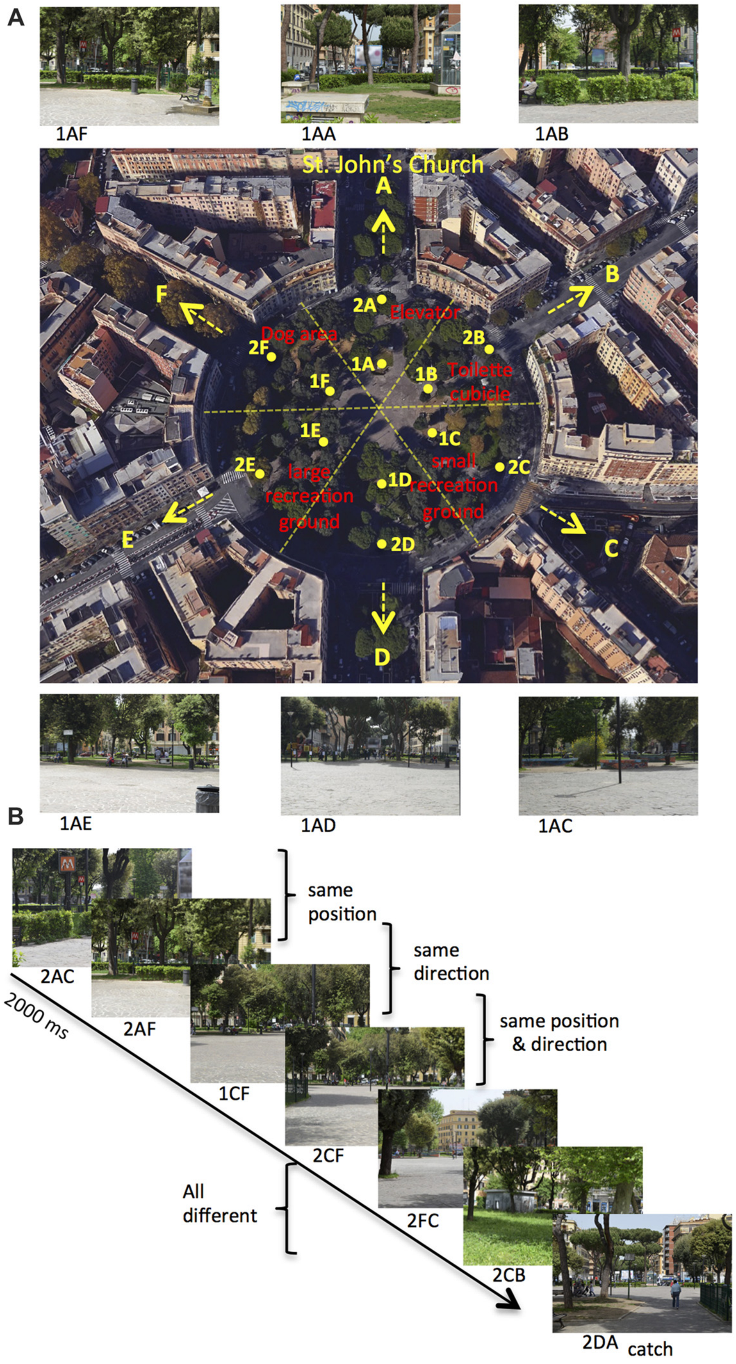

FIGURE 1 | Environment and paradigm. **(A)** Map of Rome Kings' Square. The six roads departing from the square define the six possible directions (marked as A–F), with the A direction (north) pointing towards St. John's Church. The square can be ideally divided in six wedges, and the 12 points (A–F, distributed around two concentric circles: eccentricity 1–2) represent all the possible positions within the square. Red labels indicate the relevant landmarks within the square. The label below the photograph (not shown to the participant) identifies the position from which the photograph is taken (first two letters: 1A to 2F) and its facing direction (third letter: A–F). **(B)** Example of trial sequence. Participants were presented a series of pictures and they were instructed to press a button, except when the presented picture was taken from the A direction (catch trial). Trial stimuli show the same position, the same direction or the same position and direction as compared to the previous trial.

Different landmarks are present within the square: a small recreation ground, a large recreation ground, the elevator of the tube station, a toilette cubicle and a dog area. Examples of stimuli taken from a specific position within the square, and with a specific facing direction, are shown in **Figure 1A**.

In the fMRI acquisition session, participants observed sequences of pictures, each describing a specific position and direction within Rome Kings' Square. These pictures were presented in a serially-balance sequence (carry-over sequence, see Aguirre, 2007), in which each picture was preceded by every other picture equally often so as to counterbalance main effects and first-order carry-over effects. This was crucial to allow us to use the same stimuli for both univariate (fMR adaptation) and multivariate (MVPA) analyses (Morgan et al., 2011; Epstein and Morgan, 2012). Participants were presented 72 pictures, which varied for the participants' position (A–F, **Figure 1A**) and direction (A–F, **Figure 1A**) within the square. **Figure 1B** shows an example of a brief sequence of experimental trials. On each stimulus, participants always pressed a button, except when the observed picture was directed toward the St. John's church (i.e., pictures in the A direction: catch trials). Catch trials were excluded from all the following analyses. We introduced this task to prompt participants to pay attention to all pictures and thus it was incidental to the aim of the study, that is exploring the neural representations of one's own position and direction within a familiar, real environment.

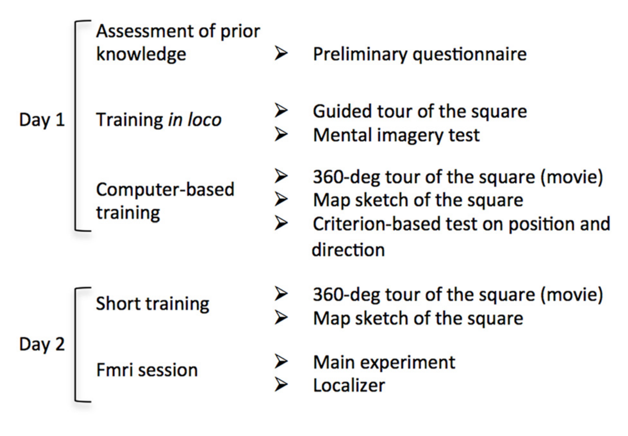

FIGURE 2 | Flow chart of the experimental procedure. Schematic description of each stage of the experimental protocol. On Day 1 participants underwent an intensive familiarization session including both *in loco* and computer-based tasks. On day 2, after a brief familiarization, participants underwent the fMRI session consisting in the main experiment and two "localizer" imaging runs.

Apparatus and Procedure

We acquired images using a 3T Siemens Allegra MR system (Siemens Medical systems, Erlangen, Germany) equipped for echo-planar imaging with a standard head coil and operating at the Neuroimaging Laboratory, Foundation Santa Lucia. Visual stimuli were presented by a control computer located outside the MR room, running in-house software (Galati et al., 2008) implemented in MATLAB (The MathWorks Inc., Natick, MA, USA). We used an LCD video projector with a customized lens to project visual stimuli to a projection screen positioned at the back of the MR tube. Visual stimuli were thus visible by participants through a mirror positioned inside the head coil. The timing of presentation of each stimulus was controlled and triggered by the acquisition of fMRI images. We recorded participants' responses through push buttons connected to the control computer via optic fibers.

We used blood-oxygenation level-dependent imaging (Kwong et al., 1992) to acquire echo-planar functional MR images (TR = 2 s, TE = 30 ms, flip angle = 70°, 64 × 64 image matrix, 3 × 3 mm in-plane resolution, 30 slices, 4.5 mm slice thickness with no gap, interleaved excitation order) in the AC–PC plane. Images were acquired for all the cerebral cortex, except for the most ventral portion of the cerebellum. For each participant we also acquired a three-dimensional high-resolution anatomical image (Siemens MPRAGE sequence, TR = 2 s, TE = 4.38 ms, flip angle = 8°, 512 × 512 image matrix, 0.5 × 0.5 mm in-plane resolution, 176 contiguous 1 mm thick sagittal slices). For each scan, we discarded the first four volumes in order to achieve steady-state, and the experimental task was initiated at the beginning of the fifth volume.

The experimental procedure was schematically described in **Figure 2**. On day one, participants underwent the same familiarization protocol used in Sulpizio et al. (2017). We first administered a preliminary questionnaire to estimate the *a priori* knowledge of the Rome Kings' Square; we asked participants to report the frequency by which they visit the square (never; one time a year or less; many times a years; many times a month; many times a week; every day). After this preliminary assessment, participants underwent an intensive training session within Rome Kings' Square aiming at ensuring the development of a long-term knowledge of the square layout. Further, we used a paper-pencil test adapted from Palermo et al. (2012) to assess the ability to build a stable cognitive map of this real environment. Specifically, participants were guided by the examiner through a 360° tour of the square. We asked participants to memorize the landmarks location as well as the six facing directions. Subsequently, they had to describe the environment from their mental imagery by responding to a 5-item questionnaire. For a detailed description of the questionnaire see Sulpizio et al. (2017).

After familiarization in the square, we asked participants to complete a series of computer-based experiments in the laboratory. Before testing, we allowed participants to familiarize again with the environment. We presented a first-person-view movie reproducing a 360° tour of the square. During this period, participants reinforced their memories about the relative locations of the streets (directions) and about landmarks location within the square. We presented the movie until participants were sure to correctly reproduce a sketch depicting the aerial view of the square. All participants reproduced the correct map after observing either one or two virtual tours of the square. We then prompted the individual ability to encode one's own position and facing direction within the explored environment (Sulpizio et al., 2017) through a training task including a series of questions about the covered position and direction within the square (for the same procedure, see Sulpizio et al., 2017). In each trial, a picture of the square taken from an unpredictable viewpoint was presented (**Supplementary Figure S1**). This picture included also the schematic sketch of the square (from a survey viewpoint) in which the six wedges and the six arms represented the six possible positions and directions, respectively (**Supplementary**

Figures S1A,B). In separate runs, participants decided whether the covered position in the square matched with the wedge highlighted in the sketch ("position" questions; **Supplementary Figure S1A**) or whether the perceived direction corresponded to the arm highlighted in the sketch ("direction" questions **Supplementary Figure S1B**). In case of matching between the experienced position/direction and the highlighted wedge/arm of the sketch, participants were instructed to press the left button on a 2-button response device with their right index; in case of mismatch they were instructed to press the right button with their middle finger. We presented a total of 144 pictures (72 for "position" questions and 72 for "direction" questions). Each picture remained on the screen until participants answered and the next trial started after a fixed inter-trial interval (ITI) of 500 ms. We took advantage of this training phase to force participants to develop a long-term knowledge of the explored environment so that they should be able to encode the current location and direction within the square. In these training sessions each participant had to reach a criterion of at least 70% of accuracy.

On the following day, we scanned participants during an fMRI acquisition session, including the main experiment and a "localizer" experiment. Before starting the experiments, we allowed participants to familiarize with the environment again. A movie reproducing a 360° tour of the square was presented again; we asked participants to watch it as long as they needed to correctly draw the schematic (aerial) view of the square. All participants reproduced the correct map of the explored environment at the first attempt.

The main experiment consisted of six fMRI scans lasting approximately 8 min each (264 functional MR volumes for the first scan and 221 for the remaining five scans), comprising 930 target trials and 31 catch trials, plus 74 randomly intermixed fixation periods each lasting 8000 ms long, providing a baseline. Each trial was presented for 2000 ms, followed by an ITI of 500 ms.

Participants also completed two localizer imaging scans consisting of eight alternating blocks (16 s) of photographs of faces and places/scenes presented for 300 ms every 500 ms, interleaved with fixation periods of 15 s on average (see Sulpizio et al., 2013). During each scan, lasting approximately 7 min (234 functional MR volumes), participants were instructed to passively view each picture. Data from these scans were used to identify scene-responsive regions in the parahippocampal, retrosplenial and occipital cortex (Epstein, 2008).

Image Processing and Analysis

Images preprocessing and analyses were carried out using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). Functional images were corrected for differences in slice timing by using the middle slice acquired in time as reference; images were spatially corrected for head movements (realignment) by using a least-squares approach and six parameter rigid body spatial transformations. We then coregistered images of each participant onto their anatomical image and spatially normalized using an automatic non-linear stereotaxic normalization routine (final voxel size: 3 mm × 3 mm × 3 mm). For spatial normalization we used a template image based on average data provided by the Montreal Neurological Institute (Mazziotta et al., 1995). Images for univariate analyses were spatially smoothed using a three dimensional Gaussian filter (6 mm full-width-half-maximum for the main experiment and 4 mm full-width-half-maximum for the localizer scans); multi-voxel patterns analyses (MVPAs) were conducted on unsmoothed images.

For each participant we analyzed time series of functional MR images separately on a voxel-by-voxel basis, according to the general linear model (GLM) as implemented in SPM12. We used a temporal high-pass filter in order to remove low-frequency confounds with a period above 128 s and estimated serial correlations with a restricted maximum likelihood (ReML) algorithm; the ReML estimates were then used to whiten the data.

Analyses were conducted on four independently defined, theoretically motivated, regions of interest (ROIs). Three of them, i.e., the PPA, the RSC and the OPA were identified on each individual's cortical surface (segmented by using an automatic procedure as implemented in Free-Surfer software package) by analyzing data from the "localizer" scans in which place/scene and face blocks were modeled as box-car functions, convolved with a canonical hemodynamic response function. On each individual hemisphere we defined PPA, RSC and OPA as the regions responding stronger to places/scenes than to faces blocks in the posterior parahippocampal cortex, in the retrosplenial/parieto-occipital sulcus, and in the transverse occipital sulcus, respectively. The RSC was defined so as to include the posterior cingulate (Brodmann areas 23–31), the retrosplenial cortex proper (Brodmann areas 29–30), and the nearby ventral parietal-occipital sulcus and anterior calcarine sulcus, according to Epstein (2008). We created these ROIs by selecting all activated voxels in the scenes vs. faces contrast ($p < 0.05$ false discovery rate (FDR)-corrected at the cluster level) at a maximum distance of 16 mm from the activation peak. Additionally, for each scene-selective ROI we selected the most responsive 100 cortical nodes, so that all regions contain the same number of nodes, thus allowing us to perform comparisons among them (for a similar procedure, see Vass and Epstein, 2017). All these ROIs were successfully identified in all participants, except for the RSC that was identified in 31/34 hemispheres.

A fourth region of interest, the HC, was instead anatomically defined: the automatic segmentation provided by FreeSurfer (Van Leemput et al., 2009) was used to reconstruct the HC of each participant so as to include all CA fields and the subiculum but not the entorhinal cortex. According to Morgan et al. (2011) we further divided each individual HC into an anterior (aHC) and a posterior (pHC) ROI based on an axial division at $z = -9$. The rendering in **Figure 3A** was created by projecting individual scene-selective ROIs onto a surface-based atlas (Conte69 atlas, Van Essen et al., 2012) using an in-house Matlab toolbox (BrainShow). **Figure 3B** shows the anatomical localization of aHC and pHC ROIs on a sagittal slice. **Table 1** reported MNI coordinates of regional peaks and size of each ROI.

For the main experiment analyses, we modeled each trial as a canonical hemodynamic response function time-locked to the trial onset. We included separate regressors for each trial type,

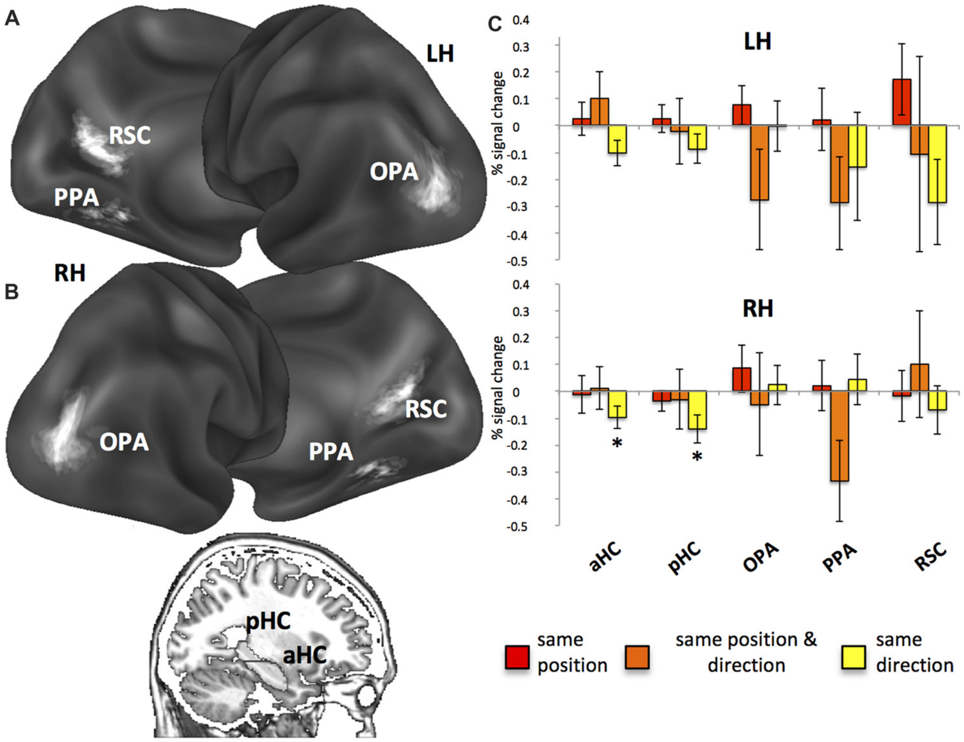

FIGURE 3 | Regions of interest (ROI) and fMR adaptation. **(A)** Anatomical localization of the occipital place area (OPA), parahippocampal place area (PPA) and retrosplenial complex (RSC) on lateral and medial/inferior views of the cortical surface of the left (LH) and right (RH) hemispheres. **(B)** Anatomical localization of the anterior (aHC) and posterior hippocampus (pHC) for one sagittal slice. **(C)** Plots show position- and direction-related adaptation effects, i.e., reduction of estimated BOLD signal in *same position*, *same direction* and *same position & direction* trials as compared to *all-different* trials. $^{*}p < 0.05$.

thus yielding parameter estimates for the average hemodynamic response evoked by each. Different features of the images presented in each trial were modeled through different GLMs. We modeled target trials with no response (2% on average across subjects), false alarms (1% on average across subjects) and catch trials as separate conditions; these conditions were then excluded from further analyses. All models were fitted to regional time courses from each subject-specific ROI, obtained by averaging preprocessed voxel time series across all voxels within each ROI.

TABLE 1 | Regional peaks (MNI coordinates) and size of the regions of interest (ROIs).

Region	Hemisphere	MNI coordinates			Area/Volume
		x	*y*	*z*	
aHC	Left	−25	−9	−32	4673 mm^3
	Right	27	−8	−32	4579 mm^3
pHC	Left	−29	−37	−9	1666 mm^3
	Right	33	−36	−9	1597 mm^3
PPA	Left	−29	−54	−11	114 mm^2
	Right	29	−47	−10	132 mm^2
RSC	Left	−20	−62	13	186 mm^2
	Right	22	−56	13	246 mm^2
OPA	Left	−32	−91	8	360 mm^2
	Right	38	−84	10	453 mm^2

aHC, anterior hippocampus; pHC, posterior hippocampus; PPA, parahippocampal place area; RSC, retrosplenial complex; OPA, occipital place area.

Further details about these analyses are reported in the following paragraphs.

fMR Adaptation Analysis

This analysis was aimed at showing the presence of a neural representation of position and direction in each ROI, based on the fMR adaptation phenomenon, i.e., a reduction of the event-related BOLD signal amplitude to the second trial produced by the repetition of the same position/direction across consecutive trials. This reduction should occur only in brain regions showing selectivity for encoding the repeated information. To this aim, we modeled each target trial with respect to its relationship with the previous target trial in terms of same/different position and direction, thus resulting in the following condition labels: (1) *same position*, for pictures taken from the same wedge of the square as the previous trial, although with a different direction; (2) *same direction*, for pictures taken along the same direction within the square as the previous trial, but from a different place; and (3) *same position and direction*, for pictures taken from the same wedge and in the same direction with respect to the previous trial; and (4) *all different* for pictures taken both from a different position and direction as compared to the previous trial. Note that the pictures shown on successive trials were never exactly identical, even on *same position and direction* trials. Indeed, pictures taken from the same wedge of the square were considered as having the same position although they were taken from two distinct (close) positions. **Figure 1B** shows an example of trial sequence and the corresponding condition labels.

To examine the neural adaptation effects, beta values associated to each repetition regressor were extracted for each individual ROI, converted to percent signal change, and compared to *all different* condition using one-tailed t-tests. We used a FDR procedure (Benjamini and Hochberg, 1995) in order to correct for multiple comparisons: the obtained distributions of p values were used to compute a p threshold that set the expected rate of falsely rejected null hypotheses to 5%. This procedure was applied for all the subsequent analyses, except when differently specified.

Multivariate Pattern Analysis

A second way to determine the presence of a neural "signature" of position and direction was based on a MVPA. This is a largely employed classification method in which multi-voxel patterns were classified so as to determine the stimulus category (for a review, see Norman et al., 2006). By training a classifier to discriminate between multi-voxel patterns of estimated BOLD responses elicited by pairs of positions and directions, we aimed at demonstrating the existence of a neural signature of these two spatial information. Specifically, classification accuracies in the analyzed regions were taken as evidence of the presence of position- and direction-related information when significantly higher than chance level.

In the MVPA, we used a GLM on unsmoothed time series, and modeled trials related to each of the six positions and five directions by using separate regressors, in order to estimate the amplitude of the response at each of the 30 trial types across all repetitions. Note that pictures taken along the A direction (catch trials) were excluded from all the analyses. We then used the resulting parameter estimate images to extract multi-voxel pattern of activity for each item in each ROI and classification was performed on these data separately for positions and directions. For each of these two information, we assigned each picture to one of the possible categories, representing the six different positions or the five different directions. The overall classification procedure consisted in splitting the imaging data into two parts: a "training" set used to train a linear classifier (support vector machine (SVM); Duda et al., 2001) using the LIBSVM implementation (Chang and Lin, 2011) to identify patterns of activity related to the stimuli being discriminated, and an independent "test" set used to probe the classification accuracy. We tried to minimize the cross-validation loss during classification by using an automatic Bayesian procedure (as implemented in Statistics and Machine Learning Toolbox^{TM} in Matlab R2017b), which chooses a typical set of hyperparameters to optimize. Hyperparameters are internal parameters of the support vector machine that can strongly affect the performance. We used a leave-one-out cross-validation procedure in which data from all scans expect one were used in turn to train the classifier and the remaining scan was used to estimate prediction accuracy. These resulting classification outcomes were then averaged across cross-validation folds and category pairs. We finally used one-sample t-tests to compare the between-subject distribution of classification outcomes with chance level (i.e., 0.5). We also compared the classification performance for both position and direction in each ROI through repeated measure ANOVAs. We conducted two separate *spatial information* × *ROI* analyses, one for surface-based ROIs (PPA, RSC and OPA) and one for the anatomical hippocampi (aHC and pHC). The rationale to separate the two ANOVAs is to avoid spurious effects due to the ROI selection procedures, that is functional mapping for surface-based ROIs and anatomical segmentation for the hippocampi.

Distance-Related Adaptation Analysis

We further looked at the fMR adaptation to explore distance-related effects, i.e., whether neural codes for position and direction reflected real distances between these spatial features. We thus explored whether adaptation effects elicited by consecutive pictures depended on the spatial differences between them. For each of the two spatial information, we used parametric modulators of the BOLD response to model the physical distances between the current and the preceding trial. For this analysis, we modeled all target trials associated with a valid response and preceded by a target trial with a valid response as trials of the same type. This allow us to explore the linear modulation of the response amplitude elicited by both position and direction distances (see below). Target trials associated with missing responses, or following a fixation period, catch trials and false alarms, were modeled separately and not considered here.

We considered two modulatory variables, i.e., position change and direction change, modeling the spatial distance in terms of position and direction, respectively. We considered two estimates of distance for position change, reflecting both the angular and the Euclidean distance between the position (the wedge of the square) from which the current and the preceding trial pictures were taken. Direction change reflects the angular displacement between the allocentric directions of the current and the preceding trial pictures. A third modulatory variable was included to control for the potential confound of visual similarities between the current and the preceding picture (texture change). We introduced this parameter according to Epstein and Morgan (2012) since fMR adaptation could reflect low-level similarities between pictures, irrespective of spatial differences. We used a texture model (Renninger and Malik, 2004) to compute the texture change between each pair of pictures. More specifically, each picture was converted to gray-scale and passed with V1-like filters to create a list of the 100 most prototypical texture features found across the pictures (MATLAB code available at renningerlab.org). For each picture we then generated a histogram of texture frequency. We thus calculated the visual similarity between pairs of pictures by comparing the distribution of the two histograms by using a chi square measure (smaller chi square values correspond to more similar pictures).

To test the hypothesis about the presence of distance-related effects, beta values associated to each modulatory variable were extracted for each individual ROI, converted to percent signal change, and compared to zero using one-tailed t-tests.

Searching for Individual Differences in Position and Direction Coding

Corollary to our main aims, we also checked for the potential link between position- and direction-based representations and individual differences in spatial abilities.

To control for the potential impact of the *a priori* knowledge of the environment on the automatic activation of position- and direction-dependent representations (for a similar procedure, see Sulpizio et al., 2017), we calculated Pearson's correlations between the behavioral/imaging results and the previous familiarity of the square as assessed, on each participant, by the preliminary questionnaire (see the "Apparatus and Procedure" paragraph).

To test whether position- and direction-related effects depended on the individual ability to build the cognitive map of the square, we calculated the correlation between the behavioral/imaging data with: (1) participants' scores to the paper-pencil questionnaire assessing the stability of the mental imagery of the square; and (2) the number of runs needed to achieve the supra-threshold accuracy during both position and direction questions of the preliminary training task (see the "Apparatus and Procedure" paragraph). One participant was excluded from this latter analysis due to his deviant data during the position questions, differing by 2.5 standard deviations from the group average. Since any position- and direction-related effects observed during the main task could be due to the ability to memorize positions and directions during the training task, we performed multiple linear regression analyses using the quantity of practice prior to scanning (numbers of runs needed to achieve the criterion in a preliminary training task) as a predictor and the neural effects observed during scanning as the dependent variable. An additional multiple regression analysis was conducted to test whether the observed effects during scanning could be due to the initial accuracy (mean accuracy during the first run) in memorizing positions/directions during the training task rather than by the learning practice.

Finally, to examine the hypothesis that the patterns of activity of scene-selective and hippocampal regions may reflect individual differences in spatial orientation (Sulpizio et al., 2016a), we analyzed the obtained data as a function of the individual navigational abilities as assessed by the SBSOD questionnaire (Hegarty et al., 2002), which is a self-report measure that has been shown to strongly reflect the actual navigation ability thus becoming increasingly used as a reliable instrument to predict real-world wayfinding performance (Janzen et al., 2008; Wegman and Janzen, 2011). For each ROI, participants were divided into two groups (good and poor navigators) by a median split of their SBSOD scores (good group mean 61.22, s.d. 9.28; poor group 47, s.d. 5.76), according to previous reports (Auger et al., 2012; Auger and Maguire, 2013; Wegman et al., 2014; Sulpizio et al., 2016a). We explored the difference between good and poor navigators through a series of mixed analysis of variance (ANOVA), with *group* as a between-subjects variable and *spatial information* (position and direction) as a repeated measure. For these analyses, we used a Bonferroni adjustment in order to create confidence intervals for all the pairwise differences between good and poor navigators.

The analyses on aHC, pHC, OPA and PPA were conducted on 16 participants, eight for each group. One individual was excluded because his score corresponded to the median value to the SBSOD questionnaire. Similarly, the analyses on the right RSC were conducted on 16 participants, eight for each group, because we failed in identifying this area in one participant. Finally, the analyses on the left RSC were conducted on 14 participants, seven for each group. We failed in defining the area in two individuals and one more individual was excluded because his score corresponded to the median value to the SBSOD questionnaire.

For all the above-mentioned analyses, we used both adaptation and decoding results to assess, in each participant, the selectivity for position- and direction-based representations. Specifically, for what concerns the adaptation data, we calculated the difference between repeated and non-repeated (all different) trials on both behavioral and imaging data as the index of the amount of behavioral/neural attenuation.

RESULTS

Priming for Repeated Positions: Insight From Behavior

On each stimulus, we asked participants to press a button, except for pictures taken from a specific facing direction (catch trials). This task prompted participants to pay attention to each picture and required them to go beyond the simple analysis of the perceptual features of the scene. Participants performed this task rapidly (median RTs of correct responses: 911 ms; S.D: 154 ms) and quite accurately (Hit: 98%; S.D: 0.3%; FA: 25%, S.D: 12%; and MISS: 0.2%; S.D: 0.3%). Crucially, on each picture, the observer's position (or facing direction or both) within the familiar place could be same as compared to the preceding trial. In *same position* and in the *same direction* trials, the position and the direction were respectively the same as compared to the previous trial, while the other spatial feature differed. In the *same position and direction* trials, both the position and the direction were the same as compared to the previous trial, while in *all different* trials neither the position nor the direction was the same as the previous trial. We used a series of one-tailed t-tests to compare repeated trials to a (common) non-repeated condition. Although participants were not aware of trials repetition, we reported a significant reduction of reaction times ($T_{16} = -8.13$; $p < 0.0001$) for the *same position* (median: 868 ms, S.D: 151 ms) as compared to *all different* trials (median: 903 ms, S.D: 150 ms), index of an implicit representation of position-related spatial information. No significant differences were found between *same direction* (median: 896 ms, S.D: 154 ms) and *all different* trials ($p > 0.05$) and between *same position and direction* (median: 918 ms, S.D: 187 ms) and *all different* trials ($p > 0.05$). Unexpectedly, we did not find any priming effect in the *same position and direction* trials although a priming effect was observed in the *same position* trials. We could speculate that position- and direction-dependent representations are not independent so that the behavioral priming does not necessarily reflect an "additive" effect. Alternatively, such a pattern of results could be explained if considering that pictures in the *same position and direction* trials were never identical since they were labeled as having the same position although they were taken from two distinct (close) positions (1–2) within each wedge of the square (see **Figure 1A**). These positions were arranged along each direction so that, in this condition, participants could experience (across consecutive trials) to move forward (from position 1 to position 2) or backward (from position 2 to position 1) along a specific direction. This might induce an illusion of self-motion through the square that might interfere with the automatic encoding of position- and direction-related information.

To check for the potential role played by individual differences on this behavioral advantage, we correlated the participants' performance during the familiarization/training sessions with the priming amount (calculated as the difference between the response time in repeated vs. all different trials) and analyzed this quantity as a function of the self-reported navigational ability. We found no significant correlations between behavior and both the *a priori* familiarization level (as assessed by the preliminary questionnaire) and the imagery-based paper-pencil test (all $|r| < 0.36$; $p > 0.15$). Further, no significant correlation was found between the behavioral priming and the quantity of practice (number of runs) required to reach the learning criterion in the preliminary training task ($r = -0.12$; $p = 0.64$). These data indicated that the observed behavioral advantage did not reflect the participants' global knowledge of the environment. When exploring the potential link between the behavioral priming and the self-reported navigational ability, we found no significant results. Good and poor navigators did not show any difference in the amount of priming effects (no significant interaction, $p > 0.05$).

Neural Codes for Position and Direction: Insight From fMR Adaptation

fMR adaptation, i.e., the neural activity decrease as a function of stimulus repetition, has been extensively used to probe sensitivity to specific visual item and to understand the nature of the underlying representations (Grill-Spector et al., 2006). For fMR adaptation, and for all the subsequent analyses, we report results from the functionally-defined scene-selective regions, RSC, PPA, OPA and from the anatomically-defined anterior (aHC) and posterior (pHC) hippocampi. We focused on these regions since previous neuroimaging studies have implicated them in navigation (Ghaem et al., 1997; Maguire et al., 1998; Rosenbaum et al., 2004; Spiers and Maguire, 2006; Epstein, 2008; Baumann and Mattingley, 2010; Sherrill et al., 2013; Boccia et al., 2017a), spatial memory (Wolbers and Büchel, 2005; Epstein et al., 2007; Brown et al., 2010; Sulpizio et al., 2013, 2016a), spatial orientation (Vass and Epstein, 2013; Marchette et al., 2014; Sulpizio et al., 2014) and spatial imagery (Boccia et al., 2015, 2017b; Vass and Epstein, 2017).

First, we used fMR adaptation to investigate position- and direction-related representations within our ROIs by comparing repeated trials (*same position*, *same direction, same position and direction*) to a common non-repeated condition (*all different*). Results from fMR adaptation are shown in **Figure 3** (for a more detailed description about the data distribution, see also **Supplementary Figure S2**). We observed significant neural adaptations in the right aHC ($t_{16} = -2.36$; $p < 0.05$; **Figure 3B**) and pHC ($t_{16} = -2.68$; $p < 0.05$) in the *same direction* trials. Significant but FDR-uncorrected results were also observed in the left aHC (left: $t_{16} = -2.18$; $p = 0.02$ uncorrected, corresponding to $p = 0.07$ FDR-corrected) in the *same direction* trials and in the right PPA ($t_{16} = -2.26$; $p = 0.02$ uncorrected, corresponding to $p = 0.06$ FDR-corrected; **Figure 3B**) in the *same position and direction* trials.

For what concern the individual differences, when controlling for the relationship between adaptation effects and the degree of individual knowledge of the environment, we found some significant (but FDR-uncorrected) correlations: position-related neural effects (calculated as the difference between the neural signal in repeated vs. no repeated trials) was positively correlated with the number of runs required to reach the criterion in the position questions of the training task. This effect was found only in the bilateral PPA (**Supplementary Figure S3**; left: $r = 0.54$; $p = 0.031$ uncorrected, corresponding to $p = 0.18$ FDR-corrected; right: $r = 0.61$; $p = 0.013$ uncorrected, corresponding to $p = 0.08$ FDR-corrected), thus indicating that the individual ability to rapidly encode the covered positions marginally impacts the neural adaptation in this region.

To further explore this relationship, and to better understand whether the ability to memorize positions/directions in the preliminary task significantly predicts the position- and direction-related neural effects observed in the main task, we performed multiple linear regression analyses using the quantity of practice (number of runs needed to achieve the criterion) as a predictor and the neural effect observed during scanning as the dependent variable. We observed that the quantity of practice in the position task significantly predicted the position-related neural effects in the bilateral PPA (left: Beta = 0.54; $T = 2.39$; $p = 0.031$; right: Beta = 0.61; $T = 2.86$; $p = 0.013$). When exploring whether the initial accuracy in memorizing positions/directions affected the neural effects observed in the main task, we failed in finding significant results (all $p > 0.1$), thus indicating that the learning practice, rather than the initial accuracy, interacts with observed neural effects.

No significant correlations were found between neural adaptation and both the *a priori* knowledge and the mental imagery of the environment (all $|r| < 0.45$; $p > 0.07$). When examining the relationship between the fMR adaption effects and the self-reported navigational ability, we found no significant results in any ROI. Additionally, good and poor navigators did not differ in the amount of fMR adaption effects (no significant interaction, $p > 0.05$).

Second, we asked whether position- and direction-related representations are topographically organized, with neural activity reflecting physical distances between consecutive positions and directions. To do this, we examined distance-related effects on adaptation effects: adaptation between pairs of pictures was taken as an index of the spatial differences

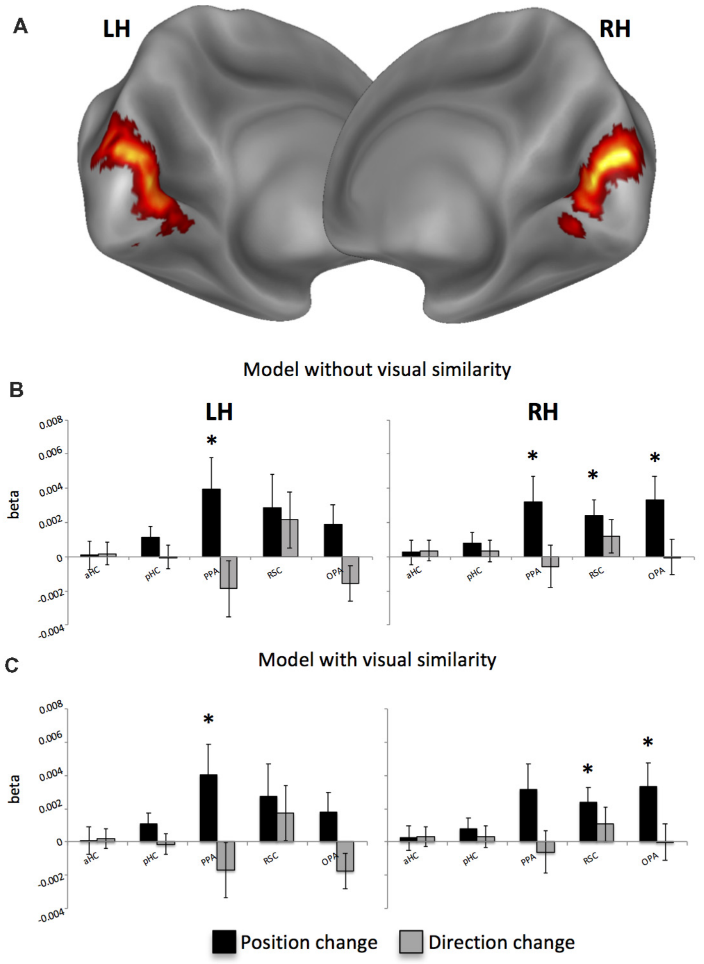

FIGURE 4 | Distance-related results. **(A)** Whole-brain analysis reveals that the visual similarity between consecutive pictures explains activity only in the bilateral early visual cortex (EVC). **(B)** Distance-related adaptation effects without removing variance explained by the visual similarity across pictures. **(C)** Distance-related adaptation effects after controlling for visual similarity across pictures. **p* < 0.05.

between them. A general picture of these effects is shown in **Figure 4**. When considering the position change as reflecting the angular distance between consecutive pictures, we found a significant positive effect of spatial distances only for position, i.e., an increase of activity as a function of the spatial distances between positions in consecutive pictures, in the bilateral PPA (left: $t_{16} = 2.21$; $p < 0.05$; right: $t_{16} = 2.16$; $p < 0.05$) and in the RSC ($t_{16} = 2.59$; $p < 0.01$) and OPA $t_{16} = 2.36$;

TABLE 2 | Decoding accuracy for both position and direction in the ROIs.

		Position			Direction		
Region	**Hemisphere**	**Mean**	**SD**	***P* value**	**Mean**	**SD**	***P* value**
aHC	Left	0.69	0.14	<0.001	0.66	0.13	<0.001
	Right	0.64	0.14	<0.001	0.64	0.14	<0.001
pHC	Left	0.66	0.17	<0.01	0.71	0.13	<0.001
	Right	0.68	0.17	<0.001	0.69	0.14	<0.001
PPA	Left	0.72	0.15	<0.001	0.64	0.13	<0.001
	Right	0.67	0.16	<0.001	0.63	0.12	<0.001
RSC	Left	0.65	0.16	<0.01	0.65	0.13	<0.001
	Right	0.67	0.15	<0.001	0.72	0.12	<0.001
OPA	Left	0.72	0.14	<0.001	0.73	0.12	<0.001
	Right	0.61	0.13	<0.01	0.70	0.14	<0.001

aHC, anterior hippocampus; pHC, posterior hippocampus; PPA, parahippocampal place area; RSC, retrosplenial complex; OPA, occipital place area.

$p < 0.05$) of the right hemisphere (**Figure 4B**). However, to account for the possibility that distance-related neural effects can be due to low-level visual similarity rather than by spatial distance across consecutive pictures, we added a further modulatory variable (texture change). We found that this variable had a significant impact on the early visual cortex (EVC; $p < 0.001$; cluster-level FDR-corrected; **Figure 4A**), which was the only area reflecting low-level visual change between consecutive pictures. After removing variance due to visual similarity, we confirmed significant linear effects for position-related distances in the left PPA ($t_{16} = 2.21$; $p < 0.05$), in the OPA ($t_{16} = 2.33$; $p < 0.05$) and RSC ($t_{16} = 2.60$; $p < 0.01$) of the right hemisphere (**Figure 4C**) and marginally in the right PPA ($t_{16} = 2.27$; $p = 0.02$ uncorrected, corresponding to $p = 0.054$ FDR-corrected). These results suggest that visual similarity between consecutive pictures only marginally impacts on distance-related adaptation effects in scene-selective regions.

When examining whether distance-related adaptation effects also reflected real-world Euclidean distances between locations, we found a significant effect in the left PPA ($t_{16} = 2.49$; $p < 0.05$) and in the right RSC ($t_{16} = 2.29$; $p < 0.05$), thus indicating that these regions are sensitive to both angular and metric distances between consecutive positions.

Decoding the Spatial Information: Insight From Multivariate Pattern Analyses

As a second way to examine the neural codes for position and direction we used multivariate classification analysis. Since visual similarity did not affect the pattern of adaptation results in our ROIs, we did not control for this aspect in the subsequent classification analyses. We also observed that the average visual dissimilarity for between-category image pairs was comparable to the average visual dissimilarity for within-category image pairs (position: between 0.37, within 0.36; $t_{2554} = -0.86$; $p = 0.19$; direction: between 0.37, within 0.37, $t_{2554} = 1.33$; $p = 0.91$) so that no texture-related effect on multi-voxel pattern was expected. We examined the accuracy of a linear classifier in decoding information about position and direction from multi-voxel patterns of neural activity. We obtained independent estimates of neural activity elicited by each of the 30 possible combinations of position and direction, and in separate analyses we grouped the resulting conditions by position and direction. A linear classifier was trained to distinguish between each possible pair of categories (chance level = 0.5) using a cross-validation procedure (leave-one-session-out). More specifically, we tried to decode the specific position (or direction) in each trial from one run from the activity patterns evoked from trials of N-1 runs. For each feature we obtained decoding rates by averaging the decoding performance across all position/direction pairs.

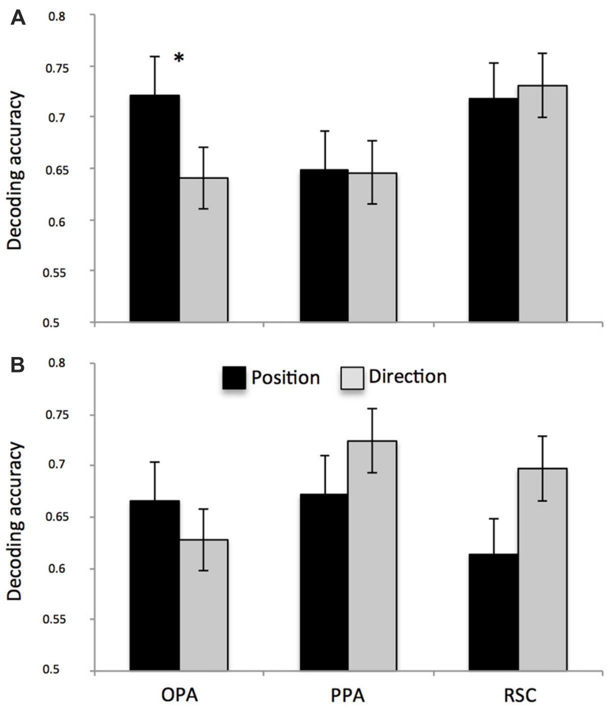

FIGURE 5 | Multivariate classification results. Plots show the mean classification accuracy in the predefined ROIs (all above chance, $p < 0.01$) for both left **(A)** and right **(B)** hemispheres. Classification performance was higher for position than for direction only in the left OPA. *$p < 0.01$.

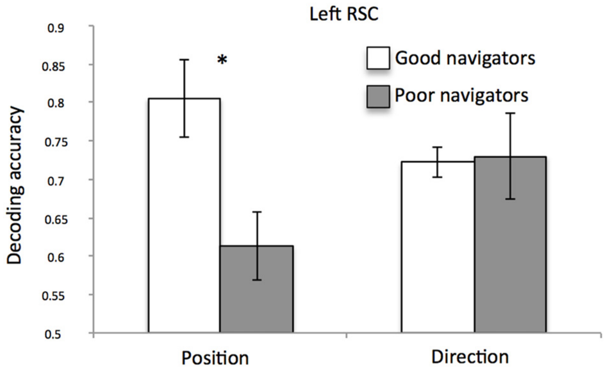

FIGURE 6 | Left RSC decoding accuracy as a function of navigational abilities. Plot shows the mean classification accuracy of the left RSC as a function of group (poor vs. good navigators). *$p < 0.01$.

We found significantly above-chance decoding accuracy for both position and direction in all ROIs (see **Table 2**). After directly comparing performance for the two features in each surface-based ROI (**Figures 5A,B**), we found no differences, except for the left OPA (**Figure 5A**; *spatial information* by *ROI* interaction, $F_{(2,28)} = 3.54$, $p = 0.04$; $\eta_p^2 = 0.20$) in which classification performance was higher for position than for direction ($p = 0.04$). See also **Supplementary Figure S4** for a more detailed description about the exact distribution of these data. No significant differences were found in the anatomically-based ROIs, i.e., aHC and pHC.

When checking for the impact of the individual differences on decoding performances for both position and direction, we found no significant correlations with both the *a priori* knowledge of the environment and the ability to create a stable map of the environment from imagery. However, we found an interesting relationship between classification accuracy and self-reported spatial ability. **Figure 6** shows the significant *spatial information* by *group* interaction ($F_{(1,12)} = 5.76$; $p = 0.03$; $\eta^2_p = 0.32$) indicating that, in the left RSC, position-related decoding accuracy was higher for good than for poor navigators ($p = 0.008$; for the exact distribution of these data, see also **Supplementary Figure S5**).

DISCUSSION

In the current study, by combining fMR adaptation and multivariate analyses, we set out to ascertain whether the human brain represents spatial information which are relevant for navigation, such as place information about our location in a real, open-field environment and directional information about which orientation we are facing to within it. We sought to clarify whether such a "vista" space is represented in the HC and in scene-selective regions (PPA, RSC and OPA) with the same map-like spatial organization previously observed in a smaller room-sized "vista" environment (Sulpizio et al., 2014), thus getting more light on the impact of the spatial scale on position- and direction-dependent representations.

Finally, we considered how individual differences in navigational abilities and in the ability to build a stable memory of the environment may interact with the function of the navigational system of encoding this two navigationally-relevant information.

Our first main finding is that the right HC contains information about facing direction. This was demonstrated by the finding of neural adaptation for repeated directions: the hippocampal fMRI response to the current trial was reduced by repetition of directional information from the previous trial. The fact that this region did not show neural adaptation for *same position and direction* trials may suggest that the right HC represents directions only when position changes, thus indicating that this area does not simply represents direction. Alternatively, it could be that the *same position and direction* trials were not informative since participants could experience (across consecutive trials) to move forward (from position 1 to position 2) or backward (from position 2 to position 1) along a specific direction, thus interfering with the automatic encoding of position- and direction-based information (see also "Priming for Repeated Positions: Insight From Behavior" paragraph in the "Results" section). Although the hippocampal involvement in directional coding seems to be unusual, this result is in accordance with previous electrophysiological and imaging evidence. For example, a previous report exploring the head-direction system in rats (Golob and Taube, 1999) revealed that lesions to the HC prevent the maintenance of an accurate representation of facing direction. More recently, it has been demonstrated that proximity and orientation toward the goal during a real-world navigation task modulate the hippocampal activity: posterior hippocampal activity increased when participants were close to and facing the goal (Howard et al., 2014). The absence of a position-dependent representation in the HC is not entirely surprising. No position-related fMR adaptation effects were observed in the HC within both virtual room-sized (Sulpizio et al., 2014) and large-scale real environments (Vass and Epstein, 2013). However, the absence of such adaptation effects does not exclude the hippocampal involvement in encoding spatial information about one's own location. According with previous studies (Hassabis et al., 2009; Sulpizio et al., 2014), we observed that HC accuracy in decoding positions from multi-voxel patterns was significantly above chance, thus indicating that the hippocampal activity contains sufficient information to discriminate different positions. Inconsistent results between fMR adaptation and multi-voxel pattern analysis have been reported before (Drucker and Aguirre, 2009; Epstein and Morgan, 2012). For instance, as suggested by Drucker and Aguirre (2009), these two techniques interrogate representations at different spatial scales: adaptation effects should be more sensitive to the tuning of single (or small populations of) neurons, while multi-voxel effects should reflect clustering distributed at a coarser anatomical scale.

Although we failed in finding adaptation effects in scene-selective regions, clear evidence of a neural "signature" associated with specific spatial locations or directions in PPA, RSC and OPA comes from the multivariate classification analysis. Beyond the HC, we found that the multi-voxel patterns of scene-selective regions contained information about the position and the direction assumed on pictures taken from specific views of the familiar circular real-world square. We previously observed that PPA and RSC contained place-, view- and heading information concerning the scene currently being viewed within a smaller room-sized vista environment, which permitted successful decoding by the classifier (Sulpizio et al., 2014). Our finding that PPA, RSC and OPA represent position and direction confirms previous neuroimaging studies. These regions have been involved previously in spatial navigation and spatial memory (for a recent review, see Epstein et al., 2017). More generally, a recent meta-analysis reported in Epstein et al. (2017) revealed that the common activation across 64 studies of human navigation well corresponded to our ROIs. More specifically, previous studies on multi-voxel pattern analysis revealed that PPA, RSC and OPA contain information about scene category (Kravitz et al., 2011; Epstein and Morgan, 2012) and specific landmarks (Morgan et al., 2011; Epstein and Morgan, 2012) within a large-scale real space and allow classification of interiors from exteriors of buildings (and vice versa) within that environment (Vass and Epstein, 2013; Marchette et al., 2014). Our results extend these previous findings, by showing that all the above-mentioned scene-selective regions contain sufficient information that allow to discriminate different location/direction within a real "vista" space, thus supporting the idea that they are recruited whenever people are exposed to pictures of scenes, independently of both environmental features and task demands.

Analyses of multi-voxel patterns also revealed that OPA is a key region in discriminating different positions within the square: it was able to distinguish (better than chance) different facing directions, but we observed higher decoding performance after applying MVPA to predict distinct locations. Previous research suggests that OPA is causally involved in scene processing (Dilks et al., 2013) and more specifically in the spatial processing of local scene elements such as environmental boundaries (Julian et al., 2016), and that it automatically encodes the structure of the navigational space, by detecting environmental features that afford relevant behaviors such as navigation (Bonner and Epstein, 2017; Patai and Spiers, 2017). The direct role of this area in the human visually-guided navigation has been further supported by previous evidence showing its involvement in supporting obstacle avoidance in the immediately visible scene (Kamps et al., 2016) and in encoding two essential kinds of information: sense (left-right) information and egocentric distance (proximal-distal) information (Dilks et al., 2011; Persichetti and Dilks, 2016). The current work purports to show that OPA represents directions and (especially) positions of vista spaces invariant to these particular scene features. It is possible that different scenes depicting similar positions or directions depict similar boundaries or affordances, but a more careful analysis of the scene content would be required to differentiate these alternatives.

Beyond distinguishing between positions and directions, another key characteristic of scene-selective regions is that they support a sort of "cognitive map" of the environment, i.e., the neural representations reflect the spatial structure of the environment they represent. By examining the fMR adaptation on each trial as a function of the real distances between consecutive positions, we observed that the activity in the bilateral PPA and in the right RSC and OPA scales with these distances: i.e., greater fMRI responses for larger distances. Interestingly, these distance-related effects were observed although participants were not given any explicit navigational task or distance estimation demands, suggesting that these distance-related representations are automatically activated. Importantly, this result cannot be explained by differences of visual features between consecutive pictures. Once explicitly modeled low-level visual similarity between consecutive views, we observed significant effect on the early visual areas only. Compatibly, after removing effects of visual similarity, we obtained the same pattern of adaptation results on scene-selective regions, thus indicating that these regions, in line with previous evidence (Epstein and Morgan, 2012; Sulpizio et al., 2014), do not represent low-level visual properties of the scene.

Further support to the PPA and RSC involvement in encoding distances between locations comes from the observation that the right RSC and the left PPA are sensitive not only to the angular but also to the Euclidean distances between consecutive positions. A similar distance–related effect was recently observed in both PPA and RSC during the exposure to pictures taken from a familiar virtual room (Sulpizio et al., 2014). Both regions exhibited adaptation effects, proportional to the physical distances between consecutive places and views. On the other side, no evidence of a relationship between the activity of RSC and PPA and real-world distances between locations were found in previous studies examining the neural codes of real positions within large-scale environments. We speculate that the critical aspect to be considered when trying to justify this discrepancy is the set of properties of the immediate visible surrounding. It is possible that a metric, map-like representation precisely preserving distance relationships between spatial locations is easier to build up in "vista" spaces, where spatial locations to be encoded are often simultaneously in view during navigation (Wolbers and Wiener, 2014).

Another important aspect we considered is the potential impact of the individual differences on spatial representations. We found a relationship between the amount of practice needed to memorize the covered positions and the fMRI attenuation in the bilateral PPA: the longer the training the participants needed to memorize all positions, the higher the signal (i.e., the lower the neural adaptation) in this region. This result accounts for a link between position-dependent representation in PPA and the individual ability to memorize the covered positions within the environment. Consistently, Epstein et al. (2005), by examining how scene representations vary across individuals as a function of individual differences, previously observed that adaptation effects in PPA was larger for people with higher navigational competence.

The relationship between the individual ability to achieve a long-term memory for locations experienced prior to scanning and the observed position-related neural effects speaks in favor of a significant impact of learning rapidity in the position-dependent representation in PPA. One could argue that the initial predisposition to memorize different positions, which should reflect the individual ability to retrieve locations experienced during the *in loco* navigation session, may account for the observed neural effects. However, we found that the initial accuracy in memorizing locations during the first run of the training task did not predict the position-related neural effects, thus indicating that the amount of practice needed to reach a stable memory of locations, rather than the individual (*a priori*) promptness to memorize different positions, affects the position-related representation in the PPA. The sensitivity to environmental learning observed in the PPA supports previous evidence that has demonstrated the PPA/PHC involvement in rapid learning of specific associations between (initially unfamiliar) scenes (Turk-Browne et al., 2012).

As a further attempt to get more light on the individual differences, we examined how position- and direction-dependent representations may explain individual differences as a function of self-reported navigational abilities. We found an interesting relationship between multi-voxel classification accuracy and self-reported spatial ability in the left RSC: classification accuracy for different positions was higher in good than in poor navigators. This result is in line with a series of previous imaging studies showing the crucial role of RSC in accounting for individual differences in spatial abilities (Auger et al., 2012; Auger and Maguire, 2013; Sulpizio et al., 2016a). For example, poor navigators were impaired at identifying the most permanent items in the environment, and exhibited reduced responses in RSC, as compared to good navigators (Auger et al., 2012). By looking at the multi-voxel activity patterns in RSC, it was observed a better decoding of the number of permanent landmarks in good rather than in poor navigators (Auger and Maguire, 2013); similarly, the resting-state functional connectivity between the posterior HC and RSC was significantly higher in good than in poor navigators (Sulpizio et al., 2016a). An unexpected finding was that the relationship between the RSC activity and individual differences was observed only when spatial abilities were assessed using self-reports rather than more objective experimental measures, such as the above-mentioned preliminary training task. One possible explanation is that, while the SBSOD has been often used as a reliable proxy for real-world navigation performance (Janzen et al., 2008; Wegman and Janzen, 2011), the training task, by focusing on giving participants a long-term knowledge of the environment, tested spatial memory rather than actual navigation abilities. To go beyond this limitation, future studies should benefit in using, besides the subjective self-reported ones, more implicit experimental tasks on actual navigation. Another potential limitation of this study should be considered. The sample size was relatively small, which may limit the statistical power especially when detecting individual differences. Thus, regression and correlation analysis results should be interpreted with caution.

For what concern the hemispheric laterality of the observed effects, we mainly reported right-lateralized results, with the right HC showing neural suppression for repeated directions, and the right RSC and OPA exhibiting distance related adaption effects for consecutive positions. These results confirm the well-established right-hemispheric dominance for spatial tasks (for reviews, see Burgess et al., 2002; Boccia et al., 2014). Additionally, we also found some left-lateralized effects in OPA, which prefers to decode locations than directions, in RSC, whose multivariate pattern in decoding different locations predicts individual differences in spatial ability, and in PPA, in which activity was modulated by both angular and metric distances between consecutive positions. However, particularly for OPA and PPA, no study to our knowledge previously reported hemispheric differences so that the question of hemispheric laterality is still a matter of dispute, and future studies should help to clarify this issue.

In summary, the present findings demonstrated that the human navigational network, including the HC and scene-selective regions, encodes spatial information about location and direction within a real "vista" environment, even in the absence of a navigational task. Furthermore, our results provide new insights into how the navigational network represents a real large-scale "vista" space. In particular we found that scene-selective regions (but not the HC) support a map-like representation of the environment, since they exhibited adaptation effects sensitive to real-world distances between consecutive positions. These results indicate that the neural code for one's own position and direction within a large-scale circular square is organized at a coarser spatial scale as compared to the metric representation observed in the small-scale, room-size environment (Sulpizio et al., 2014), thus accounting for a feeble impact of the scale of space on these spatial codes within the "vista" space. However, the spatial scale is not enough to differentiate between these two space classes that define the human navigational experience, i.e., "vista" and "environmental" spaces. A recent work, indeed, suggested that spatial memories for locations in "vista" and "environmental" spaces are qualitatively different in terms of spatio-temporal learning experience, and reference frame orientation employed during navigation: contrary to "vista" space, retrieving memory from "environmental" space requires to access to both order and distance in which objects are learned (Meilinger et al., 2016). Thus, further studies should better explore not only the role of the environmental size but also the impact of other variables, such as the amount of information to maintain, distance and order effects, or the alignment of the reference frame on such a map-like representation by directly manipulating the scale of space in both "vista" and "environmental" spaces.

AUTHOR CONTRIBUTIONS

VS, MB and GG designed the study. VS and MB collected the data. VS and GG analyzed the data and VS wrote a first draft of the manuscript. VS, MB, CG and GG contributed to the final version of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2018.00167/full#supplementary-material

FIGURE S1 | Training task. **(A)** Example of a trial of the training task about position. Participants were instructed to decide whether the position they perceived in the square corresponded to the green wedge on the sketch. The label below the photograph (not shown to the participant) identifies the position from which the photograph is taken (first two letters: 1A to 2F) and its facing direction (third letter: A–F). **(B)** Example of a trial of the training task about direction. Participants were instructed to decide whether the direction they faced at corresponded to the green arm on the sketch.

FIGURE S2 | Box plots showing a more detailed distribution of position- and direction-related adaptation effects showed in **Figure 3C**.

FIGURE S3 | Correlations between neural signal and the amount of practice. Scatterplots show the correlations between the neural signal (repeated position *minus* no repeated) and the amount of practice (number of runs needed to reach at least 70% of accuracy in the position questions of the training task) in the bilateral PPA.

FIGURE S4 | Box plots showing a more detailed distribution of multivariate classification results showed in **Figures 5A,B**.

FIGURE S5 | Box plot showing a more detailed distribution of the left RSC decoding accuracy result as a function of navigational abilities as shown in **Figure 6**.

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frontiers in Human Neuroscience

MINI REVIEW
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Modulating Spatial Processes and Navigation via Transcranial Electrical Stimulation: A Mini Review

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Transcranial electrical stimulation (tES) uses low intensity current to alter neuronal activity in superficial cortical regions, and has gained popularity as a tool for modulating several aspects of perception and cognition. This mini-review article provides an overview of tES and its potential for modulating spatial processes underlying successful navigation, including spatial attention, spatial perception, mental rotation and visualization. Also considered are recent advances in empirical research and computational modeling elucidating several stable cortical-subcortical networks with dynamic involvement in spatial processing and navigation. Leveraging these advances may prove valuable for using tES, particularly transcranial direct and alternating current stimulation (tDCS/tACS), to indirectly target subcortical brain regions by altering neuronal activity in distant yet functionally connected cortical areas. We propose future research directions to leverage these advances in human neuroscience.

Keywords: transcranial direct current stimulation, transcranial alternating current stimulation, spatial cognition, visualization, navigation, functional connectivity

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INTRODUCTION

Decades of empirical research have demonstrated involvement of diverse lateral and medial brain regions in spatial processing and navigation, including parietal, prefrontal and medial temporal areas (Spiers and Maguire, 2006; Iaria et al., 2007; Whitlock et al., 2008). The reliable involvement of these regions has made them of interest as targets for electrical neuromodulation, attempting to alter the acquisition of spatial knowledge and skills (Brunyé et al., 2014; Wright and Krekelberg, 2014; Oldrati et al., 2018). However, noninvasive electrical neuromodulation is largely limited to superficial cortical layers, limiting the ability to directly target deeper brain structures such as the retrosplenial cortex, posterior cingulate cortex (PCC), or the medial temporal lobes (de Berker et al., 2013). Recent advances in functional connectivity analyses have revealed stable functional networks (Kravitz et al., 2011; Sherrill et al., 2015; Boccia et al., 2017), suggesting that the modulation of superficial brain regions such as the inferior parietal lobule and lateral prefrontal cortex may carry powerful downstream consequences for deeper brain systems involved in spatial processing and real-world navigation. The present mini-review article provides an overview of existing literature using Transcranial electrical stimulation (tES) to modulate several spatial processes underlying navigation behavior, and then proposes that continuing electrical neuromodulation research leverages recent advances in functional connectivity to afford indirect targeting of deep brain areas of critical importance to spatial processing (Keeser et al., 2011; Weber et al., 2014).

TRANSCRANIAL ELECTRICAL STIMULATION

tES is a neuroscientific method for inducing transient alterations in neuronal membrane potential by administering electrical current via electrodes positioned on the scalp (Nitsche et al., 2008; Silva et al., 2008; Woods et al., 2016). Evidence from animal models and computational modeling demonstrates that tES can induce a subthreshold depolarization of pyramidal and possibly glial cells (Ruohonen and Karhu, 2012; Molaee-Ardekani et al., 2013; Rahman et al., 2013), and a growing body of literature demonstrates behavioral impacts of tES on a range of perceptual, cognitive, social and emotional tasks (Jacobson et al., 2012; Santiesteban et al., 2012; Berlim et al., 2013; Brunoni and Vanderhasselt, 2014; Dedoncker et al., 2016). While there are several techniques for administering tES, the present mini-review focuses on the most commonly-used method, transcranial direct current stimulation (tDCS), and incorporates some recent innovations in transcranial alternating current stimulation (tACS; Paulus, 2011; Woods et al., 2016).

With tDCS, low intensity direct current is delivered via electrodes arranged on the scalp. Traditionally, tDCS is delivered in a so-called bipolar montage, involving one anodal and one cathodal electrode, typically positioned directly over a cortical target (Paulus, 2011). For instance, one popular bipolar montage involves placing an anodal electrode over the left dorsolateral prefrontal cortex (dlPFC; 10/20 site F3), with the cathode placed on the right supraorbital area (Brunoni and Vanderhasselt, 2014; Dedoncker et al., 2016). This montage is thought to increase neuronal excitability in the left dlPFC, inducing behavioral effects on working memory and executive control (Tremblay et al., 2014). More recently, multi-electrode montages are being used in an effort to administer relatively focalized stimulation to cortical targets, typically involving 4–5 electrodes arranged in an optimal manner (i.e., higher density at target) according to finite element electrical field models of the human head (Datta et al., 2009; Ruffini et al., 2014).

With tACS, low intensity alternating current is delivered via electrodes arranged on the scalp, in a similar manner to tDCS. However, tACS typically administers sine-wave stimulation waveforms that specifically target frequency bands of cortical oscillations (Herrmann et al., 2013). tACS can thus administer current that is frequency-matched to an intrinsic frequency of a cortical area or network. Computational modeling suggests that tACS may thus be capable of promoting specific activity frequencies in brain areas or networks, perhaps via entrainment (Ali et al., 2013), or plasticity alterations (Vossen et al., 2015). If oscillatory brain activity is fundamental to information processing and behavior, then modulating oscillations with tACS should selectively alter such functions; some recent studies have found promise in this technique (Sejnowski and Paulsen, 2006; Herrmann et al., 2013; Neuling et al., 2013; Chander et al., 2016).

tES AND SPATIAL PROCESSING

Whereas many tDCS and tACS studies focus on modulating working memory task performance (e.g., Jaušovec et al., 2014; Martin et al., 2014), an emerging body of empirical research has demonstrated some impacts on the spatial processes underlying navigation behavior, including spatial perception and attention, mental rotation, and spatial visualization. This typology of spatial processes generally follows that of Linn and Petersen (1985). Below we report the results of a literature review examining tDCS and tACS influences on spatial processing and navigation, with papers identified via Google Scholar and PubMed, using the terms *tDCS, tACS, spatial cognition, spatial perception, spatial attention, mental rotation, spatial visualization, wayfinding* and/or *navigation*.

Spatial Attention

Spatial attention involves the dynamic and selective prioritization and sustainment of attention toward locations in space (Posner, 1980). A number of distributed brain areas have been implicated in spatial attention, most notably the posterior parietal cortex (PPC) in a primarily right-lateralized frontoparietal visuospatial network (Rafal and Posner, 1987; Corbetta et al., 1995; Constantinidis and Steinmetz, 1996, 2005; Corbetta, 1998; Thiebaut de Schotten et al., 2011). Several studies have targeted the PPC with tDCS, and assessed behavioral impacts on tasks demanding spatial attention. In one study, anodal tDCS administered to the right PPC improved change detection in individuals with lower than ceiling performance, presumably due to enhanced spatial attention toward relevant areas of the task (Tseng et al., 2012). Another study demonstrated that anodal tDCS administered to the right PPC can ameliorate some spatial attention deficits shown by patients with left visuospatial neglect (Sparing et al., 2009). Additional studies demonstrate impacts of tDCS over the PPC on spatial orienting (Bolognini et al., 2010), spatial reorienting (Roy et al., 2015), and tests of lateralized spatial attention bias (de Tommaso et al., 2014). In one tACS study, gamma frequency stimulation over V1 was not shown to modulate spatial attention (though it did alter contrast perception; Laczó et al., 2012). In another, anti-phase gamma frequency stimulation over the left temporal and parietal cortex enhanced visual working memory, suggesting an impact on spatial attention (Tseng et al., 2016). Additional regions implicated in spatial attention, including the superior temporal sulcus, frontal eye fields, anterior cingulate and thalamic nuclei, have not been directly targeted by tDCS or tACS, or have been targeted but not in a manner related to spatial attention.

Spatial Perception

Spatial perception involves perceiving and comprehending spatial information, particularly with regard to the body's orientation (Loomis and Philbeck, 2008). This includes perceiving spatial relationships among objects, and your position relative to those relationships. Several studies have demonstrated that spatial perception engages areas of the PPC, most notably the right inferior parietal lobule, the middle and inferior frontal gyri, and the superior temporal gyrus (Andersen et al., 1985; Andersen, 1987; Woldorff et al., 1999; Ellison et al., 2004; Straube and Chatterjee, 2010). Very few studies have examined tES influences on spatial perception. In one, tDCS of the PPC altered the perception of object location, with mislocalization biased in the direction contralateral to stimulated hemisphere (Wright and Krekelberg, 2014). Stimulating the right PPC also induces polarity-specific modulation of spatial information reliance during causality inferencing (Straube et al., 2011). Research using tDCS or tACS to target the middle and inferior frontal gyri, and superior temporal gyrus, has not examined influences on spatial perception tasks.

Mental Rotation

Mental rotation involves mental spatial transformations of objects around one or more axes of rotation. The seminal mental rotation task involves comparing two three-dimensional objects, mentally rotating one object to match or mismatch a reference object (Shepard and Metzler, 1971). An abundance of lesioning and functional neuroimaging studies has demonstrated the importance of the parietal cortex in mental rotation, with some studies suggesting a relatively right-lateralized mechanism (Ratcliff, 1979; Deutsch et al., 1988; Cohen et al., 1996; Tagaris et al., 1996, 1997; Richter et al., 1997; Gauthier et al., 2002; Jordan et al., 2002). Given the more general engagement of the prefrontal cortex in working memory and executive control tasks (D'Esposito et al., 1998), perhaps not surprisingly this region has been implicated in maintaining goals and monitoring and updating spatial relations during mental rotation (Cohen et al., 1996). Indeed targeting the dorsolateral prefrontal cortex with tDCS modulates performance on spatial working memory tasks in general (Alencastro et al., 2017), though it does not appear to specifically influence mental rotation performance (Oldrati et al., 2018). To date, no studies have specifically examined tDCS or tACS targeting the parietal cortex and measuring behavioral outcomes on a mental rotation task, however, three related studies are worth mentioning. One study leveraged an implanted array of electrodes over the parietal cortex, demonstrating that high intensity (7–12 mA) superior parietal stimulation dramatically and selectively impaired mental rotation ability (Zacks et al., 2003). Second, online and offline transcranial alternating current stimulation (tACS) was recently found to benefit mental rotation performance, though the electrode montage used did not specifically target parietal areas (Kasten and Herrmann, 2017).

Spatial Visualization

Spatial visualization involves complex, sequential manipulations of spatial information (Linn and Petersen, 1985; Kozhevnikov et al., 2007). It involves spatial attention and perception, and sometimes mental rotation, but extends these processes to multi-step spatial procedures (e.g., Rubik's cube, paper folding) with multiple analytic strategies that can be adopted to develop a solution. A broad network of functionally connected brain regions is implicated in spatial visualization, particularly executive control and working memory regions (e.g., dlPFC, anterior cingulate), and regions implicated in spatial perception, attention, and mental rotation (e.g., posterior and superior parietal cortices; Sack et al., 2007; Watson and Chatterjee, 2012). Very few studies have examined tDCS or tACS influences on spatial visualization. In one study, tDCS centered over the dlPFC enhanced training of a mental paper folding task; however, this pattern only emerged when tDCS was administered online (rather than offline, before the task; Oldrati et al., 2018).

tES AND NAVIGATION

Wayfinding involves deliberate navigation between waypoints in large-scale environments, and is one of the most complex and frequent tasks undertaken by humans. It is often distinguished from the motoric sequences underlying the navigation of well-learned routes, for instance from home to a workplace, in that it also involves developing and using spatial representations to support movement (Hartley et al., 2003). Successful wayfinding generally involves recognizing places, learning sequences, identifying decision points and making decisions and behavioral responses, developing associations among environmental features, transforming perspectives, and constantly relating the directly perceived environment with environmental knowledge and goal representations (Allen, 1999; Klippel, 2003; Montello, 2005; Wiener et al., 2009; Dudchenko, 2010).

Elements of spatial attention, perception, mental rotation, visualization and working memory are critical for supporting wayfinding, and people differ dramatically in their ability to find their way through complex environments (Hegarty and Waller, 2005). The diverse engagement of cognitive processes in wayfinding is reflected in the diversity of brain regions implicated in supporting these processes (Maguire et al., 1999; Burgess et al., 2002; Shelton and Gabrieli, 2002; Schinazi and Epstein, 2010), and the diversity of taxonomies devoted specifically to understanding the processes engaged during wayfinding (Siegel and White, 1975; Wiener et al., 2009; Chrastil, 2013). Only one study has examined tES influences on wayfinding (Brunyé et al., 2014). In that study, the authors targeted the right medial temporal lobe with a multielectrode tDCS montage and demonstrated no main effect of tDCS on virtual wayfinding performance. Targeting deep brain structures in medial temporal areas may not be feasible with tES; instead, researchers may find value in indirectly targeting these areas by stimulating nodes in functional neural networks.

FUNCTIONAL NETWORKS IN NAVIGATION

In the above typology of spatial processes, we focused primarily on focal brain regions underlying spatial performance, though stable functional networks have also been identified supporting several aspects of spatial processing. Byrne et al. (2007) described a dynamic neural model to characterize interactions among brain regions implicated in human navigation. The model distinguishes between an egocentric system (posterior parietal), allocentric system (medial temporal), and transformational (retrosplenial) system. Functional connectivity analyses have identified at least three functional pathways involved in communicating among these systems (Kravitz et al., 2011):

1. The *parieto-prefrontal pathway* connects lateral and ventral intraparietal, and middle and medial superior temporal lobe areas, to prefrontal regions, and is involved in spatial attention including the initiation and control of eye movements, and top-down executive control of visuospatial working memory processing (Xu and Chun, 2006).
2. The *parieto-premotor pathway* consists of two parallel projections, one connecting the ventral intraparietal and dorsal premotor cortices, and the other connecting the medial intraparietal and ventral premotor cortices, both engaged in initiating and controlling several visually-directed actions (e.g., reaching for and grasping objects) using parietal object representations (Blangero et al., 2009; Reichenbach et al., 2014).
3. Finally, a *parieto-medial temporal pathway* connects the caudal inferior parietal lobe (cIPL) and a range of areas including retrosplenial cortex (RSC) and PCC, and secondarily to the hippocampus and parahippocampus (Rushworth et al., 2006). Inferior parietal areas have been implicated in a range of navigation-relevant functions, including representing distant space in world- and object-centered frame of reference, egocentric heading direction, and egocentric distance (Brotchie et al., 1995; Crowe et al., 2005; Chafee et al., 2007; Harvey et al., 2012), suggesting importance for real-world navigation. Concordant with intermediary roles between posterior parietal and medial temporal regions, the PCC and RSC have been implicated in translating between egocentric (parietal) and allocentric (medial temporal) representations of space, and in relating optic flow to heading direction and movement toward goals (Vogt et al., 1992; Burgess, 2008; Epstein, 2008; Sherrill et al., 2015; Boccia et al., 2016; Wiener et al., 2016).

Research continues to better define the anatomical and functional links between brain regions implicated in spatial processing and navigation. One outcome of this research is affording better understandings of how tES may prove tractable for modulating brain circuits engaged in spatial processing.

LEVERAGING FUNCTIONAL CONNECTIVITY WITH tES

Few studies have examined the influence of modulating superficial tES targets on more distributed neural networks. In two such studies, tDCS of the left dlPFC altered resting-state connectivity in several functional networks, including the default mode network, frontal-parietal network, and self-referential network (Keeser et al., 2011; Peña-Gómez et al., 2012). In the spatial processing domain, two related studies administered tDCS over the parietal cortex and found altered functional connectivity between this region and the prefrontal cortices and several subcortical regions, both during a virtual navigation task (Hampstead et al., 2014) and during resting state (Krishnamurthy et al., 2015). No reliable impacts on behavior were found, however, in this research the stimulated electrode site (Pz) sits over bilateral superior parietal regions rather than a lateral inferior parietal lobule.

Continuing research may find value in specifically targeting the parieto-medial temporal and parieto-prefrontal pathways. High fidelity head models that predict current propagation can be used to maximize current density at relatively superficial cortical targets, such as the right inferior parietal lobule. For instance, using the HD Targets finite element model developed by Soterix Medical Incorporation (New York, NY, USA), **Figure 1** demonstrates predicted current density with a multielectrode array targeting the cIPL (i.e., angular gyrus). This montage uses two anodes at locations P6 (1.0 mA) and P4 (1.0 mA), and three cathodes at locations CP2, CP4, CP6, and PO4 (0.5 mA each). With 2.0 mA total current,

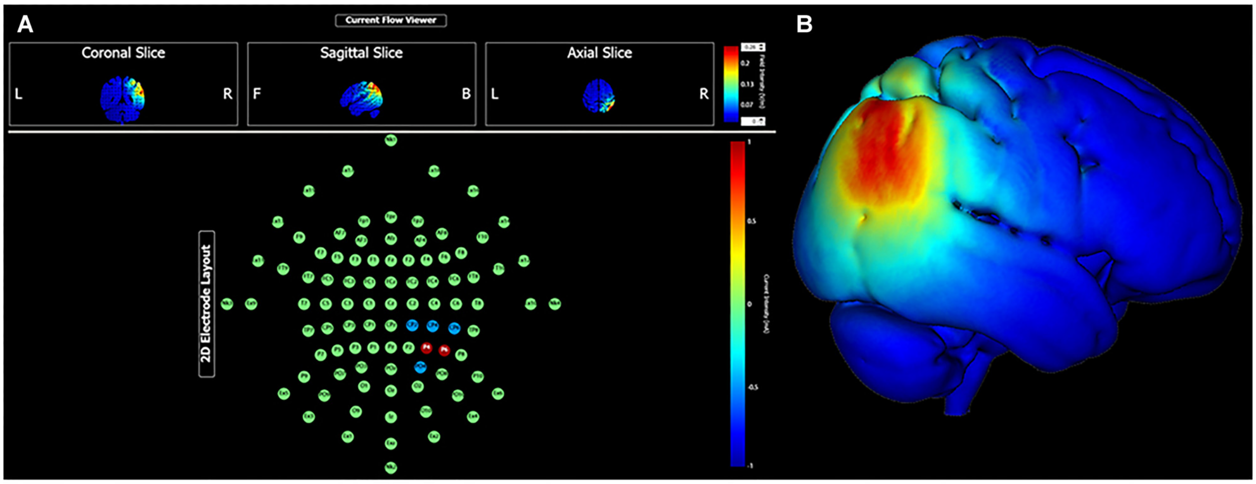

FIGURE 1 | Transcranial direct current stimulation (tDCS) targeting the right caudal inferior parietal lobule (angular gyrus) with 2.0 mA current intensity. Panel **(A)** shows electrode montage and current flow in coronal, sagittal and axial views. Panel **(B)** shows electrical field intensity overlaid onto a standard MNI head model (MNI 152).

maximum electrical field intensity at target is approximately 0.22 V/m. Given functional connectivity between the cIPL and the RSC, PCC, hippocampus and parahippocampus, targeted neuromodulation of the relatively lateral cIPL region might be expected to modulate several aspects of spatial processing with implications for large-scale navigation performance, for instance egocentric and allocentric perspective switching and integration, and maintaining orientation relative to goal locations.

Behavioral outcomes related to parieto-medial temporal pathway might be dissociated with outcomes of targeting the parieto-prefrontal pathway. Specifically, targeting lateral and ventral intraparietal areas might be expected to impact visuospatial spatial working memory performance, whereas targeting the cIPL may not. These types of dissociations between stimulation locations, stimulation conditions (e.g., tDCS, tACS), and behavioral outcomes can help elucidate behavioral influences of each pathway, and reveal methods for altering spatial performance. Furthermore, as research reveals the oscillatory dynamics of the parieto-medial temporal pathway, frequency-specific tACS might also prove valuable for modulating network resonance and behavioral outcomes (Ali et al., 2013; Marshall and Binder, 2013).

CONCLUSION

People differ dramatically in spatial abilities (Hegarty and Waller, 2005), and identifying reliable methods for enhancing or accelerating spatial skills education and training may prove valuable in both healthy and clinical populations. For instance, body- and world-centered spatial visualization skills are fundamental to many work-related domains, especially science, technology, engineering and mathematics (STEM) disciplines (Sorby, 1999; Titus and Horsman, 2009; Taylor and Hutton, 2013; Uttal et al., 2013; Burte et al., 2017). Future research might find value in using tES to selectively upregulate networks engaged in successful spatial thinking. This research will be enabled by at least three specific research areas. First, better defining functional connectivity between cortical and subcortical brain regions during spatial processing and navigation, and how these networks might vary in structure and function across individuals. Second, identifying how tES modulates cortical and network activity, and how these dynamics might vary over time and across individuals (Krause et al., 2013). Third, advances in finite element modeling that include customized (i.e., individualized) cortical targets will afford specificity and reliability of stimulation protocols (Radman et al., 2009), and possibly enhance real-world behavioral outcomes.

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TTB conceived the review and prepared the manuscript.

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