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Disambiguating the Role of the Retrosplenial Complex in Human Navigation

by

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Abstract

The role of the human retrosplenial cortex in spatial orientation and navigation has been obscured by a long history of ambiguous localization, beginning as early as Brodmann's original depiction which intentionally overrepresented it's extent. While some modern atlases of the brain exclude this region, many include a surprisingly generous delineation; this has resulted in a very large area of the medial parietal cortex implicitly viewed as being equipotentially involved in spatial orientation and navigation. In this thesis, I provide novel evidence of a more precise paradigm by which we can understand the role of the 'retrosplenial cortex', i.e. the posterior cingulate, in spatial orientation and navigation. First, from fMRI activity evoked in a novel spatial task, but subsequently from a meta-analysis of the literature more generally, we have identified that ventral portions of the posterior cingulate are relatively more engaged in *encoding* spatial information, whereas dorsal portions are more involved in *recalling* and computing spatial information or representations. Not simply descriptive, this delineation proved valuable in characterizing the neural correlates of a lifelong developmental condition in which individuals get lost on a daily basis in very familiar surroundings, a condition known as Developmental Topographical Disorientation (DTD). In fact, we identified that the dorsal posterior cingulate displays far greater differences then the ventral posterior cingulate in functional connectivity between individuals with DTD and healthy controls; these findings would not have been uncovered with traditional delineations of the retrosplenial cortex. Other studies will undoubtedly benefit from appreciating these functional subregions when analyzing or interpreting activity within the posterior cingulate evoked by spatial orientation tasks. A clear understanding of the neural correlates of spatial orientation and navigation in humans will

benefit greatly from future research validating this posterior cingulate delineation, as well as extending increasingly meticulous attention to the location of activity evoked in the posterior cingulate and other brain regions.

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List of Symbols, Abbreviations and Nomenclature

Abbreviation	Definition
AICHA	Atlas of Intrinsic Connectivity of Homotopic Areas
ARC	Autocalibrating Reconstruction for Cartesian imaging
ASSET	Array coil Spatial Sensitivity Encoding
BOLD	Blood-Oxygen Level Dependent
DTD	Developmental Topographical Disorientation
EPI	Echo Planar Imaging
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GPS	Global Positioning System
M	Mean
MKDA	Multilevel Kernel Density Analysis
MNI	Montreal Neurological Institute
MRI	Magnetic Resonance Imaging
NIFTI	The Neuroimaging Informatics Technology Initiative (file format)
RC	Retrosplenial Complex
ROI	Region of Interest
SD	Standard Deviation
SPGR	Spoiled Gradient Recalled
TE	Echo Time
TR	Repetition Time

Chapter One: The Brain Regions Supporting Spatial Orientation

In this chapter, I set out to describe some of the background knowledge on the cognitive neuroscience of spatial orientation and navigation. While my work largely focuses on a particular brain region (i.e. the retrosplenial cortex and posterior cingulate) and a particular functional paradigm (i.e. encoding vs. recall), the context and history in which these particular research questions were generated will help motivate and interpret my research. To that end, I will introduce my work by first providing some natural and technological examples of navigation and contrast their apparent simplicity and complexity. This will be followed by an introduction to the concept of the cognitive map, and the brain structure that is thought to be responsible for housing the 'map in the head'. Then we will venture beyond the map, and discuss the other mechanisms, and brain regions, which link the map to actual navigation and orientation. Once the network of brain regions supporting navigation is described, I will note some of the nuances and complexities of the roles these brain regions play, particularly accenting the relatively coarse understanding of the location, extent, and function of the retrosplenial cortex and posterior cingulate in human navigation and orientation.

The simplicity and complexity of navigation

In the modern day and age, we can benefit greatly from technological advances that offload some of the more cognitively demanding day-to-day tasks. Navigating by use of a paper map is a rare sight in 2018, with many people opting instead to utilize turn-by-turn navigational systems. To navigate to any location, such as the airport on your way to depart for a holiday, you can simply tap the maps application on your smartphone, and type 'airport' into the search bar.

Your phone likely already knows where you are, accurate to a few meters, thanks to the signals from orbiting GPS satellites, nearby cellular towers, and Wi-Fi networks. Completing it's search, and correctly assuming the local international airport, your phone will download the map between your location and the airport, and conclude with a plot of a suggested route, taking into account any traffic jams or construction. This entire process takes but a moment, and obscures the decades of data collection and countless technologies supporting the beguilingly simple query, "how do I get to the airport?".

While you could rely on your smartphone, if you are sufficiently familiar with the local city, you will likely be able to mentally summon a route to the airport in about the same amount of time it would have taken to use your smartphone. This is an impressive feat, considering that your smartphone relied on space-age technology and a satellite system that boasted a $US 1.18B budget for the 2018 fiscal year (National Coordination Office for Space-Based Positioning, Navigation, and Timing, 2018). To the average individual, the cognitive mechanisms supporting this ability are likely as opaque as the myriad of technologies which support the same capacity in your phone. Superficially, the complexity of the technologies required to 'navigate' would suggest that this system is inherently complex and demanding, but this is not necessarily the case.

A foraging desert ant, *Cataglyphis fortis*, leaves it's nest and begins searching the surrounding salt flat, primarily for other dead arthropods that have succumbed to the desert heat. These meandering searches in a relatively featureless salt flat can extend hundreds of meters before the ant successfully locates any food. *Cataglyphis*, with it's tiny brain weighing approximately a tenth of a milligram, can generate and follow a relatively direct homeward path

after locating a food source, even navigating about new obstructions or barriers without getting lost (Wehner, 2003). The process by which *Cataglyphis fortis* is believed to navigate it's environment is called Path Integration. Upon leaving their nest, the *Cataglyphis* ant uses the position of the sun to track it's heading, and appears to track distance based on the number of steps it takes (Wittlinger, Wehner, & Wolf, 2007). These two pieces of information allow the ant to continuously update the heading and distance to it's nest, and permits the effective homing behaviour observed after locating a food source. Similar path integration systems are used in many other animals, although the sources of heading information and distance estimation are not always the same as that seen in *Cataglyphis*. For instance, monarch butterflies, who can make an impressive 4,000 km migration from Canada and the United states to Mexico during the winter, appear to both make time-compensated use of the position of the sun (Perez, Taylor, & Jander, 1997; Stalleicken et al., 2005), as well as their magnetosensitive antennae to ensure they are heading in the correct direction (Guerra, Gegear, & Reppert, 2014). The use of magnetic stimuli for orientation is also seen in the blind mole rat (Kimchi, Etienne, & Terkel, 2004), pigeons (Walcott, 1996), and perhaps even dogs are sensitive to this type of stimulus (Hart et al., 2013). Distance estimations are similarly not restricted to the step-counting seen in *Cataglyphis*; the bee *Megalopta,* which forages by air, can compute distance based on optic flow, *i.e.* the rate at which visual stimuli moves across the retina (Collett & Collett, 2017). Rodents can path integrate by combining self-motion (i.e. vestibular) cues with a motor efferent copy (i.e. accounting for self-generated body movements) to generate relatively robust distance information (Mittelstaedt & Mittelstaedt, 1980).

Path integration is an impressively elegant system that can be used to perform relatively complex navigation tasks. However, navigating by path integration is not perfect. Noise and measurement errors present in any sensory modality will reduce the accuracy of the distance and heading tracking that is required for effective path integration. Suppose *Cataglyphis* measures distance primarily by counting steps (which it appears to do; Wittlinger, Wehner, & Wolf, 2006), and embarks on an outbound path from it's nest, meandering down a slope before locating food. If, like humans, *Cataglyphis* takes slightly shorter steps while walking uphill as opposed to walking downhill on on flat land, it's return path may include the appropriate number of steps, but not enough actual distance. This type of error can also interact with any heading errors to produce relatively large actual errors. An ant making a 100 m straight-line return path, but with a 1 degree heading error will end up approximately 1.75 m from it's nest. A potentially fatal error for an animal in a hostile environment, especially considering a *Cataglyphis* ant is only 1 cm long. Correcting for body length, the equivalent error for an average Canadian (Shields, Gorber, & Tremblay, 2008) would approach 300 m. Potential errors of this severity necessitate some additional mechanism to correct these errors. Indeed, *Cataglyphis* can make use of both odour cues and as well as visual landmarks to help reorient themselves, incrementally correcting errors or at least permitting a greater degree of error before becoming 'lost' (Steck, Hansson, & Knaden, 2009).

Path integration is undoubtedly a viable solution for navigation in *Cataglyphis,* but even ignoring the vastly different neural and technological architecture, it is quite apparent that mechanisms supporting navigation in *Cataglyphis* are different from those employed when you request directions from your smartphone. Yet, your smartphone is equipped with the necessary

hardware to perform path integration, it has both a magnetometer and an accelerometer, which provide data that can be used to track heading and distance, but the smartphone does not primarily use path integration to perform navigation. It seems unlikely that either of these navigational systems are the same as that employed when you yourself navigate, perhaps simply because the quantity and quality of the directly navigationally-relevant information available to you lies somewhere in between that of *Cataglyphis* and the system employed by your smartphone. Rodents, another order of animals, like the ant, in which a great deal of spatial orientation and navigation research has been performed, are a more proximal model species that may help us understand what was actually happening when you navigate without any external aids.

The rat, the map, and the seahorse

In our previous examples of navigation, the largest difference between the abridged examples of *Cataglyphis* and your smartphone is the presence of a map in the conventional sense. *Cataglyphis* may only need to represent a heading and distance to home, whereas your smartphone can compute countless routes between any pair of locations. The storage of some sort of representation or map of the environment is what affords these flexible and complex navigational behaviours. In 1948 Edward Tolman argued that such a mental representation, or cognitive map, of the environment, is indeed generated in the brain of rats, as well as humans, and that this representation is what subserves navigation (Tolman, 1948). Tolman contrasted this view with another prevalent paradigm at the time, which viewed navigational behaviours as an extension of stimulus-response pairings. The stimulus-response model requires no real spatial

representation of the environment, and assumes that an organism would begin to associate the correct navigational behaviour (i.e. making the correct turn in a maze) with a positive stimulus (e.g. escaping the maze or finding food), and through this reinforcement the organism is able to navigate. Tolman noted that reports from as early as 1929 detailed cases of rats taking clever shortcuts in mazes, often climbing out of their starting box, running across the top of the maze, directly to the position of the food reward, and dropping down to eat. The stimulus-response model can not cleanly explain this novel shortcutting behaviour, and Tolman hypothesized that these rodents had generated a spatial map that includes more than just the particular path (or the behaviours required to execute that path) in which the rat had been trained. Tolman attempted to measure this capacity experimentally by assessing the behaviour of rats in a radial arm maze. This type of task has rats first placed into a simple maze (Figure 1.1A), and has them learn the location of a food source over successive trials. After appearing to have learned the location of the food reward, rats are placed into an alternate maze configuration (Figure 1.1B) in which the learned path is blocked, but new arms project radially from the centre of the maze.

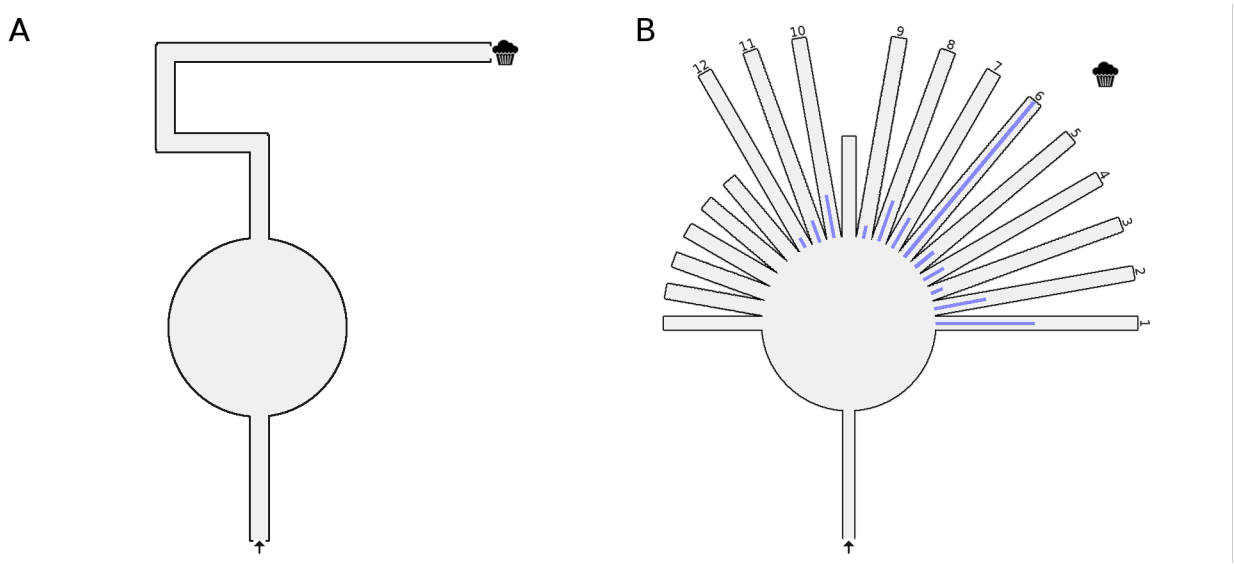

Figure 1.1. The radial arm maze as reported in Tolman's 1948 publication. Panel A depicts the configuration in which rodents are trained in, entering the maze at the arrow near the bottom, and reaching the food goal located at the top right. After twelve training sessions across four days, rodents would be placed into the environment depicted in Figure 1.1B, with the learned path blocked, and instead a series of radial paths available to the rodent. The blue bars inside each arm indicate the relative frequency of rats choosing to traverse to the end of the arm after identifying that the previously learned path was blocked. Thirty-five percent of rodents initially selected the 6th arm. It is worth noting that there was a light stimulus placed proximal to the food location in both maze configurations, significantly weakening the conclusions drawn by Tolman.

After learning that the learned path is now blocked, rodents were most likely to travel down the hallway which terminated effectively four inches to the left of the position that the food source existed in the learned maze configuration. Tolman interpreted these results as indicating that the rat had generated a mental representation of the location of the food source during training, not simply the behaviour required to get there, and subsequently recalled this 'cognitive

map' during the retrieval phase of the task to guide them to the food location. This 'cognitive map' hypothesis received more support after John O'Keefe and his student Jonathan Dostrovsky discovered neurons in the rat hippocampus which individually became active only when the rodent was positioned in a particular position and facing a certain direction in their testing environment, the first evidence of a class of neuron encoding an environmental-scale spatial property (O'Keefe & Dostrovsky, 1971)[2]. Importantly, these 'place cells' provided a neural substantiation for the cognitive map, and were strong evidence suggesting that the 'map in the head' metaphor proposed by Tolman may be a reality.

In 1978 O'Keefe and Nadel outlined the evidence and provided a more comprehensive case for the hippocampus as a critical structure providing a unitary, euclidean, three-dimensional mental representation of space (O'Keefe & Nadel, 1978). Not just restricted to rodents, many parallels can be seen in human research as well, particularly the discovery of place cells in the human hippocampus (Ekstrom et al., 2003), in addition to the well-known spatial orientation deficits following hippocampal lesions in both rodents (R. G. M. Morris, Garrud, Rawlins, & O'Keefe, 1982; O'Keefe & Nadel, 1978, p. 286) and humans (Kessels, de Haan, Kappelle, & Postma, 2001). While facets of this paradigm have met with some resistance or more updated theories (Bennett, 1996; Ekstrom, Arnold, & Iaria, 2014; Meilinger, 2008; Tversky, 1992), the hippocampus as the prototypical brain region associated with a 'cognitive map' is a widely-adopted perspective among behavioural and cognitive neuroscientists studying spatial orientation and navigation (Arnold et al., 2013; Burgess, 2014; Epstein, Patai, Julian, & Spiers, 2017; McNaughton, Battaglia, Jensen, Moser, & Moser, 2006).

2 The presence of place cells have been reported in the hippocampus as well as the nearby entorhinal cortex (Quirk, Muller, Kubie, & Ranck, 1992) and subiculum (Sharp & Green, 1994).

More than a map: scene processing in the occipital, temporal, and parietal lobes

Let us return to our example of using your smartphone to navigate to the airport. We've identified one critical component, the presence of some sort of mental representation, or map, of the environment, supported by the hippocampus in humans and rodents. Yet, a map of an environment with no way to know where *you* are on the map is not very useful for navigation. Many maps posted in parks or on campuses will include a 'you are here' marker, yet this can still be slightly confusing if you do not also know the direction you are facing, i.e. your heading. These two pieces of information, your position and heading, along with some form of representation of the environment, are the critical pieces of information needed to effectively orient, and the brain regions that support these processes are undoubtedly part of the spatial orientation network.

First, let us focus on a foundational process required to localize oneself in the environment. Whether navigating by use of a paper map or a mental map, our capacity to encode what we can see around us, the visual scene, can provide strong positional as well as heading information. For instance, if you were shown a picture of your front door, this image alone would likely evoke a strong sense of that location in your mind. In humans, the regions of the brain that are particularly sensitive to processing scenes are commonly detected using functional magnetic resonance imaging (fMRI) by contrasting the Blood Oxygen Level Dependent (BOLD) activity measured while participants view images of scenes from that measured while viewing solely objects or faces without any background context (Epstein, 2008; Epstein & Kanwisher, 1998; Poldrack, 2007). These types of analyses regularly implicate three brain areas that appear to be particularly sensitive to scenes: the occipital place area, the parahippocampal place area, and the

retrosplenial complex (Epstein, 2008; Epstein & Kanwisher, 1998; Kamps, Julian, Kubilius, Kanwisher, & Dilks, 2016). While the scene-selectivity of these regions is a common property between them, they perform significantly different functions.

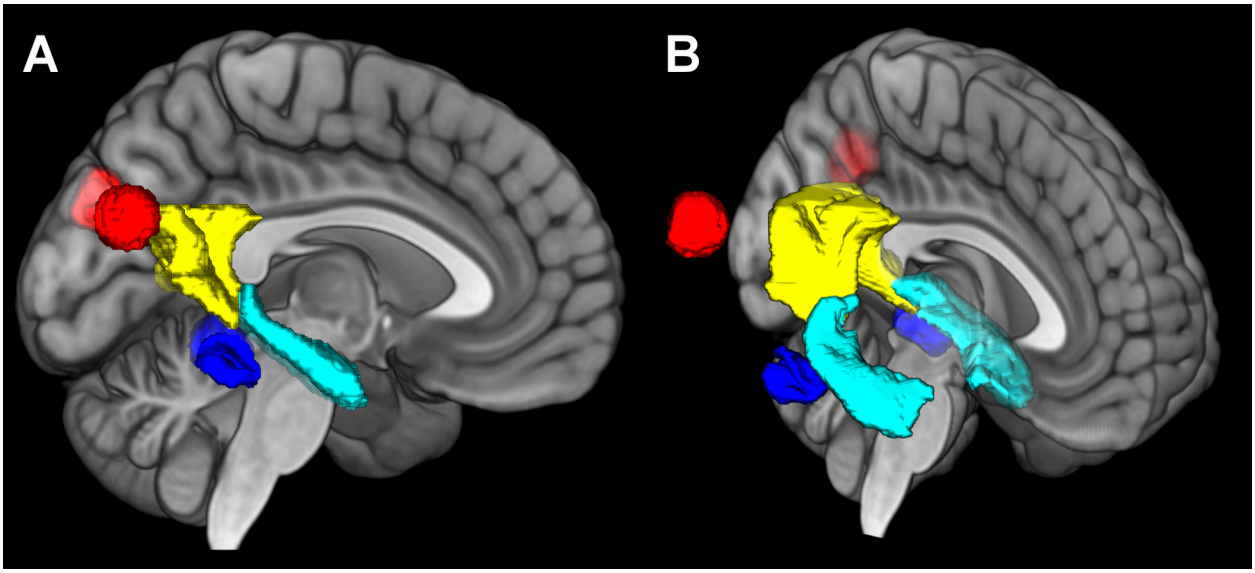

Figure 1.2. Scene-sensitive occipital place area (red), retrosplenial complex (yellow), and parahippocampal place area (blue), depicted alongside the hippocampus (teal) from a right midline (A) and oblique (B) viewpoints. Locations for the parahippocampal and occipital place areas were generated from peaks reported in (Burles, Slone, & Iaria, 2017; Park & Chun, 2009, respectively).

The occipital place area

The most posterior of the three scene-sensitive regions, the occipital place area is commonly located approximately two centimetres ventral to the most dorsal portion of the parietal-occipital fissure, deep in the transverse occipital sulcus (Grill-Spector, 2003). Kamps

and colleagues (2016) elegantly delineated the function of this region by recording BOLD activity while participants viewed images of intact scenes, fragmented scenes, and varying number of furniture pieces depicted without a background. The occipital place area displayed equivalent levels of activity irrespective if the depicted scene was intact or fragmented. Fragmented scenes included all the same elements of intact scenes, but they were split into multiple parts, and rearranged with gaps separating the parts (See Figure 1.2). This finding would indicate that the occipital place area is not necessarily processing the entire scene, as the fragmented scene is incoherent, but rather is sensitive to features present in any given scene. In the same study, Kamps and colleagues provided further support for this perspective, reporting that the occipital place area displayed greater activity as participants viewed an increasing number of pieces of furniture, without any scene context or background, reinforcing the sensitivity of this regions to scene-forming elements, irrespective if they constitute an interpretable or natural scene. However, the occipital place area is not solely sensitive to the presence scene elements, but also appears to represent navigational affordances as well, with activity relating to the number and direction of traversible paths present in a scene (Bonner & Epstein, 2017). While the occipital place area is the least well studied of the human scene-selective cortex (Kamps et al., 2016), the available literature consistently points to a low-level, fundamental, and critical role in scene processing, involved in processing basic scene features, such as elements and affordances, and providing this information to other scene-processing regions (Dilks, Julian, Paunov, & Kanwisher, 2013; Patai & Spiers, 2017).

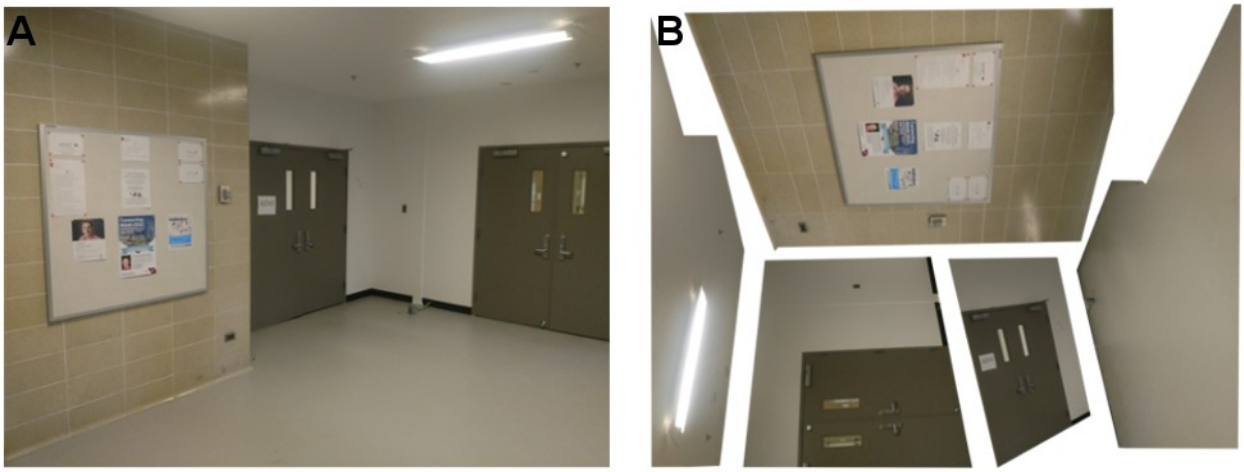

Figure 1.3. An example of an intact (A) or fragmented (B) scene, of the style used by Kamps and colleagues as well as Epstein and Kanwisher (Epstein & Kanwisher, 1998; Kamps et al., 2016). While the same elements are present in both panels, only panel A depicts a coherent scene. The occipital place area produces equivalent responses to intact and fractured scenes, whereas the parahippocampal place area and retrosplenial complex are more strongly activated by intact scenes (Kamps et al., 2016).

The parahippocampal place area

The parahippocampal place area, commonly located at the boundary between the posterior parahippocampal and anterior lingual cortex, appears to preferentially activate in response to viewing images of scenes and buildings (Aguirre, Zarahn, & D'Esposito, 1998; Epstein & Kanwisher, 1998). However, unlike the occipital place area, the parahippocampal place area appears to be processing scenes holistically; if presented with fragmented scenes, as described previously, the parahippocampal place area displays significantly less activity than if presented with intact scenes (Kamps et al., 2016). Furthermore, this region does not appear to be sensitive to the number of scene-forming elements, displaying equivalent activity to a furnished

room compared to the same room unfurnished, in stark contrast to the occipital place area which we would expect to be indexing furniture as elements of the scene (Epstein & Kanwisher, 1998; Kamps et al., 2016). Consistently, individuals with lesions to the parahippocampal and lingual cortex, often the result of a posterior cerebral artery stroke, present with notable impairments in their capacity to recognize familiar scenes, such as their bedroom, despite retaining the capacity to describe objects or elements within that scene (Aguirre & D'Esposito, 1999; Epstein, 2008). This dichotomy is exemplified in patient A.H., who presented with a notable and persistent inability to recognize places, such as his own bedroom, while retaining the capacity to draw maps of locations that were familiar to him before his illness, as well as recognize and discriminate between objects (Pallis, 1955). However, A.H. also presented with relatively profound prosopagnosia, the inability to recognize faces. Prosopagnosia often results from damage to the fusiform face area (Barton, Press, Keenan, & O'connor, 2002; Damasio, Damasio, & Van Hoesen, 1982; Kanwisher, McDermott, & Chun, 1997), which like the parahippocampal place area, is associated with *holistically* processing visual stimuli. A.H. struggled with recognizing faces of his family members, although he was entirely capable of describing their facial features, both from memory and while viewing but not recognizing them. He described similar strategies for trying to identify places and faces, both involving careful examination of singular features, e.g. the eyes, face, or hair, with the goal of detecting a distinguishing feature that uniquely identified the person or place. Due to the proximity and similar function of the parahippocampal place and fusiform face areas, disorders of face and place processing can present comorbidly (Aguirre & D'Esposito, 1999; Bate, Adams, Bennetts, & Line, 2017; Corrow et al., 2016). Another patient, G.N., with significant damage to the right posterior-inferior portion

of the temporal lobe and extending into the occipital lobe, encompassing the location of the parahippocampal place area, was unable to navigate in familiar environments (Mendez & Cherrier, 2003). Like A.H., he was still able to provide verbal directions along familiar routes, such as the route from the hospital to his house, but noted that "familiar routes now look unfamiliar". While largely disoriented in unremarkable scenes such as hallways or bathrooms, if G.N. identified a distinguishing object or major landmark (presumably supported by the occipital place area), he was often able to reorient himself and maintain a sense of direction. These cases support the view that the parahippocampal place area provides a gestalt (Goldstein & Gelb, 1918) perception of scenes as a whole, without necessarily representing distinct scene elements or deriving a sense of direction from them.

The retrosplenial complex

Like the occipital and parahippocampal place areas, the retrosplenial complex is often identified as cortex particularly sensitive to scenes (Epstein, 2008). This region is commonly located in the posterior cingulate, along the lateral portions of the anterior bank of the parietal-occipital fissure, approximately at and extending dorsally from the point at which the parietal-occipital fissure joins with the calcarine sulcus, largely avoiding the retrosplenial cortex proper. Like the parahippocampal place area, the retrosplenial complex appears sensitive to global properties of scenes, in that it displays greater sensitivity to intact as opposed to fractured rooms, and is relatively insensitive to the quantity of scene-forming elements (Kamps et al., 2016). However, the retrosplenial complex appears to be more sensitive to subjective scene properties, such as scene familiarity, to which the parahippocampal place area does not discriminate,

suggesting this region is involved in memory-related processes beyond characterizing basic stimuli properties (Epstein, 2008). Lesions to the retrosplenial region are associated most predominantly with a form of 'heading disorientation' in which individuals retain the ability to recognize scenes, but are unable to derive clear directional information from them (Aguirre & D'Esposito, 1999). Three patients with relatively focal right retrosplenial and posterior cingulate lesions, described by Takahasi and colleagues, were still able to accurately perceive landscapes and buildings, as well as encode and remember the positions of objects, such as furniture, that were visible within a scene, while unable to remember the locations of any objects or the direction to places that were outside of their current or remembered viewpoint (Takahashi, Kawamura, Shiota, Kasahata, & Hirayama, 1997). This lack of 'sense of direction' is supported by research in rodents, which has identified cells in the retrosplenial cortex, among other regions, that fire selectively when the animal is facing a particular direction, dubbed 'head direction cells' (L. L. Chen, Lin, Green, Barnes, & McNaughton, 1994; Cho & Sharp, 2001; Taube, 1998, 2007). These findings have led to the perspective that the retrosplenial complex links or translates between the egocentric current viewpoint (hence it's scene-sensitivity) and the allocentric 'cognitive map' (Alexander & Nitz, 2015; Burgess, Becker, King, & O'Keefe, 2001; Byrne, Becker, & Burgess, 2007; Sulpizio, Committeri, Lambrey, Berthoz, & Galati, 2013; Vann & Aggleton, 2004).

Functional specificity within the spatial orientation network

The network of the occipital and parahippocampal place areas, the retrosplenial complex, and hippocampus provides a distilled and simple model of the core brain structures known to be

critically involved in spatial orientation. These roles – the occipital place area processing scene elements, the parahippocampal place are processing the entire scene, the hippocampus responsible for the 'cognitive map', and the retrosplenial complex linking the present scene to the 'cognitive map' – are somewhat abstracted, and because of this, the role of these brain regions is likely more nuanced and heterogeneous than would appear at first glance.

The hippocampus, in particular, has been the target of a long history of research seeking to identify functionally discernible subregions within this structure (Poppenk, Evensmoen, Moscovitch, & Nadel, 2013). In the average adult human, the hippocampus occupies approximately four cubic centimetres of brain tissue in each hemisphere (Chaddock et al., 2010; Erickson et al., 2009; Gur, Gunning-Dixon, Bilker, & Gur, 2002; Lövdén et al., 2012; Schuff et al., 1999), and the long axis (primarily the anterior – posterior axis in humans and the equivalent ventral – dorsal axis in rodents) spans approximately 3.5 centimetres. In the rodent, the hypothesis that the hippocampus performs somewhat different functions along it's long axis has existed for at least fifty years (Nadel, 1968). Lynn Nadel compared the behaviour of rats with either dorsal or ventral bilateral hippocampal lesions across a variety of learning tasks, and noted vast differences between these two groups. Animals with ventral hippocampus lesions displayed altered fear extinction and habituation, whereas animals with dorsal hippocampus lesions displayed altered responses to motivating stimuli (Nadel, 1968). Nadel concluded that "it would seem necessary to consider the dorsal and ventral areas as functionally separate entities, and to discuss them in that way" (Nadel, 1968, p. 899); unfortunately, this perspective was not strongly maintained in her later work on spatial orientation and navigation (O'Keefe & Nadel, 1978). In humans, multiple paradigms have been proposed to explain observed differences in anterior and

posterior hippocampal functioning (for a review, see Poppenk et al., 2013). These include views of the anterior hippocampus relatively more involved in emotion and motivation (Fanselow & Dong, 2010; Murty, Ritchey, Adcock, & LaBar, 2010) and the posterior hippocampus more involved in spatial memory (Hirshhorn, Grady, Rosenbaum, Winocur, & Moscovitch, 2012; Ryan, Lin, Ketcham, & Nadel, 2010); the anterior hippocampus more involved in coarse or gist representations (Gutchess & Schacter, 2012), with the posterior hippocampus providing more fine and detailed representations (Robin & Moscovitch, 2017), and the anterior hippocampus specialized for encoding memories, with the posterior hippocampus specialized for recalling memories (H. Kim, 2015; Lepage, Habib, & Tulving, 1998).

A particularly relevant example can be drawn from Maguire and colleagues' work with London taxi drivers (Woollett & Maguire, 2012). A typical London taxi driver trainee will spend 3 to 4 years learning the irregular layout of all streets and points of interest with a 6-mile radius of Charing Cross train station, a total area approaching 300 square kilometers. To become fully licensed, the trainee must then pass a written exam as well as a series of oral examinations in which you must identify the shortest route between two landmarks (Transport for London, 2018; Woollett & Maguire, 2012). This rigorous exam format demands that trainees become expert navigators, able to recall a tremendous amount of spatial information. Interestingly, these taxi drivers generally have larger posterior hippocampus volumes as compared to controls, and this increase in volume is associated with the number of years of taxi driving experience (Maguire et al., 2000; Maguire, Woollett, & Spiers, 2006); presumably his change is representative of their expansive cognitive map of London. However, the opposite relationship was also detected with the volume of the anterior hippocampus, with taxi drivers having lower anterior hippocampus

volumes as compared to controls, and lower volumes associated with more years of experience as a taxi driver. This somewhat contradictory finding appears incongruent with the perspective that the hippocampus as a whole is equipotentially responsible for a cognitive map of the environment. Subsequent studies in this group elucidated that London taxi drivers take significantly longer to encode and memorize the locations of objects in a complex table-top array, compared to controls, and report fewer of these object-position associates after a delay (Woollett & Maguire, 2009, 2012). While not necessarily representative of a clear-cut encoding-recall dichotomy along the anterior-posterior hippocampus (Schacter & Wagner, 1999; Woollett & Maguire, 2010), these results exemplify the functional heterogeneity of the hippocampus along it's long axis and support Nadel's (1968) assertion that it should not be treated as a single homogeneous area.

Although not sharing as extensive a history as the hippocampus, the parahippocampal place area also appears to have a similar anterior-posterior functional specialization. Aguirre and D'Esposito's (Aguirre & D'Esposito, 1999) taxonomy of acquired topographical disorientation differentiated between lesions to the parahippocampus proper and lesions to the lingual gyrus; noting the former as resulting in an inability to generate new representations of environmental information, and the latter as producing an inability to recognize scenes, as described previously[3]. This is particularly relevant considering that the functionally-defined parahippocampal place area often straddles these anatomically defined-regions. Baldassano and colleagues functionally localized scene-selective parahippocampal place area, and detected

3 The symptoms of these groups overlap significantly, as individuals with lingual gyrus lesions also display impaired anterograde memory. Aguirre and D'Esposito noted that lingual and parahippocampal lesions may not constitute distinct forms of topographical disorientation, and suggested they may belong to a common system.

significant differences in the patterns of functional connectivity between it's anterior and posterior portions (Baldassano, Beck, & Fei-Fei, 2013). Posterior portions were part of a lower-level visual network, strongly connected to occipital visual cortex and more sensitive to objects, and anterior portions connected more strongly to the retrosplenial complex, as well as prefrontal and temporal cortex. These connectivity patterns are consistent with Aguirre and D'Esposito's conceptualization of the lingual and parahippocampal cortex performing slightly different processes in a common system (Aguirre & D'Esposito, 1999).

In contrast to the wealth of evidence for functional specialization in the hippocampus and parahippocampal place area, there are relatively few proposals of functional heterogeneities within the retrosplenial complex and occipital place area (Baldassano, Esteva, Fei-Fei, & Beck, 2016; Silson, Steel, & Baker, 2016). This is somewhat understandable for the occipital place area, as it is relatively poorly studied, but somewhat surprising considering the retrosplenial complex is one of the consistently implicated brain regions in a wide variety of spatial orientation and navigation tasks (Epstein, 2008; Maguire, 2001; Vann, Aggleton, & Maguire, 2009). This lack of functional specificity is further exacerbated by the fact that the retrosplenial complex occupies a poorly-defined and large volume of cortex; approximately twice as voluminous as the hippocampus, which clearly displays some form of functional specialization. These simple characteristics alone would suggest that this region, like the hippocampus, could be more appropriately conceptualized as a collection of subregions performing different but complementary roles.

Finding a functional specialization in the retrosplenial complex

In this dissertation, I present a series of experiments designed to identify the presence of a functional specialization within the retrosplenial complex. Chapter Two details the first piece of evidence we uncovered for a functional specialization along the dorsal-ventral axis of the retrosplenial complex. In that experiment, we identified dorsal portions were relatively more activated when participants were required to recall spatial information, whereas ventral portions were relatively more activated when encoding spatial information (Burles et al., 2017). In Chapter Three, we then explored beyond the particular task we used to identify these regions, and surveyed the literature more generally using a meta-analysis (Burles, Umiltá, McFarlane, Potocki, & Iaria, 2018). This analysis produced extremely similar results as those in Chapter Two, strongly reinforcing the conclusion that the ventral–dorsal encoding–recall specialization of the posterior cingulate generally valid in the spatial orientation literature. The particular subregions we identified, as well as the vast majority of activations reported in the spatial orientation literature, largely avoided the anatomically-defined retrosplenial cortex (despite commonly being labelled so), and we subsequently refer to these regions as located within the posterior cingulate.

In Chapter Four, I then made use of our novel subregion delineation to explore the functional connectivity patterns in a recently-identified developmental disorder, i.e. Developmental Topographical Disorientation (DTD). DTD is characterized by symptoms similar to those seen in cases of retrosplenial and posterior cingulate lesions (J. G. Kim, Aminoff, Kastner, & Behrmann, 2015), yet these individuals have no gross anatomical differences (e.g. lesions or malformations) that are associated with their spatial orientation difficulties (Iaria &

Barton, 2010; Iaria, Bogod, Fox, & Barton, 2009). In this analysis, the presently proposed posterior cingulate subregion delineation revealed widespread functional connectivity differences (particularly in our dorsal posterior cingulate subregion) that would not have been revealed with more traditional 'retrosplenial' localization techniques. Finally, in Chapter Five, I discuss some of the implications of this work, particularly highlighting the benefits and shortcomings of the use of functional localizers as well as the general difficulties with generating and using brain atlases.

Chapter Two: Dorso-Medial And Ventro-Lateral Functional Specialization Of The Human Retrosplenial Complex In Spatial Updating And Orienting

This chapter was adapted with permission from the following publication:
Burles, F., Slone, E., & Iaria, G. (2017). Dorso-medial and ventro-lateral functional specialization of the human retrosplenial complex in spatial updating and orienting. *Brain Structure and Function*, *222*(3), 1481-1493.

Abstract

The retrosplenial complex is a region within the posterior cingulate cortex implicated in spatial navigation. Here, we investigated the functional specialization of this large and anatomically heterogeneous region using fMRI and resting-state functional connectivity combined with a spatial task with distinct phases of spatial 'updating' (i.e., integrating and maintaining object locations in memory during spatial displacement) and 'orienting' (i.e., recalling unseen locations from current position in space). Both spatial 'updating' and 'orienting' produced bilateral activity in the retrosplenial complex, among other areas. However, spatial 'updating' produced slightly greater activity in ventro-lateral portions, of the retrosplenial complex, whereas spatial 'orienting' produced greater activity in a more dorsal and medial portion of it (both regions localized along the parieto-occipital fissure). At rest, both ventro-lateral and dorso-medial subregions of the retrosplenial complex were functionally connected to the hippocampus and parahippocampus, regions both involved in spatial orientation and navigation. However, the ventro-lateral subregion of the retrosplenial complex displayed more positive functional

connectivity with ventral occipital and temporal object recognition regions, whereas the dorso-medial subregion activity was more correlated to dorsal activity and frontal activity, as well as negatively correlated with more ventral parietal structures. These findings provide evidence for a dorso-medial to ventro-lateral functional specialization within the human retrosplenial complex that may shed more light on the complex neural mechanisms underlying spatial orientation and navigation in humans.

Introduction

The retrosplenial complex (RC) refers to the portion of the human posterior cingulate cortex commonly associated with spatial processing (Epstein, 2008). This region includes and extends from the retrosplenial cortex (Brodmann areas 26, 29, 30), which is the portion of the cingulate immediately posterior to the most posterior region of the corpus callosum (i.e., the splenium), through the posterior cingulate (Brodmann areas 23, 31), to the anterior bank of the parieto-occipital fissure (see Figure 2.1). Although numerous cognitive functions, such as language (Binder et al., 1997), emotion processing (Maddock, 1999), and episodic memory (Wagner, Shannon, Kahn, & Buckner, 2005), have been associated with the human posterior cingulate cortex, the engagement of the RC in spatial orientation and navigation has been very consistently and largely supported by evidence in both humans (Maguire, 2001) and non-human animals (Vann et al., 2009).

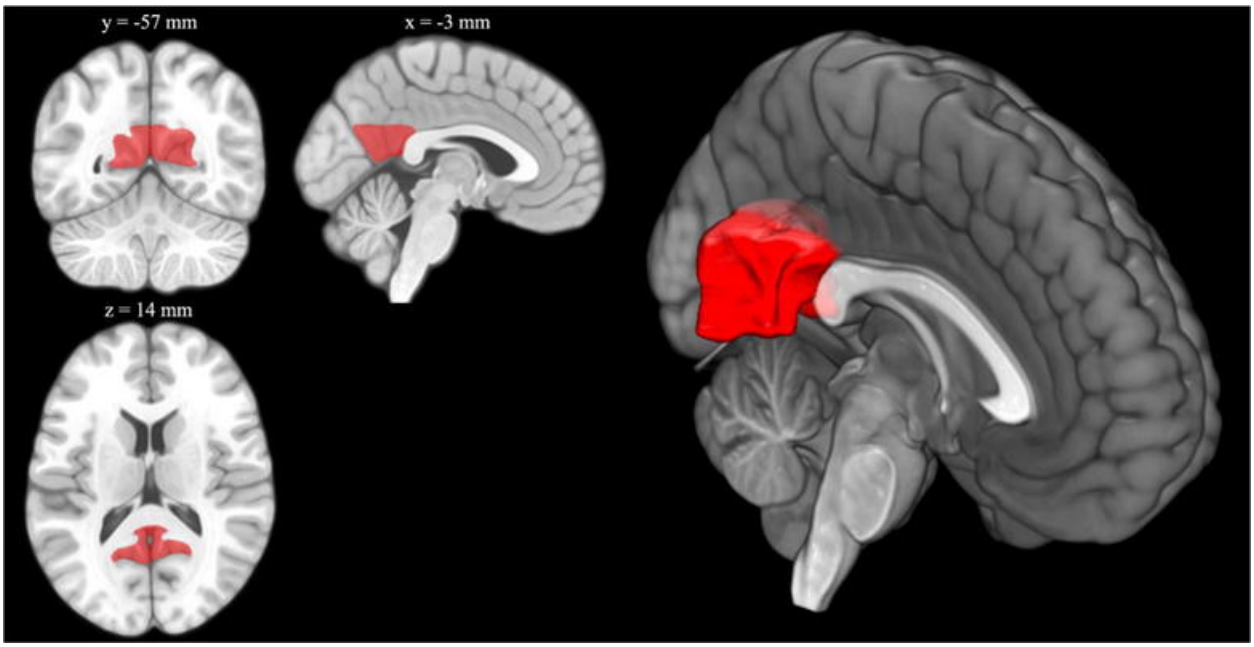

Figure 2.1. Sagittal, coronal, and horizontal view (MNI coordinates), and 3D model, of the anatomically defined Retrosplenial Complex (RC). The region includes the retrosplenial cortex and extends posteriorally through the cingulate, ending at the parieto-occipital fissure. The volume used to generate the model was truncated dorsally parallel with the dorsal border of the splenium, and orthogonally at the most ventral point of the splenium, consisting of approximately 14 cm^3 of brain tissue.

In rodents, the discovery of head-direction cells within the retrosplenial cortex reinforces the critical role of this region in spatial orientation and navigation (Cho & Sharp, 2001; Taube, 1998). Head-direction cells fire selectively when animals are facing a specific direction within the environment (Chadwick & Spiers, 2014), anchoring the organism's current position in space within a large-scale mental representation of the environment, which includes non-visible locations (Valerio & Taube, 2012). These findings in rodents are consistent with

neuropsychological evidence, reporting patients with damage to the right retrosplenial/posterior cingulate cortex being unable to utilize directional information from environmental landmarks to head towards an unseen target location (Takahashi et al., 1997), a condition known as 'heading disorientation' (Aguirre & D'Esposito, 1999); these individuals are able to recognize and identify landmarks in the environment, but are unable to derive directional information from them, and, therefore, unable to navigate to unseen target locations. Unilateral damage to the retrosplenial cortex in the left hemisphere can also produce topographical disorientation similar to that observed following damage in the right hemisphere (Ino et al., 2007), but some studies have also reported impaired verbal (McDonald, Crosson, Valenstein, & Bowers, 2001) and temporal (Bowers, Verfaellie, Valenstein, & Heilman, 1988) information processing without a spatial deficit.

A common spatial cognitive process ascribed to the human RC is a 'translational' one, with this region acting as an intermediary between areas handling sensory information gathered from the surroundings, and areas storing an internal representation of the environment (Burgess et al., 2001; Ino et al., 2002). These translational requirements are present when individuals are updating their mental representation with pertinent spatial information, as they move through the environment (Sulpizio et al., 2013; Wolbers & Büchel, 2005), and when they are recalling previously encoded information from their internal representation to perform orientation tasks (Epstein, 2008; Iaria, Chen, Guariglia, Ptito, & Petrides, 2007; Marchette, Vass, Ryan, & Epstein, 2014). Although there is convincing evidence that the RC is involved in both encoding and recall of spatial information, to date, it remains unknown whether or not subregions within the RC are equally involved in these two different processes. The hippocampus, another brain region

commonly implicated in spatial orientation and navigation, displays some subregion specialization for the encoding versus recall of spatial information (among other processes), and it is possible that a similar specialization exists within the RC (Maguire, Woollett, et al., 2006; Poppenk et al., 2013; Strange & Dolan, 1999). Here, we investigated this specific hypothesis.

We used functional Magnetic Resonance Imaging (fMRI) and resting-state functional connectivity to investigate the contribution of the RC in encoding and recalling of spatial information. We asked participants to perform a novel spatial task, i.e., the Spatial Configuration Task, appositely designed with distinct phases of 'updating' (i.e., encoding spatial information) and 'orienting' (i.e., recalling spatial information) in an environment. In each trial of the tasks, participants viewed a first-person displacement (i.e., updating) in a simple persistent virtual environment, and were subsequently asked to infer their location in the environment (i.e., orienting). We tested the hypothesis that regions within the anatomically defined RC are differentially involved in the processes of spatial 'updating' and 'orienting', and that such a difference in activity relates to different patterns of functional connectivity between the RC and the rest of the brain at rest.

Methods

Participants

Twenty-seven healthy, right-handed individuals (11 females, age $M = 25.38$, SD = 3.03 years) with no psychiatric or neurological disorders and normal or corrected-to-normal vision participated in the study. All participants provided written informed consent as approved by the local research ethics board.

Virtual environment and behavioural task

We used Presentation® (Version 16.4, neurobs.com) to create a novel task designed to assess the ability of an individual to generate and use configural knowledge of an environment. This task, namely the Spatial Configuration Task, includes five stationary geometric objects arranged pseudorandomly in a space-like virtual environment, lacking local geometry, or additional orienting cues, but with sufficient visual information to assist with motion perception. See Figure 2.2 for a depiction of the objects and task phases outlined below. At each trial, the participant is shown a viewpoint from one of the objects in the environment, in which two other objects are visible. Participants are asked to identify which object the camera is situated upon (i.e. looking *from*), with all three non-visible objects provided as response options; we refer to this phase as the "response phase". After the participant responds, the camera remains stationary for a brief period; we refer to this phase as "wait phase". Following the wait phase, the camera translates and rotates to a new object (we refer to this as "move phase"), and a new trial begins. To perform this task successfully, participants will need to combine a series of viewpoints into a coherent spatial representation of the environment, by processing the objects seen and movements performed by the camera. Initially, participants will be unfamiliar with the layout of the environment and are more likely to be guessing, but are expected to become more familiar over successive trials.

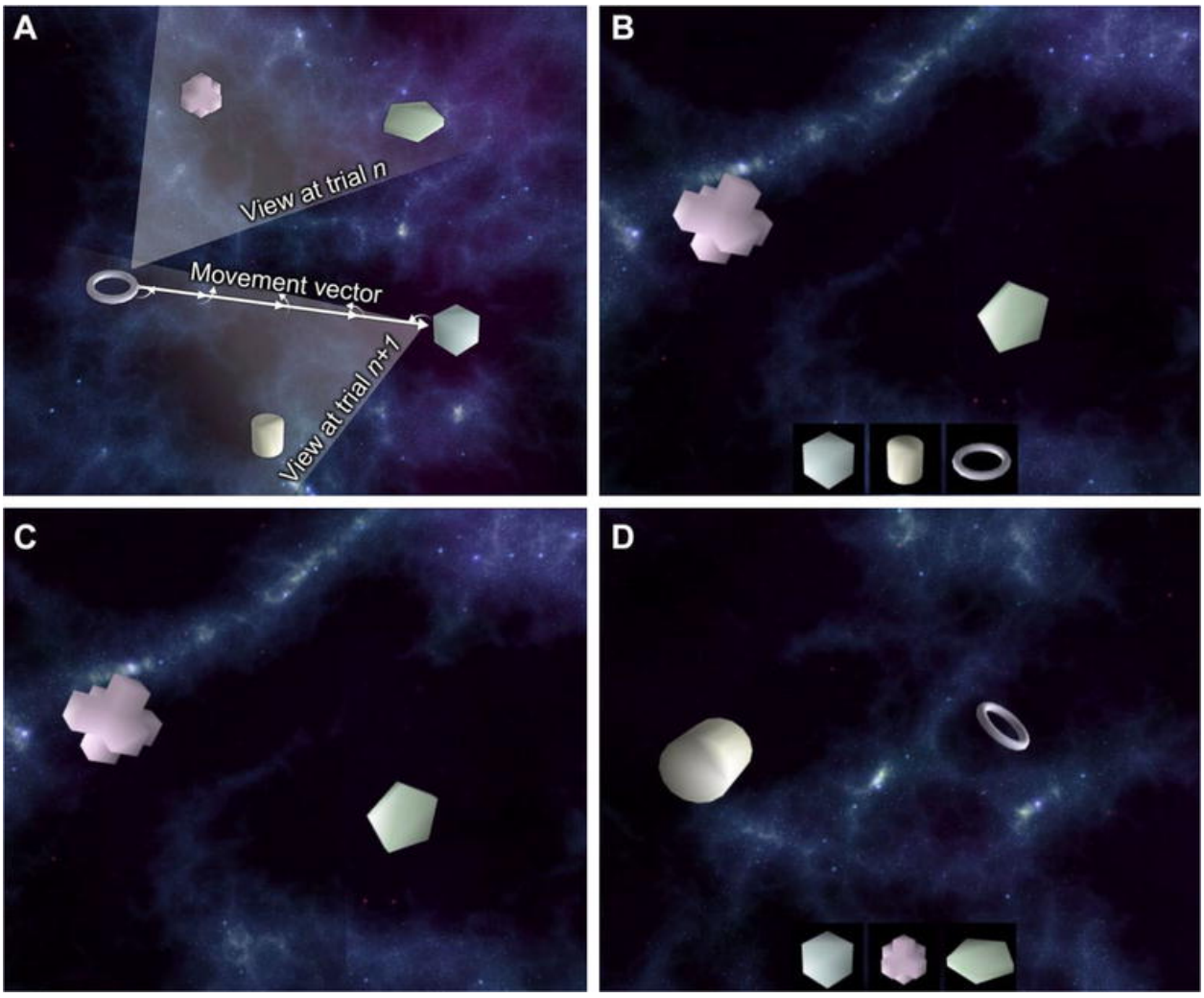

Figure 2.2. **a** Depicts a top–down view of a sample trial pair in the spatial configuration task, participants are not exposed to this type of view in the experiment. In this example, for trial *n*, the camera is situated upon the torus, viewing the complex cuboid and pentagonal prism. For trial *n*'s response phase (**b**), the cube, cylinder, and torus are response options, with the torus as the target response. After the participant responds, the camera remains stationary for the wait period (**c**), then moves from the torus to the cube, rotating leftward, and completes the motion with the cylinder and torus in view. Following this motion, trial *n* + 1's response phase begins

(**d**), and the participant as the cube, complex cuboid, and pentagonal prism as response options, with the cube as the target response.

A control task was developed using the same framework as the spatial configuration task. In this control task, however, during the response phase, participants are simply asked to identify which object they did not see in the previous trial (not including objects seen as response options). For response options, participants are presented with the two objects seen in the previous trial as well as a target object. Camera movement in the control task was constrained, such that none of the response options presented would be currently visible objects. This task requires participants to view similar stimuli as in the spatial configuration task, and to remember the identity of objects viewed in the previous trials, but without any explicit demand to remember the spatial arrangement of the objects. To preclude any unintentional formation of a mental representation of the objects' configuration (RC activity appears to be sensitive to object permanence; Auger & Maguire, 2013), at each trial of the control task, the locations of unseen objects were swapped and participants were made aware of this before the experiment began. Grand average trial duration was 11.82 s, composed of a grand average (and standard deviation) of 2.95 (1.00) s of the response phase, 5.87 (0.93) s of wait phase, and 3.00 (0.06) s of move phase. Move phase standard deviation is low because the participants' response times do not influence the duration of this phase, and no additional gaps or delays were included in the trial-to-trial timing described above. The relatively rapidly-cycling design utilized here is in stark contrast to many fMRI studies with much longer durations of continuous data collected in each phase. The present design runs the risk of poorly-characterized BOLD response being attributed

to adjacent phases of the experiment, however we felt that this risk was offset by the cognitive homogeneity afforded by the temorally compressed design. Were we to utilize a slower design, with longer move or trial phases, it is more likely that we simply allow time for participants to perform other cognitive processes, spending the additional time, for instance, ruminating on previous stimuli, thus diluting the interpretability of the BOLD activity ascribed to any of these stages.

Before entering the MRI scanner, we familiarized participants with the experimental and control tasks by asking them to perform 80 consecutive trials of each on a laptop, responding via the keyboard, with task order randomly determined for each participant. Inside the MRI scanner, we collected four functional acquisition runs; each run included 20 consecutive trials of the spatial configuration task and the control task, with task order counterbalanced across participants. For each run, new random configurations of objects were generated for both tasks. Within each run and for each task, the camera movement was constrained, such that the camera rotated to the right and to the left an equal number of times in each run. In the Spatial Configuration task, we also ensured that the camera was situated upon each of the objects in the first five trials of a run, and that there were no second-order repeats (i.e., the camera never performed the reverse movement of the preceding trial). Participants responded to the tasks via an MR-compatible button box.

MRI acquisition parameters

All participants were scanned using a 3T GE Discovery 750 MRI with an eight-channel head coil. Eyes-open resting-state functional scans were collected using a T_2*-weighted EPI

sequence (2.5 s TR, 30 ms TE, 77° flip angle, 3.75 × 3.75 × 3 mm voxels, bottom-up interleaved acquisition, 240 volumes, 24.0 cm FOV), while participants viewed a black fixation cross on a grey background. Task-based functional scans were collected over four consecutive iterations of a T_2*-weighted EPI sequence (2.0 s TR, 21 ms TE, 77° flip angle, 3 mm isotropic voxels, bottom-up interleaved acquisition, 254 volumes per run, 24.0 cm FOV). Each run consisted of both 20 consecutive trials of the configuration task and 20 consecutive trials of the control task, each task preceded with a two-second instruction reminder, and followed by 12 s of a black screen with a fixation cross. High-resolution anatomical images were acquired using a T_1-weighted SPGR sequence (Min Full TE, 11° flip angle, 1 mm isotropic voxels, bottom-up interleaved acquisition, 25.6 cm FOV).

MRI data preprocessing

We used SPM12 (v6647, Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm/) to preprocess participants' MRI data. Functional data were first slice-time corrected, and subsequently realigned to the mean functional image for each run, using a two-pass procedure. Anatomical images were coregistered to the mean functional image for each participant, and the anatomical data were used to generate deformations to normalize both functional and anatomical data to Montreal Neurological Institute (MNI) standard space. During normalization, we resampled the functional data to 2 mm isotropic voxels, and subsequently smoothed the task-based data using an 8 mm full width at half-maximum Gaussian kernel. We performed additional preprocessing on our resting-state data using the CONN toolbox (v15.g; http://www.nitrc.org/projects/conn), modelling head motion and volumes with excessive

motion using ART (https://www.nitrc.org/projects/artifact_detect), regressing out signal from white matter and cerebrospinal fluid, and by temporally bandpass filtering between 0.008 and 0.09 Hz.

MRI data analysis

Using SPM12 for task-based analyses, we first created individual, first-level models which included each task's phases (i.e., move, response, and wait) as well as three head motion and three head rotation parameters with a 1/128 Hz high-pass filter. The blood oxygen level-dependent (BOLD) signal was modelled using the canonical haemodynamic response function included in SPM12 without including time and dispersion derivatives. We then passed estimates from participants' first-level models to a second-level two by three (task by phase) repeated-measures factorial design assuming equal variances, which included participant's mean performances on both tasks as a covariate. First, we contrasted the BOLD signal from the spatial configuration task's 'wait' phase, with that from the control task's 'wait' phase, to ensure that this phase acts as a suitable baseline for the following contrasts. We then contrasted BOLD signal from the spatial configuration task ('move' vs 'wait' phase) over that from the control task ('move' vs 'wait' phase) to identify regions associated with spatial 'updating'. Similarly, we contrasted BOLD signal from the spatial configuration task ('response' vs 'wait' phases) over the control task ('response' vs 'wait' phases) to identify activity associated with spatial 'orienting'. These interactive contrasts were chosen to isolate BOLD signal changes specifically associated with generating and using a mental representation of the environment. However, it is possible that results of these contrasts will include activity due to differing levels of attention, memory

load, or visual processing demands between the tasks. We thresholded these whole-brain, task-based BOLD activity contrasts at the voxel level ($p_{FWE} < 0.05$), and cluster level ($k_E \geq 20$). Additional Region of Interest (ROI)-based contrasts were inclusively masked with the anatomical RC region outlined in Figure 2.1 and thresholded solely at the voxel level ($p_{FWE} < 0.05$). The anatomical RC ROI was generated based on Epstein's (2008) anatomical description of the RC located within the retrosplenial cortex and the posterior cingulate, and restricted based on Maguire's (2001) observation of RC activity rarely including regions dorsal to the corpus callosum.

Following these analyses, we generated resting-state seed ROIs by directly contrasting activity within the anatomical RC ROI shown in Figure 2.1, from the spatial configuration task's 'response' and 'move' phases. Within this ROI, we selected the 120 voxels (960 mm^3) with the largest *t* values in the 'response' over 'move' phase of the spatial configuration task to represent the portion of the RC most associated with spatial 'orienting', and the same number of voxels in the opposite contrast to represent the portion of the RC most associated with spatial 'updating'. These ROIs only contained clusters with peaks significant at $p_{FWE} < 0.05$. Then, we calculated the difference in functional connectivity displayed by these two RC 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 $p_{FDR} < 0.001$. For the connectivity analyses, only data from grey-matter voxels were used to calculate the Fisher-transformed correlation coefficient values used for comparison, and the reverse transform was applied to return connectivity coefficients to the reported *r* values for interpretability.

Results

Behavioural performance

Participants' average scores across all runs in both the Spatial Configuration Task (M = 68.47 %, SD = 14.88 %) and the control task (M = 85.00 %, SD = 11.78 %) were significantly higher than that expected by chance (i.e. 33.33 %; $t_{26} = 9.814$, $p < 0.001$; $t_{26} = 18.226$, $p < 0.001$). Participants displayed a linear increase in performance across runs of the Spatial Configuration task ($F_{1,26} = 13.690$, $p = 0.001$) with average accuracies of 63.33, 66.11, 71.48, and 72.96 % across runs 1 through 4, respectively. No linear change in performance across runs was detected in the control task ($F_{1,26} = 0.084$, $p = 0.774$). Participants also responded significantly faster ($t_{26} = 4.673$, $p < 0.001$) in the control task (M = 2.49 s, SD = 0.88 s) relative to the Spatial Configuration Task (M = 3.41 s, SD = 1.12 s).

Task-based functional activity

Significant changes in BOLD signal acquired using fMRI associated with spatial 'updating' and 'orienting' across the entire brain are reported in Table 2.1 and shown in Figure 2.3. There were no significant differences in BOLD signal between the 'wait' phases of the spatial configuration task and the control task. Spatial 'updating' during movement was associated with increased BOLD signal bilaterally in the RC (left k_E = 306, peak $p_{FWE} < 0.001$ at MNI: −18, −60, 14; right k_E = 267, peak $p_{FWE} < 0.001$ at MNI: 20, −54, 14), bilaterally in the lingual gyrus (k_E = 277, peak $p_{FWE} < 0.001$ at MNI: −6, −72, 0), right-lateralized in the inferior frontal junction (k_E = 208, peak $p_{FWE} < 0.001$ at MNI: 44, 12, 30), and in smaller clusters in the right parahippocampus/fusiform gyrus (k_E = 99, peak $p_{FWE} < 0.001$ at MNI: 30, −38, 12), left precuneus (k_E = 36, peak

$p_{FWE} < 0.001$ at MNI: −10, −50, 60), right supramarginal gyrus ($k_E = 58$, peak $p_{FWE} = 0.004$ at MNI: 60, −22, 34), and right fusiform gyrus ($k_E = 20$, peak $p_{FWE} = 0.012$ at MNI: 54, −56, 8). The RC as well as the lingual and parahippocampal gyri have been previously associated with processing viewpoint changes within a feature-rich environment (Sulpizio et al., 2013), and the parahippocampus specifically has been implicated in encoding object locations (Maguire, Frith, Burgess, Donnett, & O'Keefe, 1998; Mellet et al., 2000). The inferior frontal junction activity may be due to general demands to maintain and update working memory contents (Roth, Serences, & Courtney, 2006), and the activity in the supramarginal gyrus may be due to the spatial working memory demands present in this task (Silk, Bellgrove, Wrafter, Mattingley, & Cunnington, 2010).

Table 2.1. Significant clusters of BOLD signal change during spatial 'updating' and 'orienting'. Voxel height threshold at $p_{FWE} < 0.05$, cluster threshold at $k_E \geq 20$. L, left hemisphere; R, Right hemisphere. RC = Retrosplenial Complex.

			Local Peak Voxel		
Spatial 'updating'	BA	k_E	t_{130}	$p_{\text{-FWE}}$	MNI x,y,z
L RC	18, 23	306	7.75	<.001	-18, -60, 14
R RC	23	267	7.33	<.001	20, -54, 14
L Lingual Gyrus	18	277	6.39	<.001	-6, -72, 0
R Lingual Gyrus	18		5.57	.002	8, -72, 2
L Lingual Gyrus	18		5.34	.006	-18, -70, -10
L Precuneus	7	36	6.02	<.001	-10, -50, 60
R Parahippocampus	36	99	5.99	<.001	30, -38, -12
R Inferior Frontal Junction	44	208	5.92	<.001	44, 12, 30
R Supramarginal Gyrus	40	58	5.43	.004	60, -22, 34
R Fusiform Gyrus	37	20	5.15	.012	54, -56, 8
Spatial 'orienting'					
L RC	18, 23	2305	10.15	<.001	-16, -60, 14
R RC	23		9.06	<.001	16, -54, 16
R Dorsal Cerebellum			8.86	<.001	8, -48, 2
L lateral superior occipital cortex	19	356	8.14	<.001	-34, -84, 32
R lateral superior occipital cortex	19	313	7.70	<.001	42, -74, 26
L Lingual Gyrus	19	112	5.57	.002	-10, -68, -10
R Lingual Gyrus	19	58	5.22	.009	14, -66, -6

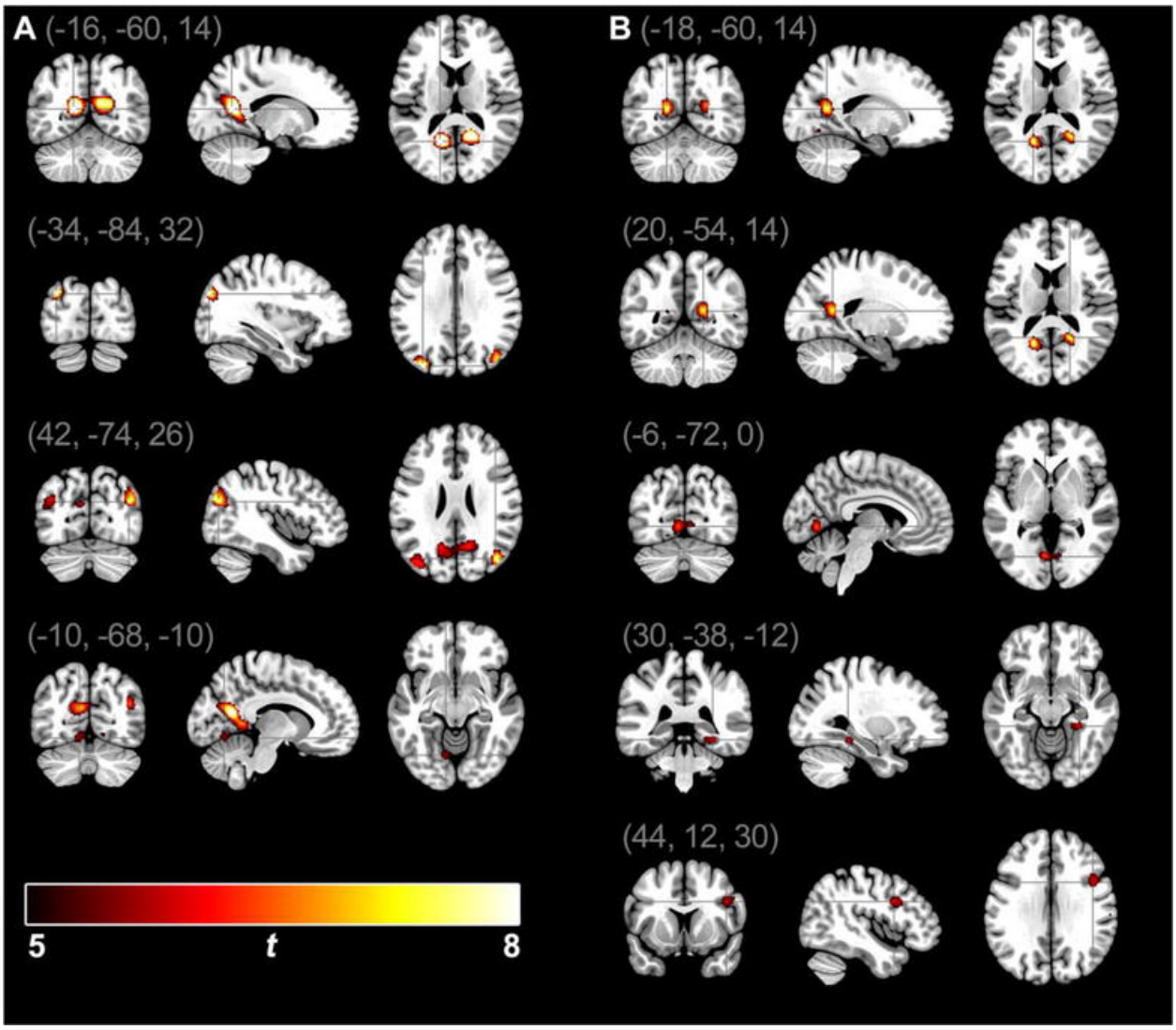

Figure 2.3. Clusters of $k_E > 90$ at a voxel height threshold of $t > 5$ (equivalent to $p_{FWE} < 0.021$) implicated in spatial 'orienting' (**a**) and spatial 'updating' (**b**). Coordinates and crosshairs provided in MNI space indicate the peak voxel for each cluster. From *top to bottom*, **a** depicts spatial 'orienting' clusters located in the retrosplenial complex, left and right lateral superior occipital cortex, and the left lingual gyrus. **b** Depicts spatial 'updating' clusters located in the left and right retrosplenial complex, left lingual gyrus, right parahippocampal cortex, and right inferior frontal junction

Spatial ‘orienting’, while participants reported the camera’s location within the environment, was associated with increased BOLD signal bilaterally in the RC (k_E = 2305, peak p_{FWE} < 0.001 at MNI: −16, −60, 14), lateral superior occipital cortex (left k_E = 356, peak p_{FWE} < 0.001 at MNI: −34, −84, 32; right k_E = 313, peak p_{FWE} < 0.001 at 42, −74, 26), and lingual gyrus (left k_E = 112, peak p_{FWE} = 0.002 at MNI: −10, −68, 10; right k_E = 58, peak p_{FWE} = 0.009 at MNI: 14, −66, −6). Beyond the expected RC activity, activity in the lateral superior occipital cortex is likely associated with maintaining object positions in short-term memory (Xu & Chun, 2006), and activity in this specific area has been found in other spatial tasks (Ino et al., 2002). As in the spatial ‘updating’ contrast, the detected lingual gyrus activity is likely due to continued processing of the viewpoint change (Sulpizio et al., 2013).

Directly comparing BOLD activity within the anatomically defined RC, while participants spatially ‘updated’ and ‘oriented’ revealed a cluster in the dorso-medial portion of the RC (BA 31), along the parieto-occipital fissure, which was more associated with spatial ‘orienting’ (k_E = 160, peak p_{FWE} < 0.001 at MNI: 4, −68, 28). This was opposed by two small clusters in the ventro-lateral banks of the parieto-occipital fissure (BA 23) more associated with spatial ‘updating’ (right k_E = 14, peak p_{FWE} = 0.002 at MNI: 24, −56, 10; left k_E = 1, peak p_{FWE} = 0.046 at MNI: -20, −56, 8). We adjusted the statistical thresholds of these contrasts to generate ROIs of equal spatial extent (a single cluster of 120 voxels for the dorso-medial ROI at *t*s > 3.770, and two clusters of 63 and 57 voxels for the right and left ventro-lateral ROI, respectively, at *t*s > 1.554; Figure 2.4a–c), for the following seed-to-ROI resting-state functional connectivity analysis.

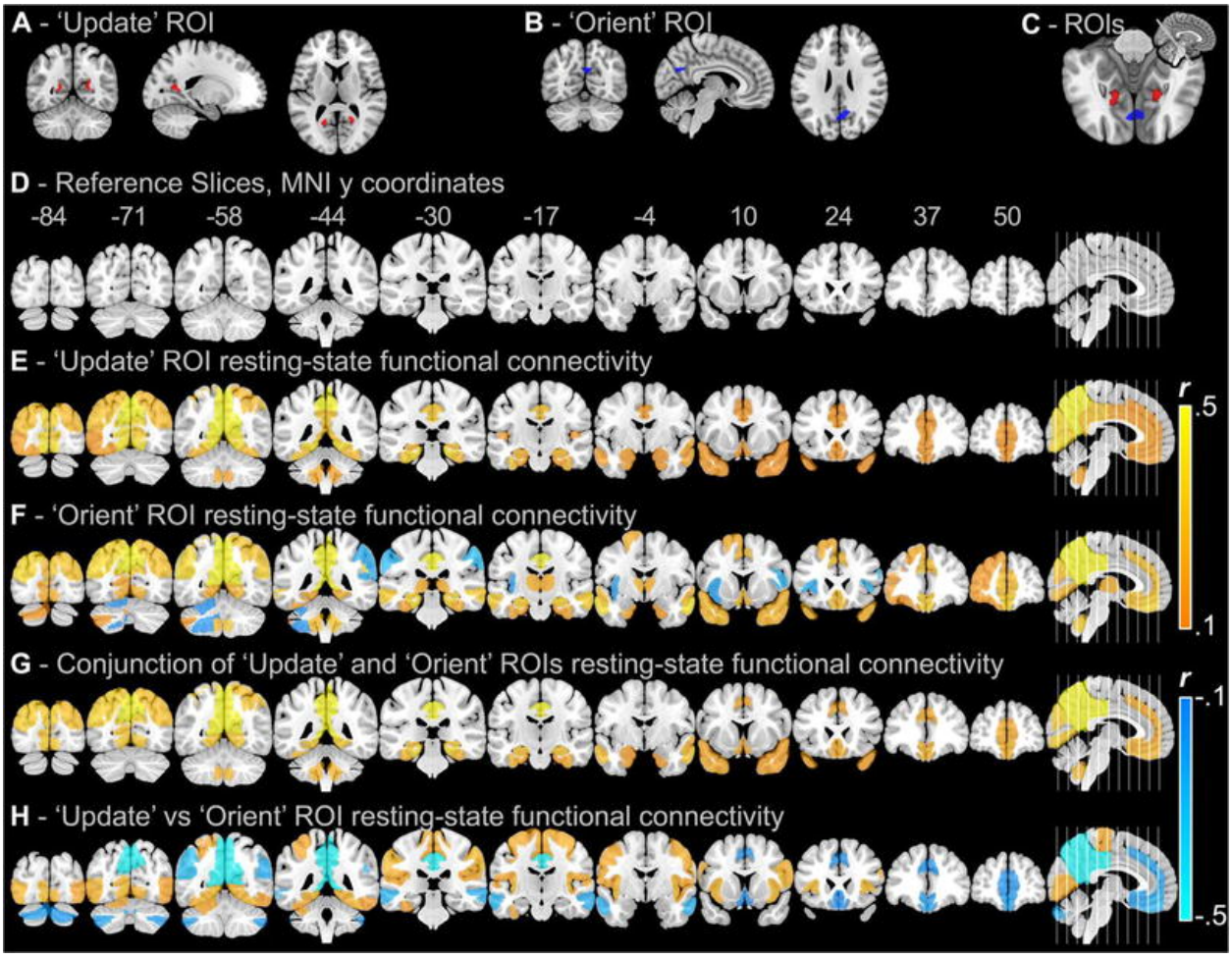

Figure 2.4. Depicts the retrosplenial complex (RC) seed ROIs used for a whole-brain seed-to-ROI resting-state functional connectivity analysis. **a** Depicts the ventro-lateral RC most implicated in spatial 'updating', **b** depicts the dorso-medial RC most implicated in spatial 'orienting'. **c** Depicts both these ROIs in the slice along the parieto-occipital fissure. **e**–**h** Display the resting-state functional connectivities of these regions on a series of coronal slices, with **d** as an anatomical reference. Panel E displays the functional connectivity of the ventro-lateral RC ROI; **f** displays that of the dorso-medial RC ROI. **g** Displays areas significantly connected to both seed ROIs independently, with *r* values averaged for display purposes. **h** depicts the difference between the functional connectivity seen in the ventro-lateral and dorso-medial RC

ROIs; regions in red–yellow are more positively correlated with the ventral-lateral RC ROI, and regions in blue-teal are more positively correlated with the dorso-medial RC ROI. These seed-to-ROI analyses were thresholded at $p_{FDR} < 0.001$

Resting-state functional connectivity

Comparing patterns of resting-state functional connectivity between the ventro-lateral seed ROI associated with spatial 'updating' and the dorso-medial RC seed ROI associated with spatial 'orienting' revealed numerous commonalities and differences across the brain (Table 2.2; Figure 2.4e–h). *p* and *t* values for the following analyses are omitted from the text for readability, but are present in Table 2.2.

Table 2.2. Selected seed-to-ROI resting-state functional connectivity metrics between ventro-lateral and dorso-medial Retrosplenial Complex (RC) seed ROIs and 131 additional ROIs with whole-brain coverage, at $p_{FDR} < .001$.

		Ventro-lateral RC			Dorso-medial RC			Difference	
		r	t_{26}	p_{FDR}	*r*	t_{26}	p_{FDR}	t_{26}	p_{FDR}
Occipital Lobe									
Superior lateral occipital cortex	R	**.27**	10.81	**<.**0001	**.30**	10.05	**<.**0001	-0.73	.5618
	L	**.29**	10.44	**<.**0001	**.38**	10.33	**<.**0001	-2.58	.0290
Inferior lateral occipital cortex	R	.14	3.30	.0070	-.01	-0.22	.8565	**4.16**	.0010
	L	**.16**	4.18	.0009	-.05	-1.85	.1049	**6.31**	<.0001
Cuneal cortex	R	**.38**	9.58	<.0001	**.33**	7.16	<.0001	1.08	.3715
	L	**.39**	9.97	<.0001	**.27**	6.17	<.0001	2.54	.0310
Supracalcarine cortex	R	**.38**	10.73	<.0001	**.21**	5.17	<.0001	4.06	.0012
	L	**.52**	11.84	<.0001	**.41**	7.44	<.0001	2.78	.0192
Intracalcarine cortex	R	**.33**	8.91	<.0001	.14	4.01	.0011	4.07	.0012
	L	**.42**	12.98	<.0001	**.20**	4.59	.0003	**5.28**	.0001
Lingual gyrus	R	**.42**	10.76	<.0001	**.24**	6.09	<.0001	**4.64**	.0004
	L	**.45**	11.29	<.0001	**.21**	5.95	<.0001	**5.03**	.0002
Occipital fusiform gyrus	R	.12	2.89	.0173	-.02	-0.55	.6625	3.31	.0063
	L	**.17**	4.18	.0001	.00	-0.06	.9605	**4.14**	.0010

		Ventro-lateral RC			Dorso-medial RC			Difference	
Temporal lobe		*r*	t_{26}	p_{FDR}	*r*	t_{26}	p_{FDR}	t_{26}	p_{FDR}
Temporal-Occipital Fusiform Gyrus	R	**.28**	7.68	<.0001	.07	1.72	.1283	**5.33**	.0001
	L	**.25**	8.76	<.0001	.06	1.53	.1780	**5.20**	.0001
Posterior Temporal Fusiform Gyrus	R	**.26**	9.29	<.0001	**.21**	7.72	<.0001	1.74	.1308
	L	**.33**	11.64	<.0001	**.19**	6.60	<.0001	**4.41**	.0006
Temporal-Occipital Inferior Temporal Gyrus	R	.04	1.31	.2693	-.08	-2.61	.0251	**4.39**	.0006
	L	.09	2.88	.0173	.00	-0.07	.9586	2.99	.0122
Anterior Middle Temporal Gyrus	R	**.18**	6.88	<.0001	**.44**	14.00	<.0001	**-8.40**	<.0001
	L	**.16**	5.37	<.0001	**.39**	12.34	<.0001	**-5.77**	<.0001
Posterior Middle Temporal Gyrus	R	**.10**	4.21	.0009	**.33**	9.83	<.0001	**-6.38**	<.0001
	L	.05	1.61	.1771	**.33**	10.55	<.0001	**-7.37**	<.0001
Temporal Pole	R	**.13**	5.07	.0001	**.24**	9.10	<.0001	-3.73	.0026
	L	**.15**	6.31	<.0001	**.26**	8.82	<.0001	-3.60	.0034
Posterior Parahippocampal Cortex	R	**.42**	12.16	<.0001	**.35**	12.55	<.0001	1.91	.1008
	L	**.42**	9.52	<.0001	**.40**	10.98	<.0001	0.36	.7739
Anterior Parahippocampal Cortex	R	**.14**	6.11	<.0001	**.14**	4.23	.0007	-0.25	.8433
	L	**.17**	7.41	<.0001	**.20**	7.83	<.0001	-0.85	.4870
Hippocampus	R	**.26**	8.93	<.0001	**.36**	9.57	<.0001	-2.41	.0400
	L	**.24**	7.04	<.0001	**.35**	9.77	<.0001	-2.88	.0154
Amygdala	R	**.14**	4.42	<.0001	.12	3.29	.0061	0.52	.6870
	L	**.16**	6.14	<.0001	**.14**	4.06	.0010	0.97	.4361
Insula	R	.09	2.61	.0308	-.16	-3.88	.0020	**5.77**	<.0001
	L	.07	2.10	.0771	**-.17**	-4.10	.0010	**6.45**	<.0001

		Ventro-lateral RC			Dorso-medial RC			Difference	
Parietal lobe		*r*	t_{26}	p_{FDR}	*r*	t_{26}	p_{FDR}	t_{26}	p_{FDR}
Precuneus		**.52**	11.22	<.0001	**.82**	24.50	<.0001	**-8.18**	<.0001
Posterior Cingulate		**.31**	8.39	<.0001	**.73**	28.73	<.0001	**-13.59**	<.0001
Paracingulate Gyrus	R	**.13**	5.12	.0001	**.27**	7.15	<.0001	**-4.49**	.0005
	L	**.15**	6.58	<.0001	**.30**	7.66	<.0001	**-4.76**	.0003
Heschl's Gyrus	R	**.16**	4.33	.0007	.07	2.65	.0235	2.27	.0520
	L	**.15**	4.85	.0002	.02	0.98	.4129	**4.12**	**.0010**
Planum Temporale	R	.12	3.40	.0058	-.04	-1.08	.3640	**4.35**	.0006
	L	.13	3.83	.0022	-.04	-0.97	.4157	**4.55**	.0005
Planum Polare	R	.11	3.32	.0069	-.04	-1.44	.2081	**4.18**	.0010
	L	.07	2.14	.0731	-.06	-1.92	.0922	3.45	.0046
Angular Gyrus	R	.09	3.48	.0050	**.34**	8.18	<.0001	**-5.89**	<.0001
	L	.08	2.43	.0425	**.39**	11.11	<.0001	**-8.29**	<.0001
Anterior Supramarginal Gyrus	R	-.02	-0.59	.6376	**-.28**	-6.14	<.0001	**5.93**	<.0001
	L	.00	0.02	.9869	**-.25**	-6.08	<.0001	**6.26**	<.0001
Precentral Gyrus	R	.09	2.56	.0332	-.10	-2.77	.0179	**6.21**	<.0001
	L	.09	3.24	.0078	-.08	-2.91	.0138	**7.18**	<.0001
Superior Parietal Lobule	R	.04	1.28	.2807	-.13	-3.07	.0099	3.63	.0032
	L	.05	1.80	.1332	-.11	-3.07	.0099	**4.80**	.0003
Parietal Operculum	R	.09	2.24	.0604	-.09	-1.80	.1156	**4.30**	.0007
	L	.06	1.41	.2356	-.13	-2.98	.0119	**5.10**	.0002

		Ventro-lateral RC	Dorso-medial RC	Difference

Frontal Lobe		*r*	t_{26}	p_{FDR}	*r*	t_{26}	p_{FDR}	t_{26}	p_{FDR}
Central Operculum	R	.09	1.94	.1074	-.08	-2.00	.0823	**4.67**	.0004
	L	.07	1.55	.1946	-.08	-2.38	.0402	**4.44**	.0006
Frontal Operculum	R	-.02	-0.59	.6376	**-.25**	-6.19	<.0001	**5.23**	<.0001
	L	-.03	-1.06	.3735	**-.24**	-7.80	<.0001	**6.93**	<.0001
Inferior Frontal Gyrus - Pars Opercularis	R	.02	0.62	.6284	**-.25**	-5.53	<.0001	**5.55**	**<.0001**
	L	-.02	-0.69	.5777	**-.17**	-3.68	.0024	3.59	.0034
Subcallosal Cortex		**.14**	5.27	<.0001	**.27**	8.82	<.0001	**-4.43**	.0006
Frontal Medial Cortex		**.14**	5.77	<.0001	**.34**	8.05	<.0001	**-5.06**	.0001
		Ventro-lateral RC			Dorso-medial RC			Difference	
Cerebellum		*r*	t_{26}	p_{FDR}	*r*	t_{26}	p_{FDR}	t_{26}	p_{FDR}
Cerebellar Lobule 2	R	-.05	-1.79	.1332	.14	3.83	.0017	**-4.**39	.0006
	L	-.07	-2.82	.0196	**.15**	5.02	.0001	**-5.56**	<.0001
Cerebellar Lobule 6	R	.07	2.31	.0524	-.07	-1.98	.0835	3.74	.0026
	L	.03	1.15	.3293	**-.13**	-4.52	.0004	**4.59**	.0004
Cerebellar Lobule 9	R	**.18**	4.57	.0004	**.32**	7.13	<.0001	-2.93	.0142
	L	**.21**	6.72	<.0001	**.27**	9.76	<.0001	-2.08	.0747

Thresholded at $p_{FDR} < 0.001$, both RC seed ROIs displayed similar positive functional connectivity levels with occipital ROIs, including the superior lateral occipital cortex (right: $r_{v.lat.} = 0.27$, $r_{d.med.} = 0.30$; left: $r_{v.lat.} = 0.29$, $r_{d.med.} = 0.38$), the cuneal cortex (right: $r_{v.lat.} = 0.38$, $r_{d.med.} = 0.33$; left: $r_{v.lat.} = 0.39$, $r_{d.med.} = 0.27$), and the supracalcarine cortex (right: $rv_{.lat.} = 0.38$, $r_{d.med.} = 0.21$; left: $r_{v.lat.} = 0.52$, $r_{d.med.} = 0.41$), but the ventro-lateral 'updating' ROI more positively connected with the inferior lateral occipital cortex (Right: $r_{v.lat.} = 0.14$, $r_{d.med.} = -0.01$; Left: $r_{v.lat.} = 0.16$, $r_{d.med.} = -0.05$) and the left intracalcarine cortex (Right: $r_{v.lat.} = 0.33$, $r_{d.med.} = 0.14$; Left: $r_{v.lat.} = 0.42$, $r_{d.med.} = 0.20$). Both seed ROIs were functionally connected to posterior ventral areas, including the lingual gyrus, but the ventro-lateral 'updating' ROI more so (right: $r_{v.lat.} = 0.42$, $r_{d.med.} = 0.24$; left: $r_{v.lat.} = 0.45$, $r_{d.med.} = 0.21$).

The ventro-lateral RC ROI also displayed more positive functional connectivity measures with the left occipital ($r_{v.lat.} = 0.17$, $r_{d.med.} = 0.00$), bilateral temporal-occipital (right: $r_{v.lat.} = 0.28$, $r_{d.med.} = 0.07$; left: $r_{v.lat.} = 0.25$, $r_{d.med.} = 0.06$), and left posterior temporal fusiform gyri ($r_{v.lat.}$

= 0.33, $r_{d.med.}$ = 0.19), as well as left Heschl's gyrus ($r_{v.lat.}$ = 0.15, $r_{d.med.}$ = 0.02) and planum temporale (right: $r_{v.lat.}$ = 0.12, $r_{d.med.}$ = −0.04; left: $r_{v.lat.}$ = 0.13, $r_{d.med.}$ = −0.04). However, resting-state activity in the dorso-medial RC ROI was more positively correlated with activity in the anterior (Right: $r_{v.lat.}$ = 0.18, $r_{d.med.}$ = 0.44; Left: $r_{v.lat.}$ = 0.16, $r_{d.med.}$ = 0.39) and posterior (right: $r_{v.lat.}$ = 0.10, $r_{d.med.}$ = 0.33; left: $r_{v.lat.}$ = 0.05, $r_{d.med.}$ = 0.33) middle temporal gyrus, as well as the precuneus ($r_{v.lat.}$ = 0.52, $r_{d.med.}$ = 0.82), posterior cingulate ($r_{v.lat.}$ = 0.31, $r_{d.med.}$ = 0.73), paracingulate gyrus (right: $r_{v.lat.}$ = 0.13, $r_{d.med.}$ = 0.27; left: $r_{v.lat.}$ = 0.15, $r_{d.med.}$ = 0.30), angular gyrus (right: $r_{v.lat.}$ = 0.09, $r_{d.med.}$ = 0.34; left: $r_{v.lat.}$ = 0.08, $r_{d.med.}$ = 0.39), subcallosal cortex ($r_{v.lat.}$ = 0.14, $r_{d.med.}$ = 0.27), frontal medial cortex ($r_{v.lat.}$ = 0.14, $r_{d.med.}$ = 0.34), and cerebellar lobule 2 (right: $r_{v.lat.}$ = −0.05, $r_{d.med.}$ = 0.14; left: $r_{v.lat.}$ = −0.07, $r_{d.med.}$ = 0.15).

Both RC ROIs exhibited similar, positive, levels of functional connectivity with anterior (right: $r_{v.lat.}$ = 0.14, $r_{d.med.}$ = 0.14; left: $r_{v.lat.}$ = 0.17, $r_{d.med.}$ = 0.20) and posterior (right: $r_{v.lat.}$ = 0.42, $r_{d.med.}$ = 0.35; left: $r_{v.lat.}$ = 0.42, $r_{d.med.}$ = 0.40) parahippocampal cortices, hippocampus (right: $r_{v.lat.}$ = 0.26, $r_{d.med.}$ = 0.36; left: $r_{v.lat.}$ = 0.24, $r_{d.med.}$ = 0.35), left amygdala ($r_{v.lat.}$ = 0.16, $r_{d.med.}$ = 0.14), the temporal pole (right: $r_{v.lat.}$ = 0.13, $r_{d.med.}$ = 0.24; left: $r_{v.lat.}$ = 0.15, $r_{d.med.}$ = 0.26), and the ventro-medial cerebellar lobule 9 (right: $r_{v.lat.}$ = 0.18, $r_{d.med.}$ = 0.32; left: $r_{v.lat.}$ = 0.21, $r_{d.med.}$ = 0.27).

Finally, the dorso-medial RC ROI displayed significantly more negative functional connectivity coefficients with the insula (right: $r_{v.lat.}$ = 0.09, $r_{d.med.}$ = -0.16; left: $r_{v.lat.}$ = 0.07, $r_{d.med.}$ = -0.17), the adjacent parietal (right: $r_{v.lat.}$ = 0.09, $r_{d.med.}$ = −0.09; left: $r_{v.lat.}$ = 0.06, $r_{d.med.}$ = −0.13), central (right: $r_{v.lat.}$ = 0.09, $r_{d.med.}$ = −0.08; left: $r_{v.lat.}$ = 0.07, $r_{d.med.}$ = −0.08), and frontal operculum (right: $r_{v.lat.}$ = −0.02, $r_{d.med.}$ = −0.25; left: $r_{v.lat.}$ = −0.02, $r_{d.med.}$ = −0.24), anterior

supramarginal gyrus (right: $r_{v.lat.} = -0.02$, $r_{d.med.} = -0.28$; left: $r_{v.lat.} = 0.00$, $r_{d.med.} = -0.25$), the precentral gyrus (right: $r_{v.lat.} = 0.09$, $r_{d.med.} = -0.10$; left: $r_{v.lat.} = 0.09$, $r_{d.med.} = -0.08$), and left cerebellar lobule 6 ($r_{v.lat.} = 0.03$, $r_{d.med.} = -0.13$).

Discussion

The involvement of the RC in spatial orientation and navigation has been supported by numerous recent neuroimaging studies. For instance, Sulpizio and colleagues (2013) acquired fMRI data from participants encoding the location of objects in a virtual environment. Participants were required to identify if an object was in the same relative position to a referent (i.e., the room, the other objects, or their point of view) after the environment was potentially manipulated by camera displacement and/or a rotation of the object set. Increased RC activity was detected when participants were judging object locations relative to stable environmental features (i.e., the room), especially when the camera was displaced. In a different study, Marchette and colleagues (Marchette et al., 2014) had participants learn the locations of objects in a multi-building virtual environment, and subsequently collected fMRI data, while participants performed a task requiring them to imagine viewing one object in the environment and report the general direction to a second object. Using the multi-voxel pattern analysis, the authors determined that the RC coded for the participant's imagined location, as well as local direction, within an environment. In a more ecologically valid study, Spiers and Maguire (2006) used a commercially available video game that included an accurate reconstruction of London's city centre. Participants played the role of a taxi driver, navigating throughout the city, ferrying virtual participants to requested destinations during fMRI scanning. RC activity was observed,

while participants planned routes, inspected the environment, and when their expectations of the environment were confirmed or violated (e.g., if a planned route was blocked). While it seems clear that the RC is involved in spatial processing, one would assume that there is some functional specialization within this large region for the slightly different cognitive demands present in tasks, such as those outlined above. While the exact spatial extent of the RC has not been agreed upon, it spans at least five distinct Brodmann areas (i.e. 23, 26, and 29–31) and demonstrates heterogeneous functional connectivity profiles (Beckmann, Johansen-Berg, & Rushworth, 2009; Leech, Braga, & Sharp, 2012; Margulies et al., 2009; Zhang & Li, 2012). The varying cytology and functional connectivity of regions within and adjacent to the RC hint towards some intraregional specialization, which are likely related to the varying cognitive demands present in the spatial orientation tasks outlined above.

In this study, we attempted to disambiguate the RC's involvement in two somewhat distinct cognitive components that are common in many large-scale spatial orientation tasks: Spatial 'updating' (i.e., processing self-motion information while tracking and maintaining visible and non-visible objects in spatial working memory), and spatial 'orientation' (i.e., utilizing a visual scene and spatial memory to infer the location of unseen objects). After confirming the RC was involved in both spatial 'updating' and 'orienting' in our whole-brain analysis, we compared RC activity in these two conditions directly. This comparison revealed that spatial 'updating' produced greater BOLD responses in the ventro-lateral banks of the parieto-occipital fissure, whereas spatial 'orienting' produced greater BOLD responses in dorso-medial portions of the parieto-occipital fissure.

Ventral-dorsal differences in the RC along the parieto-occipital fissure have been detailed in a handful of human cytology studies. Beyond Brodmann's initial subdivision of the posterior cingulate into the relatively ventral region 23 and more dorsal region 31 (Brodmann, 2006), Vogt and colleagues have identified more nuanced dorsal–ventral subdivisions within BA 23, specifically a more dorsal v23b and a more ventral v23a (Vogt, Nimchinsky, Vogt, & Hof, 1995; Vogt, Vogt, Perl, & Hof, 2001; Vogt, Vogt, & Laureys, 2006). Both these subregions have well-developed pyramidal neurons in cortical layer IIIc and a large layer IV, but relative to region v23a, v23b has more large pyramidal neurons in cortical layers IIIc and Va (Vogt et al., 1995). The ventro-lateral RC clusters more active in spatial 'updating' appear to lie in the more ventral area v23a (Vogt et al., 2006). Additional evidence for dorsal–ventral differences within Brodmann area 23 of the posterior cingulate is provided by retrograde tracer studies in the macaque, identifying a decrease in projections to the thalamus between ventral and dorsal Brodmann area 23 (Aggleton, Saunders, Wright, & Vann, 2014). However, we did not detect significant differences in resting-state functional connectivity with the thalamus between the RC seed ROIs used in this study ($r_{\text{v.lat.}} \cong 0.15$ vs $r_{\text{d.med.}} \cong 0.21$).

Beyond the cytological differences likely present between the dorso-medial and ventro-lateral RC ROIs, they exhibited significantly different patterns of resting-state functional connectivity. Resting activity in the ventro-lateral RC ROI was more positively correlated with activity in numerous 'ventral-stream' occipital and temporal regions, including the inferior lateral occipital cortex, intracalcarine cortex, the fusiform gyrus, and lingual gyrus often related to processing and encoding object identity (Machielsen, Rombouts, Barkhof, Scheltens, & Witter, 2000; Milner & Goodale, 2008). The ventro-lateral RC seed was generated from voxels more

active while participants were passively moved through an environment as opposed to recalling unseen locations. This contrast implicates this area in relatively more stimulus-driven visual processing, supported by the resting-state functional connectivity profile of this area, with functional connections to visual encoding regions in the brain.

The dorso-medial RC ROI was more positively correlated with the middle temporal gyrus, and parietal regions, such as the precuneus, posterior cingulate, and the angular gyrus, but displayed relatively negative functional connectivity coefficients with the anterior supramarginal gyrus, as well as the precentral gyrus, insula, and adjacent operculum. This pattern of functional connectivity is consistent with the cognitive demands present in the task used to select this ROI, where participants recalled the location of unseen objects. At rest, this RC subregion displays more positive functional connectivity coefficients with regions of the brain associated with recalling spatial information, such as the precuneus (Cavanna & Trimble, 2006), posterior cingulate (Maddock, Garrett, & Buonocore, 2001; Wagner et al., 2005), and lateral superior occipital cortex (Seghier, 2013), and potentially influenced by goal-directed cognitive control mechanisms related to the medial frontal cortex (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). The anticorrelations seen between the dorso-medial RC ROI and other brain regions are present in other resting-state studies, as the posterior cingulate is considered part of a ‘task-negative’ network, which displays strong anticorrelations with the precentral sulcus, insula, and intraparietal sulcus (Fox et al., 2005). However, the fontal operculum has been implicated in processing visuo-spatial sequences (Bahlmann, Schubotz, Mueller, Koester, & Friederici, 2009) and chunking actions or movement into higher order representations (Koechlin & Jubault, 2006). The insula and precentral gyrus, along with the opercular regions, are related to

managing working memory or directing attention (de Fockert, Rees, Frith, & Lavie, 2001; Karnath, 2004; Menon & Uddin, 2010; Roth et al., 2006). Such processes likely play a role in a number of laboratory spatial tasks (such as the task employed in this study) as well as more ecological navigation.

Conclusions

In summary, spatial 'updating' and 'orienting' in the current experiment both produced significantly increased BOLD signal in the RC, with spatial 'updating' recruiting more ventro-lateral portions of the RC along the parieto-occipital fissure, and spatial 'orienting' producing significantly greater activity in dorsal and medial portions of the RC. ROIs generated by selecting the most significant voxels of equal spatial extent differentially involved in spatial 'updating' and 'orienting' displayed different patterns of functional connectivity at rest. Resting-state activity in the ventro-lateral RC ROI involved in spatial 'updating' was more temporally correlated with ventral-stream visual processing regions of the brain, whereas resting-state activity in the bilateral RC ROI associated with spatial 'orienting' was more functionally coupled with areas associated with recalling object locations, as well as directing attention. Previous research has identified similar functional specialization within the hippocampus (Iaria et al., 2007; Maguire et al., 2000; Woollett & Maguire, 2009) and, possibly, the parahippocampal gyrus (Baldassano et al., 2013), our findings provide evidence for a task-relevant dorso-medial to ventro-lateral functional specialization of the retrosplenial complex along the anterior bank of the parieto-occipital fissure. A more nuanced understanding of both the differences between subregions within the retrosplenial complex, from both an anatomical and functional perspective,

will facilitate understanding of the complex neural mechanisms underlying spatial orientation and navigation in humans.

Chapter Three: Ventral – Dorsal Functional Contribution Of The Posterior Cingulate Cortex In Human Spatial Orientation: A Meta-Analysis.

This chapter was adapted with permission from the following publication:
Burles, F., Umiltá, A., McFarlane, L., Potocki, K., & Iaria, G. (2018). Ventral-Dorsal functional contribution of the posterior cingulate cortex in human spatial orientation: A meta-analysis. *Frontiers in Human Neuroscience*, *12*, 190.

Abstract

The retrosplenial cortex has long been implicated in human spatial orientation and navigation. However, neural activity peaks labelled '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 heterogeneous region being ascribed numerous roles in spatial orientation and navigation. Here, we performed a meta-analysis of 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 labelled 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.

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, p 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 neighbouring posterior cingulate areas 23 and 31; Brodmann 2006, p 123), more recently, this tiny region has been ascribed important functions involving emotion processing (Maddock 1999) and episodic memory (Spreng, Mar, and Kim 2009), with substantial literature reporting its critical role in spatial orientation and navigation (Maguire 2001; Epstein et al. 2017; Vann, Aggleton, and Maguire 2009; Aguirre and D'Esposito 1999).

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 and colleagues (Vogt et al. 2001; Figure 3.1C) 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 labelled as 'retrosplenial cortex' lying in the posterior cingulate cortex (Vogt, Absher, and Bush 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; Vogt, Vogt, and Laureys 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 3.1A), 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 3.1; Fatterpekar et al. 2002; Morris, Paxinos, and Petrides 2000; Vogt et al. 2001).

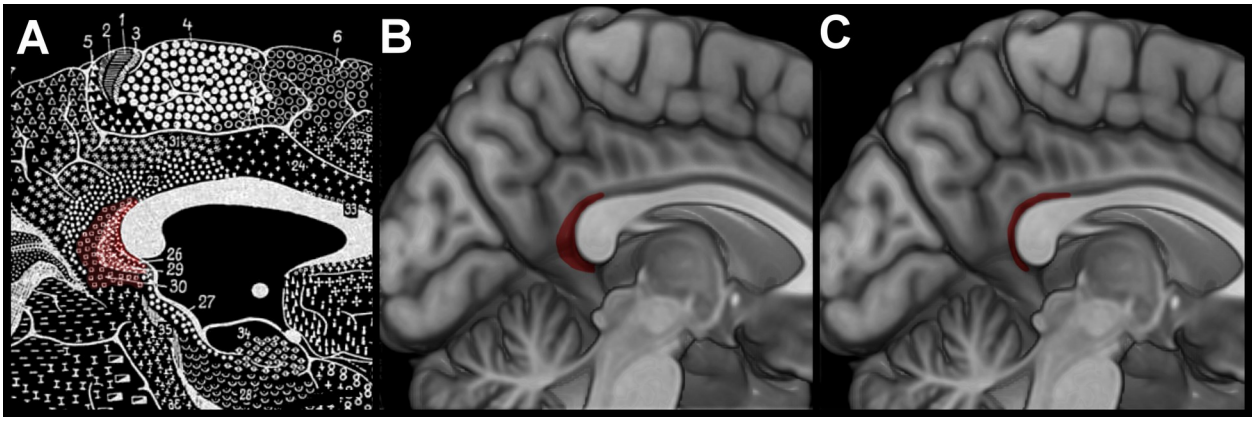

Figure 3.1. Brodmann's original depiction of the retrosplenial cortex (A), which was intentionally overrepresented (Brodmann 2006). More modern illustrations based off the work by Morris and colleagues (R. Morris, Paxinos, & Petrides, 2000), and Vogt and colleagues (Vogt et al., 2001) in panels B and C, respectively, depict a substantially humbler region. Brodmann's figures, originally published in 1910, are in the public domain.

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; Silson, Steel, and Baker 2016; Marchette et al. 2014). 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. 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, Slone, and Iaria 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 neighbouring cortex supporting the processes of encoding and recalling spatial information.

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 (i.e. this was not intended to be as rigorous as a systematic review), but rather generate a sample that is adequately representative of the state of the cognitive neuroscience literature investigating human spatial orientation and navigation. Due

to the lack of direct health-related outcomes of this meta-analysis we chose not to pre-register with PROSPERO.

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, Kamba, and Ogawa 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 and colleagues (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 (Aguirre, Detre, Alsop, & D'Esposito, 1996).

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 and colleagues (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 and colleagues (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 3.1[4]). 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, Lindquist, and Kaplan 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 them into NeuroElf (neuroelf.net/) 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

4 These data available online at https://doi.org/10.3389/fnhum.2018.00190

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* versus *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 Five thousand 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 $p < .001$.

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 versus *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 (Glasser et al. 2013; Van Essen et al. 2012). We performed additional preprocessing on our resting state data using the CONN toolbox (v17.f; nitrc.org/projects/conn), modelling 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 $p_{fdr} < .001$. 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 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 3.2A 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 and colleagues (Vogt et al., 2001).

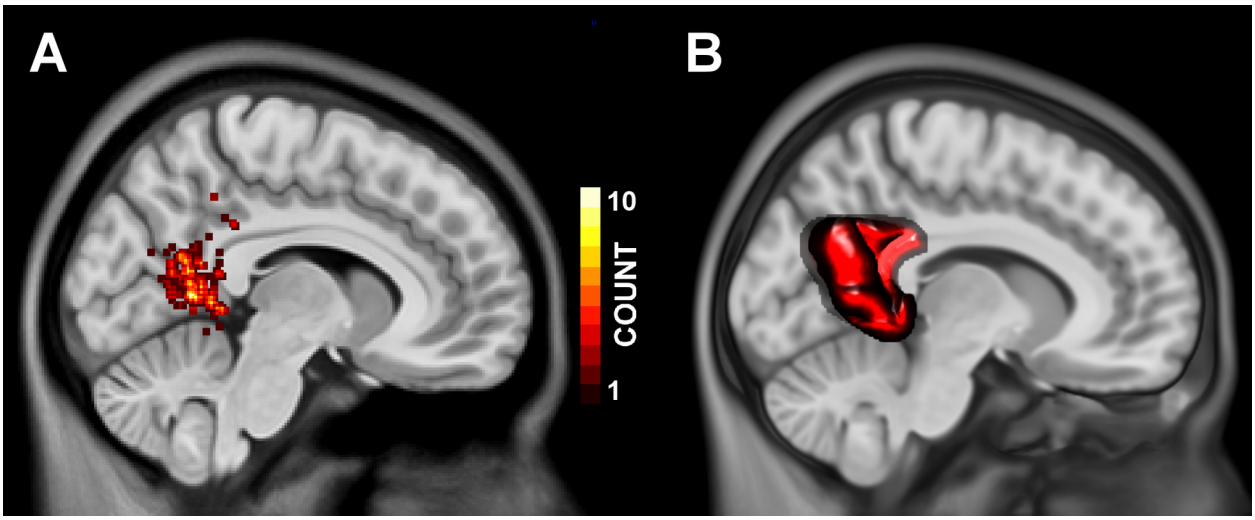

Figure 3.2. Panel A depicts the frequency at which a coordinate label included 'Retrosplenial Cortex' appeared within 2 mm of any given MNI Y, Z position, projected onto an MNI standard brain at x = 8 mm. Panel B depicts the volume of interest generated to encompass the brain tissue commonly referred to as 'retrosplenial cortex' in the spatial cognition literature.

Multilevel Kernel Density Analysis

We performed an MKDA to identify regions within the retrosplenial cortex and posterior cingulate (Figure 3.2B) 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 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 3.3, the MKDA with a threshold of $p < .001$ 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, Slone, and Iaria 2017). A conjunction analysis did not detect any voxels engaged in both *spatial encoding* and *spatial recall* (peak $t_{14} = 3.719$, $p = .002062$ at MNI -14, -60, 14).

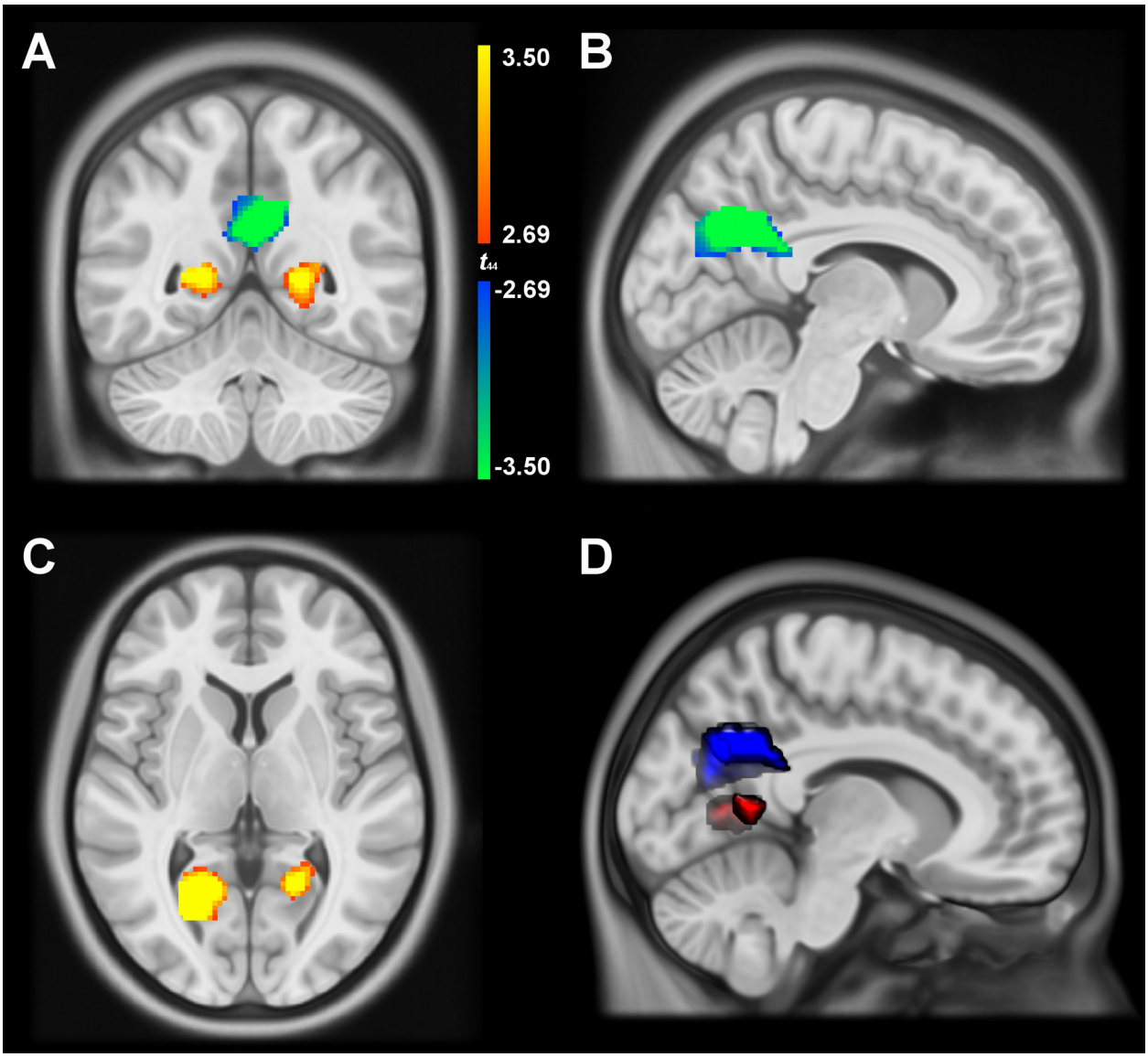

Figure 3.3. MKDA results depicting regions more likely to be activated by spatial encoding (red/yellow) and spatial recall (blue/green). Panels A-C are displayed at MNI 8, -53, 5, colour range bounds represent uncorrected thresholds of $p < .01$ at $t_{44} = 2.69$ and $p < .001$ at $t_{44} = 3.50$ in an 8385-voxel region of interest (Figure 3.2B). Panel D displays a volumetric depiction of the significant clusters at $p < .001$.

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 Supplemental Table 2. Across the 132 brain regions tested, the ventro-lateral and dorso-medial posterior cingulate seeds displayed significantly ($p_{fdr} < .001$) 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 functionally connected to the posterior cingulate, as well as the frontal pole and dorsomedial prefrontal cortex (see Figure 3.4).

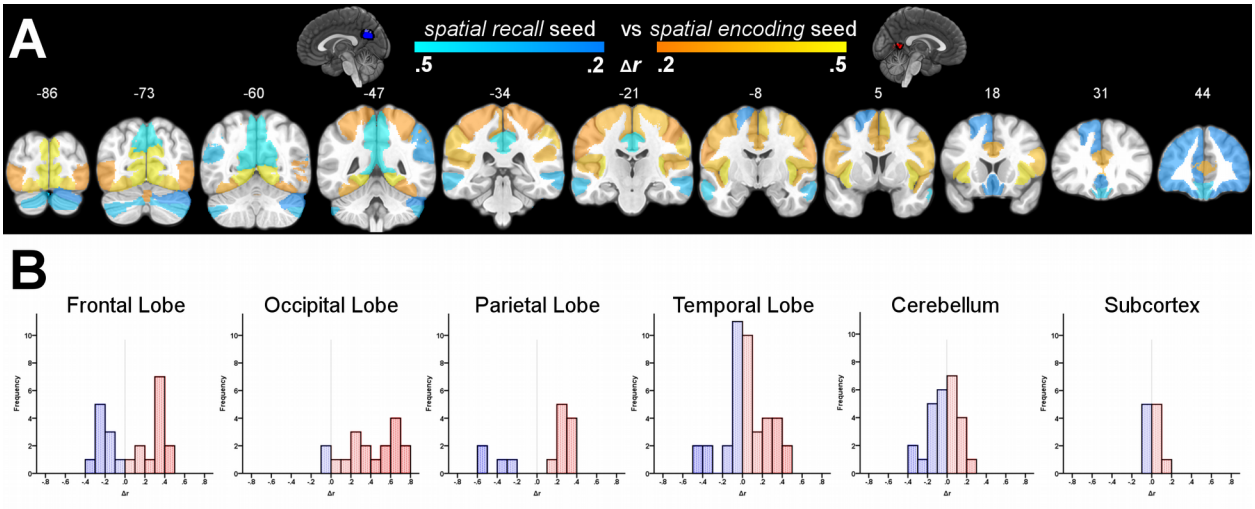

Figure 3.4. Panel A depicts the difference in functional connectivity between the ventro-lateral posterior cingulate seeds more associated with spatial encoding, and the dorso-medial posterior

cingulate seed more associated with spatial recall. Highlighted regions display significantly different functional connectivity profiles at $p_{fdr} < .001$. $N = 38$. 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.

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 labelled '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 labelled '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 labelled 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 (Burles, Slone, and Iaria 2017; Bzdok et al. 2015; Hagmann et al. 2008; Vogt, Vogt, and Laureys 2006; Zhang and Li 2012; Silson, Steel, and Baker 2016), 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 centred 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 as relatively more involved in bottom-up or lower level perceptual processing and passive updating. In contrast, the *spatial recall* seed was centred 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 (Addis et al. 2009; Cavanna

and Trimble 2006; Maddock, Garrett, and Buonocore 2001; Okuda et al. 2003; Ridderinkhof 2004; Wagner et al. 2005).

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 and colleagues (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. 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 and colleagues (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.

Conclusion

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 homogeneous.

Chapter Four: The Role Of The Posterior Cingulate In Developmental Topographical Disorientation

Introduction

Orienting and navigating throughout familiar environments often seems like a task that can be performed with little conscious effort. Superficially, the ease of performing these tasks would obscure the fact that topographical orientation is an exceedingly complex skill that relies on the proper functioning of a wide variety of cognitive processes, including perception, attention, mental imagery, memory, and decision-making (Berthoz & Viaud-Delmon, 1999; Burgess, 2006; Burgess et al., 2001; Corbetta, Kincade, & Shulman, 2002; Lepsien & Nobre, 2006). Paralleling this cognitive complexity, a wide variety of brain regions have been implicated in topographical orientation, and damage or lesions to any of these brain regions can result in impairments in spatial orientation and navigation, a disorder referred to as acquired topographical disorientation (Aguirre & D'Esposito, 1999). These impairments can result from lesions to the lingual and posterior parahippocampal cortex, which produces an inability to recognize familiar places (Epstein, 2008). Lesions to the hippocampal complex can produce inabilities to form and use, cognitive maps, *i.e.* detailed mental representations of the environment (Iaria et al., 2017; Maguire, Nannery, & Spiers, 2006), and lesions to the retrosplenial cortex and posterior cingulate can produce an inability to derive directional information from landmarks (Maeshima et al., 2001; Maguire, 2001; Takahashi et al., 1997). However, lifelong impairments in the ability to orient and navigate in one's surroundings have also been reported in the absence of brain damage or lesions. This recently-discovered condition is termed Developmental Topographical Disorientation (DTD) and is characterized by i) getting

lost in familiar surroundings, such as one's neighbourhood or place of work, ii) this issue presenting since childhood or adolescence, with iii) no brain damage, malformation, or head injury, and iv) no other cognitive or neurological complaints (Iaria & Barton, 2010).

Iaria and colleagues reported the first case of developmental topographical disorientation less than a decade ago (Iaria et al., 2009). Pt1 was a middle-aged woman, who reported getting lost in very familiar environments since approximately six years of age. As a teenager, she relied on her friends to accompany her if she left her house, and as an adult made use of very stereotyped and inflexible routes to travel to and from her place of work. Pt1 reported no other cognitive or neurological complains beyond her navigational difficulties, which Iaria and colleagues confirmed with a normal result on a comprehensive neuropsychological battery and neuroradiological assessment. Further testing revealed that Pt1 was able to utilize a verbal strategy to follow short, newly-learned routes with distinct landmarks and use a map to plan and execute short paths, but struggled to form and use a more flexible cognitive map of her environment. When performing a spatial task that requires the formation and subsequent use of a cognitive map while undergoing functional magnetic resonance imaging (fMRI), activity in the hippocampus and posterior cingulate was readily detectable in controls and Pt1 during the retrieval phases[5], but during the formation phase this activity was conspicuously absent in Pt1, while remaining present in controls. These findings of no apparent structural alterations (Bianchini et al., 2010) but perturbed functioning of regions of the navigational network,

5 Despite similar hippocampal activation magnitudes, the activity detected in Pt1 was located in the anterior hippocampus, whereas the activity detected in controls was located more posteriorally. Similarly, the right retrosplenial complex activity was also located more ventrally compared to the activity seen in controls (Iaria, Chen, Guariglia, Ptito, & Petrides, 2007).

particularly the posterior cingulate and/or the retrosplenial complex, have been consistently implicated in the handful of subsequent neuroimaging investigations of DTD.

Palermo and colleagues (2014) reported an additional and similar case of DTD; L.A. was a middle-aged male who has been getting lost in familiar environments since he was 13 years old. Like Pt1, there were no additional cognitive issues nor structural brain abnormalities detected from an extensive neuropsychological battery and neuroradiological assessment (Palermo et al., 2014). The authors utilized fMRI to assess the activity evoked while L.A. performed a landmark sequencing task, in which he was required to identify if a series of landmarks, presented visually, were sequenced along a coherent path in a familiar environment. In this task, control subjects generally display robust retrosplenial and posterior cingulate activity (Nemmi et al., 2013). Not only was L.A.'s performance on this task notably poorer than controls, he also displayed no significant increase in posterior cingulate activity while performing the task, a result replicated in an additional case of DTD (Nemmi et al., 2015). Likewise, in their case study of DTD, Kim and colleagues reported altered functional connectivity profiles of the retrosplenial complex despite largely typical structural connectivity of this region (J. G. Kim et al., 2015). In an additional case of DTD, Conson and colleagues identified widespread perturbations of resting-state functional connectivity of the posterior cingulate, among other regions, again with no notable structural abnormalities present (Conson et al., 2018).

These case studies, as a whole, implicate the posterior cingulate as a likely structure responsible for the deficits seen in DTD. Considering the lack of gross structural abnormalities present, DTD may very well be a disorder best characterized by altered functioning of a brain network, of which the posterior cingulate cortex is an important hub (Conson et al., 2018;

Ekstrom et al., 2014; J. G. Kim et al., 2015). Our previous work investigating the functional network connectivity in a group of nine DTD participants failed to identify any involvement of the retrosplenial cortex, instead identifying a decrease in functional connectivity between the right hippocampus and prefrontal cortex as the most notable alteration of functional connectivity in regions known to be involved in spatial orientation and navigation (Iaria et al., 2014). However, this analysis utilized an anatomical demarcation of the retrosplenial cortex, which as we have identified in Chapter Three, is largely exclusive of the scene-sensitive region of the posterior cingulate known to be involved in spatial orientation and navigation, despite this being commonly referred to as the retrosplenial cortex[6] (Burles et al., 2018). In this meta-analysis, we additionally refined our understanding of the role of the posterior cingulate, identifying disparate engagement and connectivity of the more ventral and dorsal portions of this region. This provided important and novel evidence for a functional specialization of the posterior cingulate, with ventral regions relatively more involved in bottom-up spatial processing and demands to encoding spatial information, and dorsal portions relatively more engaged by recalling spatial information or performing spatial computation (Burles et al., 2017, 2018). Indeed, similar refinements of our understanding of many regions involved in spatial orientation have been proposed, including the potential specializations between anterior and posterior portions of the parahippocampal place area (Baldassano et al., 2013; Epstein, 2008) as well as the hippocampus (Poppenk et al., 2013). Properly modelling and delineating brain connectivity with respect to these subregions my be necessary for detecting more subtle changes present in DTD and other

6 This region is sometimes referred to as the retrosplenial complex (Epstein, 2008), unfortunately this more appropriate term has seen limited adoption. The term ‘medial place area’ has also been proposed by Silson and colleagues (Silson, Steel, & Baker, 2016).

conditions. In the present study, we set out to investigate the role of the retrosplenial complex and posterior cingulate in the largest group study of DTD to date, to not only validate the utility of our recently-identified posterior cingulate delineation, but also attempt to replicate and validate the common claim of functional deviance of the retrosplenial complex and posterior cingulate in DTD.

Methods

Participants

A total of 15 right-handed females with DTD were included in the present study (age range 25 to 64, $M = 43.93$, $SD = 11.84$ years), as well as an age-matched ($t_{28} = 0.632$, $p = .532$) group of 15 right-handed female control participants (Age range 19 to 65, $M = 40.80$, $SD = 15.10$ years). These participants included the nine DTD and nine control participants from Iaria and colleagues' previous group study of DTD (Iaria et al., 2014), as well as three control subjects from our previous work presented in Chapter Two (Burles et al., 2017). All participants reported no psychiatric or neurological disorders and normal or corrected-to-normal vision, and provided written informed consent as approved by the local research ethics board.

MRI acquisition parameters

All participants were scanned using a 3T GE Discovery 750 MRI with an eight-channel head coil. For the 21 participants included from previously published work (Burles et al., 2017; Iaria et al., 2014), eyes-open resting-state functional scans were collected using a T_2*-weighted EPI sequence (2.5 s TR, 30 ms TE, 77° flip angle, 3.75 × 3.75 × 3 mm voxels, bottom-up

interleaved acquisition, 240 volumes for all but three DTD participants and one control participant with only 120 volumes, 24.0 cm FOV, 45 slices), while participants viewed a black fixation cross on a grey background. High-resolution anatomical images were acquired using a T_1-weighted SPGR sequence (Minimum Full TE, 11° flip angle, 1 mm isotropic voxels, 25.6 cm FOV). For the remaining nine participants, eyes-open resting-state functional scans were collected using a T_2*-weighted EPI sequence (2.6 s TR, 29 ms TE, 90° flip angle, 1.75 × 1.75 × 3 mm voxels, bottom-up interleaved acquisition, 236 volumes in one DTD participant and 272 volumes in the remainder, 22.4 cm FOV, 44 slices, ASSET factor 2), while participants viewed a black fixation cross on a grey background. High-resolution anatomical images were acquired using a T_1-weighted fast SPGR sequence (Minimum Full TE, 10° flip angle, 1 mm isotropic voxels, 25.6 cm FOV, ARC factor 2).

MRI data preprocessing

We primarily used SPM12 (v7219, Wellcome Trust Centre for Neuroimaging; fil.ion.ucl.ac.uk/spm/) to preprocess MRI data. We first repositioned participants' anatomical data such that the anterior commissure and posterior commissure were both located along the x = 0 mm and z = 0 mm planes, with y = 0 mm located at the anterior commissure, and the medial longitudinal fissure largely along x = 0 mm. The transform required to reorient participants' anatomical scans were then applied to their functional data. Functional data were then realigned to the mean functional image for each participant, using a two-pass procedure. From this procedure, we calculated 24 realignment parameters, representing the translations and rotations, their first temporal derivatives, and the square of each of these values. These

parameters were then z-scored, and compressed using a principal components analysis, retaining the fewest orthogonal components that explained 99% of the variance present in the original 24 parameters. Using the mean functional image, functional data were then coregistered to the anatomical image for each participant, and the anatomical data were segmented and used to generate deformations to move all data into standardized Montreal Neurological Institute (MNI) space. During normalization, we resampled all functional data to 2mm isotropic voxels, and smoothed the functional data with a 6 mm full with at half-maximum Gaussian kernel. Data were then imported into the CONN toolbox (18.a; nitrc.org/projects/conn) for additional preprocessing, including regressing out signal associated with the compressed realignment parameters, as well as regressing the first five principal components from signal both from white matter and cerebrospinal fluid from that in gray matter (aCompCor; Behzadi, Restom, Liau, & Liu, 2007), as well as temporally bandpass filtering between 0.008 and 0.09 Hz.

Regions of interest

For the reasons outlined in the introduction, we identified the posterior cingulate (including the retrosplenial complex) as well as the hippocampus, as primary regions of interest for the present analysis. Additionally, we included the parahippocampus and lingual gyrus, as these regions are associated with scene-sensitivity and forming spatial memories (Aguirre & D'Esposito, 1999; Epstein, 2008), and the caudate nucleus due to it's involvement in route learning (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Maguire, Burgess, et al., 1998).

The posterior cingulate region of interest, depicted in Figure 4.1B, included dorsal and ventral portions, created by inclusively masking the region outlined in Figure 2.1 with the

thresholded ($|t| > 1.5$) results of the multilevel kernel density analysis (MKDA) detailed in Chapter Three. The hippocampal regions of interest were generated by splitting the hippocampal masks from the FSL Harvard-Oxford atlas into anterior (MNI y ≥ -21 mm) and posterior (MNI y < -21 mm) sections (Poppenk et al., 2013). For the anterior and posterior parahippocampus, as well as the lingual gyrus and caudate nucleus, the delineations from the FSL Harvard-Oxford atlas were utilized. These regions, excluding the caudate nucleus, are depicted in Figure 4.1A. These 16 regions of interest were then utilized as seed regions in our whole-brain seed-to-voxel resting state functional connectivity analysis.

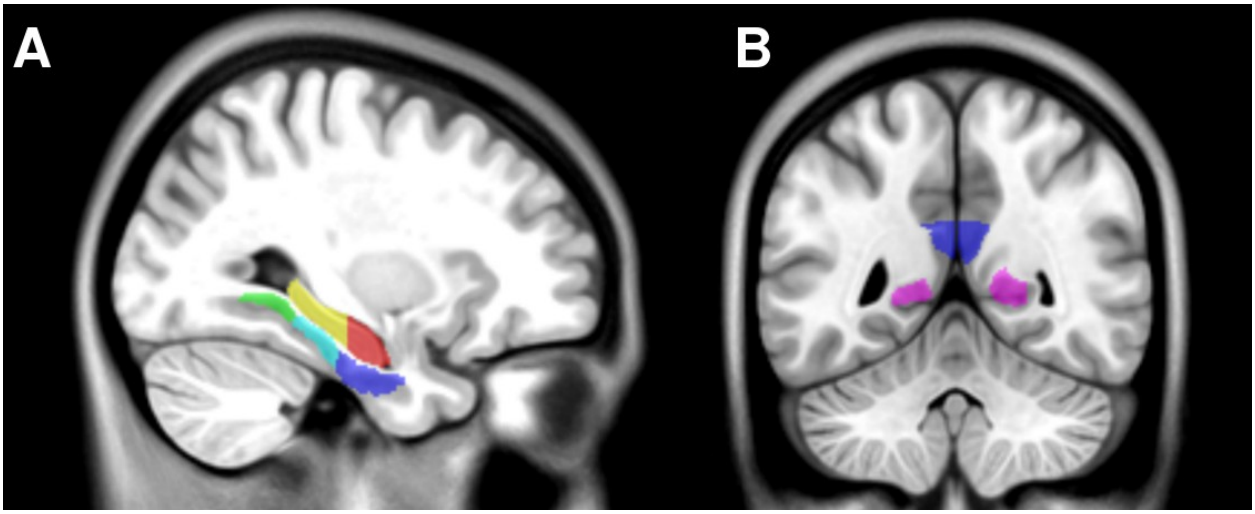

Figure 4.1. A subset of the regions of interest used for the seed-to-voxel resting-state functional connectivity analysis. Panel A, at MNI x = 30 mm, depicts the anterior (red) and posterior (yellow) portions of the hippocampus, as well as the anterior (blue) and posterior (teal) portions of the parahippocampal gyrus. The lingual gyrus (green) extends significantly further into the occipital lobe than depicted in the figure. Panel B, at MNI y = -51 mm depicts the dorsal (blue) and ventral (violet) portions of the posterior cingulate.

MRI data analysis

In CONN, for each seed region of interest, the mean timeseries was computed from unsmoothed preprocessed data, and the temporal correlation coefficients between the 16 seed regions and each voxel of the smoothed preprocessed data were computed. For these analyses the Fisher-transformed correlation coefficient values used for comparison, and the reverse transform was applied to return connectivity coefficients to any reported *r* values for interpretability. Our primary analysis of interest was contrasting the resting state functional connectivity profiles of individuals with DTD from controls. In these analyses, age was included as a covariate, as well as a 'scanner parameter' factor, to account for any alteration in functional connectivity that may be attributable to the large differences in the MRI protocol between subjects. Analyses were performed with a one-tailed voxel level thresholding at $p < .001$ uncorrected, as well as parametric cluster extent thresholding at $p_{fdr} < .05$, as implemented in CONN.

Results

The investigation of the resting-state functional connectivity profiles of individuals with DTD revealed a notable decrease in the connectivity between many brain regions known to be involved in spatial orientation and navigation. Control participants displayed relatively greater resting state functional connectivity between the right ventral posterior cingulate as well as the dorsal posterior cingulate seeds and a cluster split between the right thalamus and posterior hippocampus (mean Δr: right ventral = .22, right dorsal = .21, left dorsal = .20). While the peaks of these clusters lie in the thalamus, the analysis with the right posterior hippocampus as a seed also revealed decreased functional connectivity with the right dorsal posterior cingulate (mean

Δr = .18). The left posterior hippocampus, on the other hand, displayed relatively greater functional connectivity with the middle frontal gyrus (mean Δr = .21), a region implicated in spatial memory, among other functions (Leung, Gore, & Goldman-Rakic, 2002). Interestingly, control participants also exhibited greater functional connectivity between the left dorsal posterior cingulate seed and the cerebellar vermis (mean Δr = .18), with a similar increase in functional connectivity seed with the posterior parahippocampal gyri as seeds (mean Δr: right = .17, left = .17). The left posterior parahippocampal gyrus seed also displayed a significantly greater level of functional connectivity with a cluster located in the right posterior internal capsule (mean Δr = .17), a white matter structure, but this cluster extended somewhat into the dorsal thalamus.

Individuals with DTD, however, exhibited greater levels of functional connectivity from the right dorsal posterior cingulate seed and a cluster located on the posterior portion of the left superior temporal sulcus and middle temporal gyrus (mean Δr = .26). In these individuals, the left dorsal posterior cingulate seed displayed greater functional connectivity to the left anterior insula (mean Δr = .20). Additionally, in individuals with DTD the right anterior hippocampus displayed significantly greater levels of functional connectivity with clusters located the posterior superior temporal sulcus (mean Δr = .18), the dorsal portions of the right frontal-parietal operculum (mean Δr = .17), as well as a cluster located approximately at cerebellar lobule VIIb (mean Δr = .17). No other seed region displayed significantly different patterns of functional connectivity. Tabular results are detailed in Table 4.1 and a simplified network schematic is depicted in Figure 4.2.

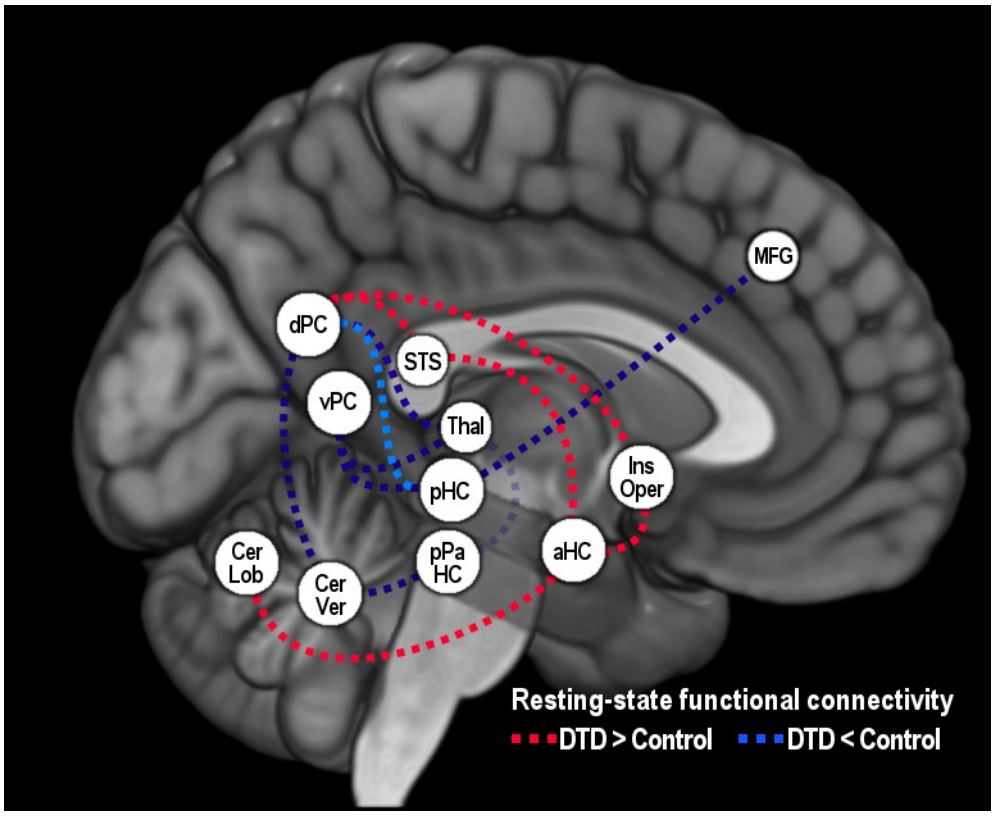

Figure 4.2. A schematic representation of the differences in resting-state functional connectivity between individuals with DTD and controls. MFG: middle frontal gyrus, dPC: dorsal posterior cingulate, vPC: ventral posterior cingulate, STS: superior temporal sulcus, Thal: thalamus, Ins: Insula, Oper: Operculum, pHC: posterior hippocampus, aHC: anterior hippocampus, pPaHC: posterior parahippocampal cortex, CerVer: cerebellar vermis, CerLob: cerebellar lobule.

Table 4.1. Significant differences in seed-to-voxel resting-state functional connectivity metrics between individuals with DTD and controls. N = 30, one tailed voxel height p < .001, cluster extent $p_{fdr} < .05$.

		Cluster		Peak			
Direction	Region Labels	K_E	p_{fdr}	x	y	z	*p*
R Ventral Posterior Cingulate seed							
Control > DTD	Thalamus / Posterior Hippocampus	64	.0170	20	-26	-2	< .0001
R Dorsal Posterior Cingulate seed							
Control > DTD	Thalamus / Posterior Hippocampus	86	.0091	22	-26	-2	< .0001
DTD > Control	Posterior Superior Temporal Sulcus	71	.0219	-60	-52	6	.0001
L Dorsal Posterior Cingulate seed							
Control > DTD	Cerebellar Vermis	112	.0018	6	-62	-32	< .0001
Control > DTD	Thalamus / Posterior Hippocampus	67	.0130	22	-28	-2	< .0001
DTD > Control	Anterior Insula	61	.0387	-28	22	-10	< .0001
R Anterior Hippocampus seed							
DTD > Control	Cerebellar Lobule	71	.0218	18	-76	-40	< .0001
DTD > Control	Frontal-Parietal Operculum	65	.0218	38	8	24	< .0001
DTD > Control	Posterior Middle Temporal Gyrus	52	.0359	-54	-48	-4	< .0001
R Posterior Hippocampus seed							
Control > DTD	Dorsal Posterior Cingulate	86	.0139	12	-48	30	< .0001
L Posterior Hippocampus seed							
Control > DTD	Middle Frontal Gyrus	67	.0361	44	32	44	< .0001
R Posterior Parahippocampus seed							
Control > DTD	Cerebellar Vermis	56	.0444	-2	-56	-30	.0001
L Posterior Parahippocampus seed							
Control > DTD	Cerebellar Vermis	194	< .0001	0	-56	-28	< .0001
Control > DTD	Posterior Internal Capsule / Thal.	81	.0058	26	-22	18	< .0001

Discussion

In the present study, we have investigated the resting-state functional connectivity profiles of a variety of brain regions involved in spatial orientation and navigation in individuals with DTD. Most notably, individuals with DTD displayed significantly lower levels of functional connectivity between dorsal posterior cingulate and the right posterior hippocampus. These regions have both been associated with recalling spatial information, the posterior cingulate purportedly translating between the egocentric viewpoint and a mental representation of space (Byrne et al., 2007); the mental representation traditionally presumed to be supported by the hippocampus (O'Keefe & Nadel, 1978). While not conclusive, previous research has suggested the recall of spatial information is relatively more likely to involve posterior portions of the hippocampus (H. Kim, 2015; Sheldon & Levine, 2018), with some studies specifically implicating the right hippocampus (Bohbot et al., 1998; Iaria et al., 2007; Kühn & Gallinat, 2014; Smith & Milner, 1981). Iaria and colleagues (Iaria et al., 2007) in particular identified relatively distinct activity within the ventral posterior cingulate, left anterior hippocampus, and right middle temporal gyrus, among other regions, engaged when forming a cognitive map; whereas the dorsal posterior cingulate and right posterior hippocampus active when making use of a previously-learned cognitive map, and the cerebellar vermis implicated in both cases. When recording the activity evoked in the same task in an individual with DTD (i.e. Pt1; Iaria et al., 2009), they identified no significant activity in the posterior cingulate, hippocampus, or cerebellar vermis, instead finding increased activity in regions including the superior temporal sulcus, insula, operculum, and cerebellar lobules while attempting to form a cognitive map, with activity in relatively more anterior hippocampal regions when attempting to recall this cognitive

map. Our functional connectivity results largely parallel these findings, with the spatial recall / cognitive-map-use regions poorly integrated in individuals with DTD, and an alternative network of the posterior superior temporal sulcus and middle temporal gyrus, insula and operculum, cerebellar lobules, and the anterior hippocampus potentially supporting a compensatory network attempting to perform these tasks.

The cerebellum has traditionally been associated with coordination of motor processes (Houk, Buckingham, & Barto, 1996), but there is mounting evidence that it plays a significant role in non-motor processes as well (Rapoport, van Reekum, & Mayberg, 2000; Timmann et al., 2010). Indeed, cerebellar lesions can produce a dizzying array of deficits, including impairments in paired associate learning, planning, language processing, visuo-spatial processing, and emotion regulation (Schmahmann & Sherman, 1998). It's wide-reaching effects less surprising once one considers the cerebellum contains the majority of neurons in the brain (despite accounting for only 10% of total brain mass) and has structural connections, primarily via the thalamus, to a wide variety of cortical sites (c.i. Rapoport, van Reekum, & Mayberg, 2000). In the present study of DTD, we identified generally decreased connectivity of the cerebellar vermis (i.e. a midline structure) with the posterior parahippocampal and dorsal posterior cingulate, but an increase in connectivity between right ventral cerebellar lobule VIIb and the right anterior hippocampus. The cerebellar vermis in particular is associated with transforming head-centred vestibular information into self-motion and spatial orientation signals (Yakusheva et al., 2007), important information for generating and maintaining a coherent head-direction signal (Rochefort, Lefort, & Rondi-Reig, 2013). This missing connection likely associated with this directional instability in individuals with DTD, as they struggle with indicating the direction to

unseen landmarks. Some individuals with DTD also report frequent reorientation illusions, i.e. a distinct sense that the direction towards unseen landmarks (e.g. the direction to their parked car or a bathroom), has shifted, often by increments of 90 degrees. This same type of phenomenon can occur in otherwise healthy individuals in situations such as exiting a subway station in an unfamiliar city and experiencing a spontaneous reorientation, suddenly realizing that you struck off in an incorrect direction.

When coping with these navigational difficulties, individuals with DTD often rely heavily on route-based strategies, memorizing a series of action-landmark pairings to permit successful navigation despite the lack of a sense of direction (Bianchini et al., 2010; Iaria et al., 2009; Nemmi et al., 2015). Interestingly, the brain region commonly associated with performing route-based navigation, the caudate nucleus (Dahmani & Bohbot, 2015; Iaria et al., 2003), displayed no significant differences in connectivity. While individuals with DTD may rely more heavily on caudate-dependant navigational strategies, they often utilize explicit verbal strategies and sequences to help represent and maintain route information to navigate successfully (for an example, see Coomber, 2013). Supporting this behavioural compensatory strategy, the increases in functional connectivity detected in DTD correspond to a set of regions implicated in verbal working memory (i.e. cerebellar lobule VIIb; S. H. A. Chen & Desmond, 2005a, 2005b), refreshing contents of a phonological loop (i.e. frontal operculum[7]; Paulesu, Frith, & Frackowiak, 1993), and processing information on word or action order (i.e. the superior temporal sulcus; Redcay, 2008). This verbal network more strongly linked with the hippocampus in DTD is likely supporting the increased demand to encode verbal action-related sequences as a proxy or replacement for directly encoding spatial information or sequences.

7 This region includes Broca's area

Notably, our novel ventral – dorsal subdivision of the posterior cingulate was very important for detecting some of the present results, as the connectivity profile of the dorsal posterior cingulate seed was particularly sensitive to differences between DTD and controls. This region is not characterized by functional localizers like those utilized by Kim and colleagues (J. G. Kim et al., 2015), nor does it correspond well with commonly-used default mode network posterior cingulate seeds, which are located more dorsally (Conson et al., 2018). Furthermore, the ventral posterior cingulate to posterior hippocampus functional connectivity levels seen in DTD is no worse than is seen in otherwise healthy but poor navigators. Sulpizio and colleagues compared the functional connectivity of the retrosplenial complex, hippocampus, and parahippocampal place area between groups based on their self-reported level of spatial ability (Sulpizio, Boccia, Guariglia, & Galati, 2016). Poor navigators showed generally lower functional connectivity between the retrosplenial complex (equivalent to our ventral posterior cingulate seed) and posterior hippocampus; this effect observed bilaterally in males, but restricted to the right hemisphere in females. Interestingly, the functional connectivity levels are similar to that seen in the present study, their good and poor female navigators with right posterior hippocampus – right retrosplenial complex connectivity rs ≈ .24 and .15, respectively; our control and DTD groups with right posterior hippocampus – right ventral posterior cingulate connectivity rs ≈ .23 and .13, respectively. While it is possible that Sulpizio and colleagues' sample included individuals with DTD, the 'poor navigators' group was defined based on a sample-based median-split of self-reported sense of direction, making this group representative of the lower half of the population's normal distribution of spatial skills.

In conclusion, we have identified a network of poorly-integrated brain regions associated with DTD, most notably including the right posterior hippocampus, dorsal posterior cingulate, and the cerebellar vermis. These changes were found alongside notable increases in connectivity, including the anterior hippocampus, frontal operculum and insula, and superior temporal sulcus, which may be supporting the verbal compensatory behaviours often employed by these individuals. Future work will need to characterize the functional connectivity patterns of the dorsal posterior cingulate in healthy but poor navigators to determine which portions of the presently reported connectivity differences are unique to DTD, and if these results are common between females and males with DTD. The dorsal and ventral subdivisions of the posterior cingulate identified in Chapter Three clearly demonstrated their utility and will likely provide similar usefulness in other neuroimaging studies of spatial orientation and navigation.

Chapter Five: The Retrosplenial Cortex By Any Other Name

Summary of findings

Human spatial orientation and navigation is a complex behaviour involving many cognitive processes and supported by numerous brain regions (Ekstrom, Huffman, & Starrett, 2017). Of these regions, the hippocampus is the most prototypical, and is believed to be responsible for the 'cognitive map', i.e. a mental representation of the locations and relationships between landmarks in the environment. However, the retrosplenial cortex is one of the most commonly-implicated brain regions in fMRI studies of human spatial orientation and navigation (Maguire, 2001; Vann et al., 2009). Like many brain areas, there is some disagreement on the extent of the anatomically-defined retrosplenial cortex (See Figure 3.1), but the manner in which the 'retrosplenial cortex' label is used in the human spatial orientation literature frequently exceeds even the most liberal anatomical delineation (See Figure 3.2). This diffusion of the retrosplenial cortex across the posterior cingulate is not limited the spatial orientation literature; similar inspecificity in the emotion processing literature had prompted a rather scathing critique from anatomist Brent Vogt and colleagues, who stated: "The human retrosplenial cortex is in the callosal sulcus where Brodmann identified it in 1909, but *nothing* is known about its function" (emphasis mine; Vogt, Absher, & Bush, 2000). Vogt and colleagues indicating that the overwhelming majority of processes attributed to the human retrosplenial cortex are actually being performed by the posterior cingulate. Some attempts have been made to popularize more appropriate labels for this region; Epstein and colleagues generally refer to the scene-sensitive portion of the posterior cingulate as 'retrosplenial complex' and Silson and colleagues have proposed referring to this region as the 'medial place area' (Epstein, 2008; Silson et al., 2016).

While these labels provide a more appropriate alternative, they were not intended to characterize the entirety of the posterior cingulate involvement in spatial orientation and navigation. This has resulted in a large and anatomically heterogeneous chunk of the posterior cingulate cortex implicated in a wide variety of spatial tasks, with a relatively low degree of care taken to distinguish and differentiate the particular location of activity evoked by spatial tasks in this region.

In Chapter Two, we provided initial evidence for a ventral – dorsal functional specialization within this navigationally-relevant portion of the posterior cingulate. Participants in this study performed the spatial configuration task, in which they are tasked with learning the locations of five objects in a simple virtual environment explored via passive movement. Importantly, these objects are generally viewed in pairs, requiring participants to build a mental representation of the object locations by combining spatial information gathered across multiple viewpoints. During the task, there are distinct phases of *spatial updating*, in which participants encode object locations and self-motion information into their mental representation of the environment, and *spatial orienting,* in which participants are required to recall the positions of unseen objects to accurately localize themselves in the environment. When contrasting the evoked BOLD activity between these conditions, we identified that ventral portions of the posterior cingulate were relatively more engaged in *spatial updating*, whereas dorsal portions were move involved in *spatial orienting*, and that these identified regions displayed very disparate resting-state functional connectivity profiles.

In Chapter Three, we searched for additional evidence of a ventral – dorsal functional specialization in the posterior cingulate by performing a meta-analysis across the human spatial

orientation literature. From this literature, we attempted to classify neuroimaging contrasts as either *spatial encoding* or *spatial recall*, which were meant to be more general classifications inductively generated from the *spatial updating* and *spatial orienting* paradigm from Chapter Two. The *spatial encoding* category was characterized by bottom-up or stimulus-driven activity in which there was no explicit demand to localize oneself in the environment or recall any previously-learned spatial information. This category included the functional localizers commonly used to identify the parahippocampal place area or retrosplenial complex, in which participants passively view scenes (Epstein, Parker, & Feiler, 2007; Silson et al., 2016). In contrast, the *spatial recall* category included contrasts in which participants were required to recall spatial information about previously-learned environments, perform spatial computations (e.g. estimating distances between landmarks in your hometown), or perform active goal-directed navigation, as well as parametric contrasts that assess environmental knowledge (e.g. parametric distance-to-goal contrasts). Contrasting the activity associated with each of these conditions revealed an extremely similar pattern to that seen in Chapter Two, with ventral portions of the posterior cingulate associated with *spatial updating*, and dorsal portions more associated with *spatial orienting*. This result indicating that the ventral – dorsal specialization proposed in Chapter Two is represented in the human spatial orientation literature more generally, and reinforces the importance of appreciating the significantly different roles that these portions of the medial parietal cortex in spatial orientation and navigation.

In Chapter Four, I utilized these novel posterior cingulate subregions to investigate the neural correlates of developmental topographical disorientation (DTD), a disorder characterized by symptoms that are commonly seen in individuals with lesions to the retrosplenial cortex and

posterior cingulate (J. G. Kim et al., 2015). However, individuals with DTD have no brain damage or lesions, and their deficits are presumably associated with perturbed functioning of the retrosplenial cortex and posterior cingulate in absence of any gross structural perturbations. A resting-state functional connectivity analysis revealed the connectivity patterns of the dorsal posterior cingulate as particularly disparate between individuals with DTD and controls. In individuals with DTD, this region displayed relatively lower functional connectivity with the right posterior hippocampus and cerebellar vermis, and relatively greater connectivity to a verbal compensatory network including the posterior superior temporal sulcus, the anterior insula and frontal operculum, and the anterior hippocampus. Importantly, these striking connectivity differences would not have been detected if an anatomical delineation of the retrosplenial cortex or a functionally-defined delineation of the retrosplenial complex was utilized. This strongly supports the conclusion that the delineation identified in Chapter Three can provide valuable insights into the neurological correlates of spatial orientation and navigation.

The map is not the territory

While I generally have been critical of the use of the 'retrosplenial cortex' label in the spatial orientation literature, there is a very understandable set of factors that have precipitated the flexible use of this term. Part of this problem stems from the fact that many of the accurate cytological delineations of the retrosplenial and posterior cingulate cortex (e.g. Vogt et al., 2001, 2006) are not readily available in formats commonly utilized by cognitive neuroscientists (e.g. NIFTI masks in MNI space). The atlases that are available and widely used often do not present a consistent or coherent representation of the extent or location of this region. For instance, the

complete cortical atlases packaged with FSL, a popular neuroimaging analysis software package, include the Harvard-Oxford atlas, the Talairach atlas, and the MNI structural atlas. The MNI structural atlas divides the cortex into nine regions, and is therefore of little use in the present discussion. The Talairach atlas includes a retrosplenial region (i.e. Brodmann areas 29 and 30), however these regions inexplicably extend through the parahippocampal gyrus, lingual gyrus, posterior cingulate, and occipital lobe (as labelled in the atlas). At some axial slices, the retrosplenial cortex has territory beginning from the splenium, reaching to and including both the anterior and posterior portions of the parietal-occipital fissure. The Harvard-Oxford atlas does not include a retrosplenial region, which by Vogt's delineations (See Figure 3.1) is likely the least inaccurate of the bunch. However, in this atlas' delineation the posterior cingulate does not reach the parietal-occipital fissure, and by it's authority I would consider the posterior cingulate delineations in Chapters Two and Three as primarily belonging to the precuneus.

The variance in the borders and labels in these atlases illustrates the very real possibility that three different researchers would label the exact same MNI coordinate as 'retrosplenial cortex', 'posterior cingulate', and 'precuneus', respectively, ignoring the possibly of the difficult-to-interpret but likely more appropriate modern delineations (e.g. 'AICHA area 135'; Joliot et al., 2015). While in many ways, the label that is assigned to an activation peak or cluster does not change it's location, it absolutely changes the manner in which the average scientist would think about and interpret the role these brain regions are playing. The issue becomes most apparent when a finding of e.g. 'viewing of scenes over faces produces BOLD activity in the retrosplenial cortex / posterior cingulate / precuneus' is reinterpreted as 'the retrosplenial cortex / posterior cingulate / precuneus is more sensitive to scenes than faces'. This problematic induction, which

is an easy mistake to make in good faith, may lead to delineating a region of interest for a study of scene perception with either of these *anatomical* delineations as representative of a *functional* delineation. This issue compounded upon if activity in this entire region is averaged, which would result is a potentially overwhelming amount of signal from cortex that is effectively outside of the intended region of interest included in an analysis. In extreme cases, if data were labelled based on one atlas, but regions were delineated from a different atlas (as the reference atlas used for label delineation is often not included in methods sections), this could unintentionally lead to an entirely different chunk of cortex as the subject of investigation.

One way to address this is to avoid the use of anatomical delineations for regions that are defined based on their function, and instead use regions drawn specifically from spheres based on previously-reported peak activity or functional localizers (Poldrack, 2007). However, both of these techniques have very distinct shortcomings. Producing spherical regions of interest about reported peak coordinates assumes that the identified functional region is distributed isotropically about the identified peak[8], and ignores the convolutions present in the cortex that make the 'cortical distance' not equivalent to the euclidean distance in standardized space. Utilizing functional localizers, like those used for identifying scene-sensitive cortex, is a much more appropriate manner to localize regions for subsequent analysis. However, these techniques cannot easily be used to localize regions involved in higher-order or more abstracted processes, as they are by nature, more difficult to distill into a concrete task. While future studies may focus on developing some methodological approach to functionally localizing our *'spatial recall'* dorsal posterior cingulate region, the currently-used functional localizers often do not

8 Although this assumption is undoubtedly incorrect, the inability to effectively communicate activity morphology in a format suitable for publication makes this inevitable.

characterize activity precisely enough to produce objective and consistent delineations. For instance, depictions of scene-sensitive cortex resulting from a typical localizer protocol used by Kim and colleagues, identifies activity spanning the parahippocampal, fusiform, and lingual gyri, making the extent of the parahippocampal place area largely the result of a subjective thresholding judgment (J. G. Kim et al., 2015; for more examples see: Epstein et al., 2007; Silson et al., 2016). This inspecificity and variability is not constrained to neuroimaging of spatial orientation and navigation, and I would make the claim that it is inherent in most if not all neuroimaging studies. The danger lies in treating any map as a true representation of the territory, when it is actually like any other model in that it is an intentionally simplified and therefore inaccurate representation of reality. Much like if I asked you to imagine the 'map of the world', this is prototypically in the form of a Mercator projection, in which space further from the equator is significantly over-represented[9]. Despite the general knowledge of this distortion, it is clear that it permeates our thinking about the form of the world.

The findings presented in this dissertation serve to mitigate and disambiguate the 'distortions' and roles applied to the relatively diffuse region in the medial parietal cortex involved in spatial orientation and navigation. The thinking of the location of this region is largely misrepresented by a 'retrosplenial cortex' label, and this misrepresentation is strongly ingrained in the thinking of the neurological correlates of spatial orientation in the human brain (e.g. Vann et al., 2009).

9 This distortion present in Mercator projections provides an important purpose, allowing straight lines on the map to be followed by maintaining a constant bearing relative to true or magnetic north.

Limitations and future work

The spatial encoding versus spatial recall framework by which we have scrutinized and fragmented the posterior cingulate is one of many viable paradigms that could explain activity in this region. This particular paradigm was primarily borrowed from theories of long-axis specialization in the human hippocampus (Poppenk et al., 2013), and it is very likely that some of the other possible paradigms reviewed by Poppenk or proposed by other researchers would produce valid alernate representations of the specialization within the posterior cingulate (e.g. Ranganath & Ritchey, 2012; Silson et al., 2016). One particular shortcoming of the present delineation is the lack of a strong identity and role ascribed to the intermediate cortex between the ventral and dorsal subdivisions identified in Chapter Three. Despite failing to reach significance, the peak voxel in a conjunctive analysis of *spatial encoding* and *spatial recall* activation maps was located in intermediate cortex; the tempting conclusion to be drawn that this portion of cortex is not only spatially but functionally intermediate, remaining inconclusive. Another distinct possibility – that can be applied to any region thought to handle spatial information – is that the processing performed by this region is not spatial *per se*, but performing a process that is more domain-agnostic, simply applying some algorithm which happens to be commonly applied to spatial information, but also involved in episodic memory and emotional involvement, other processes that commonly produce activity in this region (Maddock, 1999; Vann et al., 2009).

With respect to the investigation of the neural correlates of DTD in Chapter Four, this section was notably lacking a functionally-defined delineation of the parahippocampal place area. Kim and colleagues identified the ‘retrosplenial cortex’ as the primary source of

neurological differences between their individual with DTD and comparable controls, but the parahippocampal place area also exhibited significantly different functional connectivity patterns. While our seed-to-voxel analysis *should* have detected any robust differences in functional connectivity between our posterior cingulate seeds and any other region, inter-individual variability in function localization as well as in template normalization may not have sufficiently concentrated this region to ensure the analysis was sensitive enough to replicate this finding. In our most recent phase of data collection for this project we include a functional scene localizer, but currently do not have sufficient data to generate a valid parahippocampal place area region of interest. Considering the frequent use of these localizers from multiple different labs, it is somewhat surprising that there is no commonly-available probabilistic atlas of the scene-sensitive cortex in the human brain. While using a generalized delineation of scene-sensitive cortex would not be as powerful as making use of individually-delineated functional localizers, it would serve to better characterize the location, extent, and individual variability in scene-sensitive cortex. Much like the present work in the posterior cingulate, similar description and disambiguation of the domain and role of the parahippocampal place area will help ascribe more concrete processes to this brain region.

It is worth noting that a variety of statistical thresholds were utilized across the different analyses presented in this document. The task-based functional analyses were thresholded primarily with voxel-level family-wise error corrections, whereas the resting state ROI-to-ROI functional connectivity analyses utilized false-discovery rate corrections at $p < .001$, and the ROI-to-voxel functional connectivity analyses made use of an uncorrected voxel-extent threshold of $p < .001$, with a false-discovery-rate-corrected extent threshold of $p < .05$. While some the

differences in threshold use are simply due to necessity (there are no voxel-level corrections to be applied in ROI-to-ROI analyses), the remaining differences were intentionally chosen to accomodate the differences in data type and quantity. The task-based functional analyses in Chapter Two had a far more conservative threshold applied primarily due to the relatively large quantity of data collected (over a half-hour of task fMRI data per participant), resulting in very powerful analyses in which we had the luxury of utilizing a conservative statistical threshold to improve the spatial specificity of our results.

General Conclusions

The role of the 'retrosplenial cortex' in human spatial orientation and navigation has been obscured by imprecise and ambiguous localization. In the present study, we present evidence of a more precise paradigm by which we can understand the role of the 'retrosplenial cortex', i.e. the posterior cingulate, in spatial orientation and navigation. From activity in a novel spatial task, as well as the literature more generally, we have identified that ventral portions of the posterior cingulate are relatively more engaged in stimulus-driven processing, or encoding spatial information, whereas dorsal portions are more involved in recalling and computing spatial information or representations. Not simply descriptive, this delineation proved valuable in the investigation of the neural correlates of DTD, in which the dorsal posterior cingulate displayed far greater differences in functional connectivity between individuals with DTD and controls than the ventral posterior cingulate. Other studies will undoubtedly benefit from appreciating these functional subregions in interpreting or analysing activity evoked within the posterior cingulate in spatial orientation tasks. Future work will need to critically analyze this posterior

cingulate delineation from other theoretical perspectives, as well as extend increasingly meticulous attention to the location of activity evoked in the posterior cingulate and other brain regions supporting spatial orientation and navigation in humans.

References

Aggleton, J. P., Saunders, R. C., Wright, N. F., & Vann, S. D. (2014). The origin of projections from the posterior cingulate and retrosplenial cortices to the anterior, medial dorsal and laterodorsal thalamic nuclei of macaque monkeys. *European Journal of Neuroscience*, *39*(1), 107–123. https://doi.org/10.1111/ejn.12389

Aguirre, G. K., & D'Esposito, M. (1999). Topographical disorientation: a synthesis and taxonomy. *Brain*, *122*(9), 1613–1628. https://doi.org/10.1093/brain/122.9.1613

Aguirre, G. K., Detre, J. A., Alsop, D. C., & D'Esposito, M. (1996). The Parahippocampus Subserves Topographical Learning in Man. *Cerebral Cortex*, *6*(6), 823–829. https://doi.org/10.1093/cercor/6.6.823

Aguirre, G. K., Zarahn, E., & D'Esposito, M. (1998). An Area within Human Ventral Cortex Sensitive to "Building" Stimuli: Evidence and Implications, 11.

Alexander, A. S., & Nitz, D. A. (2015). Retrosplenial cortex maps the conjunction of internal and external spaces. *Nature Neuroscience*, *18*(8), 1143–1151. https://doi.org/10.1038/nn.4058

Arnold, A. E. G. F., Burles, F., Krivoruchko, T., Liu, I., Rey, C. D., Levy, R. M., & Iaria, G. (2013). Cognitive mapping in humans and its relationship to other orientation skills. *Experimental Brain Research*, *224*(3), 359–372. https://doi.org/10.1007/s00221-012-3316-0

Auger, S. D., & Maguire, E. A. (2013). Assessing the mechanism of response in the retrosplenial cortex of good and poor navigators. *Cortex*, *49*(10), 2904–2913. https://doi.org/10.1016/j.cortex.2013.08.002

Bahlmann, J., Schubotz, R. I., Mueller, J. L., Koester, D., & Friederici, A. D. (2009). Neural circuits of hierarchical visuo-spatial sequence processing. *Brain Research*, *1298*, 161–170. https://doi.org/10.1016/j.brainres.2009.08.017

Baldassano, C., Beck, D. M., & Fei-Fei, L. (2013). Differential connectivity within the Parahippocampal Place Area. *NeuroImage*, *75*, 228–237. https://doi.org/10.1016/j.neuroimage.2013.02.073

Baldassano, C., Esteva, A., Fei-Fei, L., & Beck, D. M. (2016). Two Distinct Scene-Processing Networks Connecting Vision and Memory. *ENeuro*, *3*(5). https://doi.org/10.1523/ENEURO.0178-16.2016

Barton, J. J., Press, D. Z., Keenan, J. P., & O'connor, M. (2002). Lesions of the fusiform face area impair perception of facial configuration in prosopagnosia. *Neurology*, *58*(1), 71–78.

Bate, S., Adams, A., Bennetts, R., & Line, H. (2017). Developmental prosopagnosia with concurrent topographical difficulties: A case report and virtual reality training programme. *Neuropsychological Rehabilitation*, 1–23. https://doi.org/10.1080/09602011.2017.1409640

Beckmann, M., Johansen-Berg, H., & Rushworth, M. F. S. (2009). Connectivity-Based Parcellation of Human Cingulate Cortex and Its Relation to Functional Specialization. *Journal of Neuroscience*, *29*(4), 1175–1190. https://doi.org/10.1523/JNEUROSCI.3328-08.2009

Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. https://doi.org/10.1016/j.neuroimage.2007.04.042

Bennett, A. T. (1996). Do animals have cognitive maps? *Journal of Experimental Biology*, *199*(1), 219–224.

Berthoz, A., & Viaud-Delmon, I. (1999). Multisensory integration in spatial orientation. *Current Opinion in Neurobiology*, *9*(6), 708–712. https://doi.org/10.1016/S0959-4388(99)00041-0

Bianchini, F., Incoccia, C., Palermo, L., Piccardi, L., Zompanti, L., Sabatini, U., … Guariglia, C. (2010). Developmental topographical disorientation in a healthy subject.

Neuropsychologia, *48*(6), 1563–1573. https://doi.org/10.1016/j.neuropsychologia.2010.01.025

Binder, J. R., Frost, J. A., Hammeke, T. A., Cox, R. W., Rao, S. M., & Prieto, T. (1997). Human brain language areas identified by functional magnetic resonance imaging. *Journal of Neuroscience*, *17*(1), 353–362.

Bohbot, V. D., Kalina, M., Stepankova, K., Spackova, N., Petrides, M., & Nadel, L. (1998). Spatial memory deficits in patients with lesions to the right hippocampus and to the right parahippocampal cortex. *Neuropsychologia*, *36*(11), 1217–1238. https://doi.org/10.1016/S0028-3932(97)00161-9

Bonner, M. F., & Epstein, R. A. (2017). Coding of navigational affordances in the human visual system. *Proceedings of the National Academy of Sciences*, *114*(18), 4793–4798. https://doi.org/10.1073/pnas.1618228114

Bowers, D., Verfaellie, M., Valenstein, E., & Heilman, K. M. (1988). Impaired acquisition of temporal information in retrosplenial amnesia. *Brain and Cognition*, *8*(1), 47–66. https://doi.org/10.1016/0278-2626(88)90038-3

Brodmann, K. (2006). *Brodmann's localisation in the cerebral cortex: the principles of comparative localisation in the cerebral cortex based on cytoarchitectonics*. (L. J. Gary, Trans.). New York, NY: Springer.

Burgess, N. (2006). Spatial memory: how egocentric and allocentric combine. *Trends in Cognitive Sciences*, *10*(12), 551–557. https://doi.org/10.1016/j.tics.2006.10.005

Burgess, N. (2014). The 2014 Nobel Prize in Physiology or Medicine: A Spatial Model for Cognitive Neuroscience. *Neuron*, *84*(6), 1120–1125. https://doi.org/10.1016/j.neuron.2014.12.009

Burgess, N., Becker, S., King, J. A., & O'Keefe, J. (2001). Memory for events and their spatial context: models and experiments. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *356*(1413), 1493–1503. https://doi.org/10.1098/rstb.2001.0948

Burles, F., Slone, E., & Iaria, G. (2017). Dorso-medial and ventro-lateral functional specialization of the human retrosplenial complex in spatial updating and orienting. *Brain Structure and Function*, *222*(3), 1481–1493. https://doi.org/10.1007/s00429-016-1288-8

Burles, F., Umiltá, A., McFarlane, L., Potocki, K., & Iaria, G. (2018). Ventral-Dorsal functional contribution of the posterior cingulate cortex in human spatial orientation: A meta-analysis. *Frontiers in Human Neuroscience*, *12*. https://doi.org/10.3389/fnhum.2018.00190

Byrne, P., Becker, S., & Burgess, N. (2007). Remembering the past and imagining the future: A neural model of spatial memory and imagery. *Psychological Review*, *114*(2), 340–375. https://doi.org/10.1037/0033-295X.114.2.340

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, *129*(3), 564–583. https://doi.org/10.1093/brain/awl004

Chaddock, L., Erickson, K. I., Prakash, R. S., Kim, J. S., Voss, M. W., VanPatter, M., … Kramer, A. F. (2010). A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. *Brain Research*, *1358*, 172–183. https://doi.org/10.1016/j.brainres.2010.08.049

Chadwick, M. J., & Spiers, H. J. (2014). A local anchor for the brain's compass. *Nature Neuroscience*, *17*(11), 1436–1437. https://doi.org/10.1038/nn.3841

Chen, L. L., Lin, L.-H., Green, E. J., Barnes, C. A., & McNaughton, B. L. (1994). Head-direction cells in the rat posterior cortex. *Experimental Brain Research*, *101*(1), 8–23. https://doi.org/10.1007/BF00243212

Chen, S. H. A., & Desmond, J. E. (2005a). Cerebrocerebellar networks during articulatory rehearsal and verbal working memory tasks. *Neuroimage*, *24*(2), 332–338.

Chen, S. H. A., & Desmond, J. E. (2005b). Temporal dynamics of cerebro-cerebellar network recruitment during a cognitive task. *Neuropsychologia*, *43*(9), 1227–1237. https://doi.org/10.1016/j.neuropsychologia.2004.12.015

Cho, J., & Sharp, P. E. (2001). Head direction, place, and movement correlates for cells in the rat retrosplenial cortex. *Behavioral Neuroscience*, *115*(1), 3–25.

Collett, M., & Collett, T. S. (2017). Path Integration: Combining Optic Flow with Compass Orientation. *Current Biology*, *27*(20), R1113–R1116. https://doi.org/10.1016/j.cub.2017.09.004

Conson, M., Bianchini, F., Quarantelli, M., Boccia, M., Salzano, S., Di Vita, A., & Guariglia, C. (2018). Selective map-following navigation deficit: A new case of developmental topographical disorientation. *Journal of Clinical and Experimental Neuropsychology*, 1–11. https://doi.org/10.1080/13803395.2018.1451493

Coomber, M. (2013, April 29). Lost Every Day. *The New York Times*. Retrieved from https://www.nytimes.com/2013/04/30/opinion/lost-every-day.html

Corbetta, M., Kincade, J. M., & Shulman, G. L. (2002). Neural Systems for Visual Orienting and Their Relationships to Spatial Working Memory. *Journal of Cognitive Neuroscience*, *14*(3), 508–523. https://doi.org/10.1162/089892902317362029

Corrow, J. C., Corrow, S. L., Lee, E., Pancaroglu, R., Burles, F., Duchaine, B., … Barton, J. J. S. (2016). Getting lost: Topographic skills in acquired and developmental prosopagnosia. *Cortex*, *76*, 89–103. https://doi.org/10.1016/j.cortex.2016.01.003

Dahmani, L., & Bohbot, V. D. (2015). Dissociable contributions of the prefrontal cortex to hippocampus- and caudate nucleus-dependent virtual navigation strategies. *Neurobiology of Learning and Memory*, *117*, 42–50. https://doi.org/10.1016/j.nlm.2014.07.002

Damasio, A. R., Damasio, H., & Van Hoesen, G. W. (1982). Prosopagnosia Anatomic basis and behavioral mechanisms. *Neurology*, *32*(4), 331–331.

de Fockert, J. W., Rees, G., Frith, C. D., & Lavie, N. (2001). The role of working memory in visual selective attention. *Science (New York, N.Y.)*, *291*(5509), 1803–1806. https://doi.org/10.1126/science.1056496

Dilks, D. D., Julian, J. B., Paunov, A. M., & Kanwisher, N. (2013). The Occipital Place Area Is Causally and Selectively Involved in Scene Perception. *Journal of Neuroscience*, *33*(4), 1331–1336. https://doi.org/10.1523/JNEUROSCI.4081-12.2013

Ekstrom, A. D., Arnold, A. E. G. F., & Iaria, G. (2014). A critical review of the allocentric spatial representation and its neural underpinnings: toward a network-based perspective. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00803

Ekstrom, A. D., Huffman, D. J., & Starrett, M. (2017). Interacting networks of brain regions underlie human spatial navigation: a review and novel synthesis of the literature. *Journal of Neurophysiology*, *118*(6), 3328–3344. https://doi.org/10.1152/jn.00531.2017

Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., & Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature*, *425*(6954), 184–188. https://doi.org/10.1038/nature01964

Epstein, R. A. (2008). Parahippocampal and retrosplenial contributions to human spatial navigation. *Trends in Cognitive Sciences*, *12*(10), 388–396. https://doi.org/10.1016/j.tics.2008.07.004

Epstein, R. A., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature*, *392*(6676), 598–601.

Epstein, R. A., Parker, W. E., & Feiler, A. M. (2007). Where Am I Now? Distinct Roles for Parahippocampal and Retrosplenial Cortices in Place Recognition. *Journal of Neuroscience*, *27*(23), 6141–6149. https://doi.org/10.1523/JNEUROSCI.0799-07.2007

Epstein, R. A., Patai, E. Z., Julian, J. B., & Spiers, H. J. (2017). The cognitive map in humans: spatial navigation and beyond. *Nature Neuroscience*, *20*(11), 1504–1513. https://doi.org/10.1038/nn.4656

Erickson, K. I., Prakash, R. S., Voss, M. W., Chaddock, L., Hu, L., Morris, K. S., … Kramer, A. F. (2009). Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus*, *19*(10), 1030–1039. https://doi.org/10.1002/hipo.20547

Fanselow, M. S., & Dong, H.-W. (2010). Are the Dorsal and Ventral Hippocampus Functionally Distinct Structures? *Neuron*, *65*(1), 7–19. https://doi.org/10.1016/j.neuron.2009.11.031

Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678.

Goldstein, K., & Gelb, A. (1918). Psychologische Analysen hirnpathologischer Fälle auf Grund von Untersuchungen Hirnverletzter. *Zeitschrift für die gesamte Neurologie und Psychiatrie*, *41*(1), 1–142. https://doi.org/10.1007/BF02874477

Grill-Spector, K. (2003). The neural basis of object perception. *Current Opinion in Neurobiology*, *13*(2), 159–166. https://doi.org/10.1016/S0959-4388(03)00040-0

Guerra, P. A., Gegear, R. J., & Reppert, S. M. (2014). A magnetic compass aids monarch butterfly migration. *Nature Communications*, *5*, 4164. https://doi.org/10.1038/ncomms5164

Gur, R. C., Gunning-Dixon, F., Bilker, W. B., & Gur, R. E. (2002). Sex Differences in Temporo-limbic and Frontal Brain Volumes of Healthy Adults. *Cerebral Cortex*, *12*(9), 998–1003. https://doi.org/10.1093/cercor/12.9.998

Gutchess, A. H., & Schacter, D. L. (2012). The neural correlates of gist-based true and false recognition. *NeuroImage*, *59*(4), 3418–3426. https://doi.org/10.1016/j.neuroimage.2011.11.078

Hart, V., Nováková, P., Malkemper, E., Begall, S., Hanzal, V., Ježek, M., … Burda, H. (2013). Dogs are sensitive to small variations of the Earth's magnetic field. *Frontiers in Zoology*, *10*(1), 80. https://doi.org/10.1186/1742-9994-10-80

Hirshhorn, M., Grady, C., Rosenbaum, R. S., Winocur, G., & Moscovitch, M. (2012). Brain regions involved in the retrieval of spatial and episodic details associated with a familiar environment: an fMRI study. *Neuropsychologia*, *50*(13), 3094–3106.

Houk, J. C., Buckingham, J. T., & Barto, A. G. (1996). Models of the cerebellum and motor learning, *19*(3), 368–383.

Iaria, G., Arnold, A. E. G. F., Burles, F., Liu, I., Slone, E., Barclay, S., … Levy, R. M. (2014). Developmental topographical disorientation and decreased hippocampal functional connectivity: Dtd and Hippocampal Functional Connectivity. *Hippocampus*, *24*(11), 1364–1374. https://doi.org/10.1002/hipo.22317

Iaria, G., & Barton, J. J. S. (2010). Developmental topographical disorientation: a newly discovered cognitive disorder. *Experimental Brain Research*, *206*(2), 189–196. https://doi.org/10.1007/s00221-010-2256-9

Iaria, G., Bogod, N., Fox, C. J., & Barton, J. J. S. (2009). Developmental topographical disorientation: Case one. *Neuropsychologia*, *47*(1), 30–40. https://doi.org/10.1016/j.neuropsychologia.2008.08.021

Iaria, G., Chen, J.-K., Guariglia, C., Ptito, A., & Petrides, M. (2007). Retrosplenial and Hippocampal Brain Regions in Human Navigation: Complementary Functional Contributions to the Formation and Use of Cognitive Maps. *European Journal of Neuroscience*, *25*(3), 890–899. https://doi.org/10.1111/j.1460-9568.2007.05371.x

Iaria, G., Petrides, M., Dagher, A., Pike, B., & Bohbot, V. D. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *23*(13), 5945–5952.

Iaria, G., Wentzel, G. M., Boon, J., Burles, F., Liu, I., & Federico, P. (2017). The effects of selective amygdalo-hippocampectomy on different spatial orientation skills. *Current Trends in Neurology*, *10*, 39–52.

Ino, T., Doi, T., Hirose, S., Kimura, T., Ito, J., & Fukuyama, H. (2007). Directional disorientation following left retrosplenial hemorrhage: a case report with fMRI studies. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *43*(2), 248–254.

Ino, T., Inoue, Y., Kage, M., Hirose, S., Kimura, T., & Fukuyama, H. (2002). Mental navigation in humans is processed in the anterior bank of the parieto-occipital sulcus. *Neuroscience Letters*, *322*(3), 182–186. https://doi.org/10.1016/S0304-3940(02)00019-8

Joliot, M., Jobard, G., Naveau, M., Delcroix, N., Petit, L., Zago, L., … Tzourio-Mazoyer, N. (2015). AICHA: An atlas of intrinsic connectivity of homotopic areas. *Journal of Neuroscience Methods*, *254*, 46–59. https://doi.org/10.1016/j.jneumeth.2015.07.013

Kamps, F. S., Julian, J. B., Kubilius, J., Kanwisher, N., & Dilks, D. D. (2016). The occipital place area represents the local elements of scenes. *NeuroImage*, *132*, 417–424. https://doi.org/10.1016/j.neuroimage.2016.02.062

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The Fusiform Face Area: A Module in Human Extrastriate Cortex Specialized for Face Perception. *Journal of Neuroscience*, *17*(11), 4302–4311. https://doi.org/10.1523/JNEUROSCI.17-11-04302.1997

Karnath, H.-O. (2004). The Anatomy of Spatial Neglect based on Voxelwise Statistical Analysis: A Study of 140 Patients. *Cerebral Cortex*, *14*(10), 1164–1172. https://doi.org/10.1093/cercor/bhh076

Kessels, R. P., de Haan, E. H., Kappelle, L. J., & Postma, A. (2001). Varieties of human spatial memory: a meta-analysis on the effects of hippocampal lesions. *Brain Research Reviews*, *35*(3), 295–303.

Kim, H. (2015). Encoding and retrieval along the long axis of the hippocampus and their relationships with dorsal attention and default mode networks: The HERNET model. *Hippocampus*, *25*(4), 500–510. https://doi.org/10.1002/hipo.22387

Kim, J. G., Aminoff, E. M., Kastner, S., & Behrmann, M. (2015). A Neural Basis for Developmental Topographic Disorientation. *Journal of Neuroscience*, *35*(37), 12954–12969. https://doi.org/10.1523/JNEUROSCI.0640-15.2015

Kimchi, T., Etienne, A. S., & Terkel, J. (2004). A subterranean mammal uses the magnetic compass for path integration. *Proceedings of the National Academy of Sciences*, *101*(4), 1105–1109. https://doi.org/10.1073/pnas.0307560100

Koechlin, E., & Jubault, T. (2006). Broca's Area and the Hierarchical Organization of Human Behavior. *Neuron*, *50*(6), 963–974. https://doi.org/10.1016/j.neuron.2006.05.017

Kühn, S., & Gallinat, J. (2014). Segregating cognitive functions within hippocampal formation: A quantitative meta-analysis on spatial navigation and episodic memory. *Human Brain Mapping*, *35*(4), 1129–1142. https://doi.org/10.1002/hbm.22239

Leech, R., Braga, R., & Sharp, D. J. (2012). Echoes of the Brain within the Posterior Cingulate Cortex. *Journal of Neuroscience*, *32*(1), 215–222. https://doi.org/10.1523/JNEUROSCI.3689-11.2012

Lepage, M., Habib, R., & Tulving, E. (1998). Hippocampal PET activations of memory encoding and retrieval: the HIPER model. *Hippocampus*, *8*(4), 313–322. https://doi.org/10.1002/(SICI)1098-1063(1998)8:4<313::AID-HIPO1>3.0.CO;2-I

Lepsien, J., & Nobre, A. C. (2006). Cognitive control of attention in the human brain: Insights from orienting attention to mental representations. *Brain Research*, *1105*(1), 20–31. https://doi.org/10.1016/j.brainres.2006.03.033

Leung, H.-C., Gore, J. C., & Goldman-Rakic, P. S. (2002). Sustained Mnemonic Response in the Human Middle Frontal Gyrus during On-Line Storage of Spatial Memoranda. *Journal of Cognitive Neuroscience*, *14*(4), 659–671. https://doi.org/10.1162/08989290260045882

Lövdén, M., Schaefer, S., Noack, H., Bodammer, N. C., Kühn, S., Heinze, H.-J., … Lindenberger, U. (2012). Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiology of Aging*, *33*(3), 620.e9-620.e22. https://doi.org/10.1016/j.neurobiolaging.2011.02.013

Machielsen, W., Rombouts, S. A., Barkhof, F., Scheltens, P., & Witter, M. P. (2000). FMRI of visual encoding: reproducibility of activation. *Human Brain Mapping*, *9*(3), 156–164.

Maddock, R. J. (1999). The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends in Neurosciences*, *22*(7), 310–316.

Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2001). Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. *Neuroscience*, *104*(3), 667–676.

Maeshima, S., Ozaki, F., Masuo, O., Yamaga, H., Okita, R., & Moriwaki, H. (2001). Memory impairment and spatial disorientation following a left retrosplenial lesion. *Journal of Clinical Neuroscience*, *8*(5), 450–451.

Maguire, E. A. (2001). The retrosplenial contribution to human navigation: a review of lesion and neuroimaging findings. *Scandinavian Journal of Psychology*, *42*(3), 225–238.

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S. J., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science (New York, N.Y.)*, *280*(5365), 921–924.

Maguire, E. A., Frith, C. D., Burgess, N., Donnett, J. G., & O'Keefe, J. (1998). Knowing Where Things Are: Parahippocampal Involvement in Encoding Object Locations in Virtual Large-Scale Space. *Journal of Cognitive Neuroscience*, *10*(1), 61–76. https://doi.org/10.1162/089892998563789

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences*, *97*(8), 4398–4403.

Maguire, E. A., Nannery, R., & Spiers, H. J. (2006). Navigation around London by a taxi driver with bilateral hippocampal lesions. *Brain*, *129*(11), 2894–2907. https://doi.org/10.1093/brain/awl286

Maguire, E. A., Woollett, K., & Spiers, H. J. (2006). London taxi drivers and bus drivers: A structural MRI and neuropsychological analysis. *Hippocampus*, *16*(12), 1091–1101. https://doi.org/10.1002/hipo.20233

Marchette, S. A., Vass, L. K., Ryan, J., & Epstein, R. A. (2014). Anchoring the neural compass: coding of local spatial reference frames in human medial parietal lobe. *Nature Neuroscience*, *17*(11), 1598–1606. https://doi.org/10.1038/nn.3834

Margulies, D. S., Vincent, J. L., Kelly, C., Lohmann, G., Uddin, L. Q., Biswal, B. B., … Petrides, M. (2009). Precuneus shares intrinsic functional architecture in humans and monkeys. *Proceedings of the National Academy of Sciences*, *106*(47), 20069–20074.

McDonald, C. R., Crosson, B., Valenstein, E., & Bowers, D. (2001). Verbal encoding deficits in a patient with a left retrosplenial lesion. *Neurocase*, *7*(5), 407–417. https://doi.org/10.1076/neur.7.5.407.16250

McNaughton, B. L., Battaglia, F. P., Jensen, O., Moser, E. I., & Moser, M.-B. (2006). Path integration and the neural basis of the'cognitive map'. *Nature Reviews Neuroscience*, *7*(8), 663–678.

Meilinger, T. (2008). The Network of Reference Frames Theory: A Synthesis of Graphs and Cognitive Maps. In C. Freksa, N. S. Newcombe, P. Gärdenfors, & S. Wölfl (Eds.), *Spatial Cognition VI. Learning, Reasoning, and Talking about Space* (Vol. 5248, pp. 344–360). Berlin, Heidelberg: Springer Berlin Heidelberg. https://doi.org/10.1007/978-3-540-87601-4_25

Mellet, E., Bricogne, S., Tzourio-Mazoyer, N., Ghaëm, O., Petit, L., Zago, L., … Denis, M. (2000). Neural Correlates of Topographic Mental Exploration: The Impact of Route versus Survey Perspective Learning. *NeuroImage*, *12*(5), 588–600. https://doi.org/10.1006/nimg.2000.0648

Mendez, M. F., & Cherrier, M. M. (2003). Agnosia for scenes in topographagnosia. *Neuropsychologia*, *41*(10), 1387–1395. https://doi.org/10.1016/S0028-3932(03)00041-1

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Structure and Function*, *214*(5–6), 655–667. https://doi.org/10.1007/s00429-010-0262-0

Milner, A. D., & Goodale, M. A. (2008). Two visual systems re-viewed. *Neuropsychologia*, *46*(3), 774–785. https://doi.org/10.1016/j.neuropsychologia.2007.10.005

Mittelstaedt, M.-L., & Mittelstaedt, H. (1980). Homing by path integration in a mammal. *Naturwissenschaften*, *67*(11), 566–567.

Morris, R. G. M., Garrud, P., Rawlins, J. N. P., & O'Keefe, J. (1982). Place navigation impaired in rats with hippocampal lesions. *Nature*, *297*(5868), 681–683. https://doi.org/10.1038/297681a0

Morris, R., Paxinos, G., & Petrides, M. (2000). Architectonic analysis of the human retrosplenial cortex. *The Journal of Comparative Neurology*, *421*(1), 14–28.

Murty, V. P., Ritchey, M., Adcock, R. A., & LaBar, K. S. (2010). fMRI studies of successful emotional memory encoding: A quantitative meta-analysis. *Neuropsychologia*, *48*(12), 3459–3469. https://doi.org/10.1016/j.neuropsychologia.2010.07.030

Nadel, L. (1968). Dorsal and ventral hippocampal lesions and behavior. *Physiology & Behavior*, *3*(6), 891–900. https://doi.org/10.1016/0031-9384(68)90174-1

National Coordination Office for Space-Based Positioning, Navigation, and Timing. (2018). GPS.gov: Fiscal Year 2018 Program Funding. Retrieved May 7, 2018, from https://www.gps.gov/policy/funding/2018/

Nemmi, F., Bianchini, F., Piras, F., Péran, P., Palermo, L., Piccardi, L., … Guariglia, C. (2015). Finding my own way: an fMRI single case study of a subject with developmental topographical disorientation. *Neurocase*, *21*(5), 573–583. https://doi.org/10.1080/13554794.2014.960424

Nemmi, F., Piras, F., Péran, P., Incoccia, C., Sabatini, U., & Guariglia, C. (2013). Landmark sequencing and route knowledge: An fMRI study. *Cortex*, *49*(2), 507–519. https://doi.org/10.1016/j.cortex.2011.11.016

O'Keefe, J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research*, *34*(1), 171–175. https://doi.org/10.1016/0006-8993(71)90358-1

O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford : New York: Clarendon Press ; Oxford University Press.

Palermo, L., Piccardi, L., Bianchini, F., Nemmi, F., Giorgio, V., Incoccia, C., … Guariglia, C. (2014). Looking for the compass in a case of developmental topographical disorientation: A behavioral and neuroimaging study. *Journal of Clinical and Experimental Neuropsychology*, *36*(5), 464–481. https://doi.org/10.1080/13803395.2014.904843

Pallis, C. A. (1955). Impaired Identification of Faces and Places with Agnosia for Colours: Report of a Case Due to Cerebral Embolism. *Journal of Neurology, Neurosurgery & Psychiatry*, *18*(3), 218–224. https://doi.org/10.1136/jnnp.18.3.218

Park, S., & Chun, M. M. (2009). Different roles of the parahippocampal place area (PPA) and retrosplenial cortex (RSC) in panoramic scene perception. *NeuroImage*, *47*(4), 1747–1756. https://doi.org/10.1016/j.neuroimage.2009.04.058

Patai, E. Z., & Spiers, H. J. (2017). Human Navigation: Occipital Place Area Detects Potential Paths in a Scene. *Current Biology*, *27*(12), R599–R600. https://doi.org/10.1016/j.cub.2017.05.012

Paulesu, E., Frith, C. D., & Frackowiak, R. S. J. (1993). The neural correlates of the verbal component of working memory. *Nature*, *362*(6418), 342–345. https://doi.org/10.1038/362342a0

Perez, S. M., Taylor, O. R., & Jander, R. (1997). A sun compass in monarch butterflies. *Nature*, *387*(6628), 29. https://doi.org/10.1038/387029a0

Poldrack, R. A. (2007). Region of interest analysis for fMRI. *Social Cognitive and Affective Neuroscience*, *2*(1), 67–70. https://doi.org/10.1093/scan/nsm006

Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Sciences*, *17*(5), 230–240. https://doi.org/10.1016/j.tics.2013.03.005

Quirk, G. J., Muller, R. U., Kubie, J. L., & Ranck, J. B. (1992). The positional firing properties of medial entorhinal neurons: description and comparison with hippocampal place cells. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *12*(5), 1945–1963.

Ranganath, C., & Ritchey, M. (2012). Two cortical systems for memory-guided behaviour. *Nature Reviews Neuroscience*, *13*(10), 713–726. https://doi.org/10.1038/nrn3338

Rapoport, M., van Reekum, R., & Mayberg, H. (2000). The Role of the Cerebellum in Cognition and Behavior. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(2), 193–198. https://doi.org/10.1176/jnp.12.2.193

Redcay, E. (2008). The superior temporal sulcus performs a common function for social and speech perception: Implications for the emergence of autism. *Neuroscience & Biobehavioral Reviews*, *32*(1), 123–142. https://doi.org/10.1016/j.neubiorev.2007.06.004

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The Role of the Medial Frontal Cortex in Cognitive Control. *Science*, *306*(5695), 443–447. https://doi.org/10.1126/science.1100301

Robin, J., & Moscovitch, M. (2017). Details, gist and schema: hippocampal–neocortical interactions underlying recent and remote episodic and spatial memory. *Current Opinion in Behavioral Sciences*, *17*, 114–123. https://doi.org/10.1016/j.cobeha.2017.07.016

Rochefort, C., Lefort, J., & Rondi-Reig, L. (2013). The cerebellum: a new key structure in the navigation system. *Frontiers in Neural Circuits*, *7*. https://doi.org/10.3389/fncir.2013.00035

Roth, J. K., Serences, J. T., & Courtney, S. M. (2006). Neural System for Controlling the Contents of Object Working Memory in Humans. *Cerebral Cortex*, *16*(11), 1595–1603. https://doi.org/10.1093/cercor/bhj096

Ryan, L., Lin, C.-Y., Ketcham, K., & Nadel, L. (2010). The role of medial temporal lobe in retrieving spatial and nonspatial relations from episodic and semantic memory. *Hippocampus*, *20*(1), 11–18. https://doi.org/10.1002/hipo.20607

Schacter, D. L., & Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*, *9*(1), 7–24.

Schmahmann, J. D., & Sherman, J. C. (1998). The cerebellar cognitive affective syndrome. *Brain*, *121*(4), 561–579. https://doi.org/10.1093/brain/121.4.561

Schuff, N., Amend, D. L., Knowlton, R., Norman, D., Fein, G., & Weiner, M. W. (1999). Age-related metabolite changes and volume loss in the hippocampus by magnetic resonance spectroscopy and imaging. *Neurobiology of Aging*, *20*(3), 279–285.

Seghier, M. L. (2013). The angular gyrus: multiple functions and multiple subdivisions. *The Neuroscientist*, *19*(1), 43–61.

Sharp, P. E., & Green, C. (1994). Spatial correlates of firing patterns of single cells in the subiculum of the freely moving rat. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *14*(4), 2339–2356.

Sheldon, S., & Levine, B. (2018). The medial temporal lobe functional connectivity patterns associated with forming different mental representations. *Hippocampus*. https://doi.org/10.1002/hipo.22829

Shields, M., Gorber, S. C., & Tremblay, M. S. (2008). Methodological issues in anthropometry: Self-reported versus measured height and weight. In *Proceedings of Statistics Canada Symposium*.

Silk, T. J., Bellgrove, M. A., Wrafter, P., Mattingley, J. B., & Cunnington, R. (2010). Spatial working memory and spatial attention rely on common neural processes in the intraparietal sulcus. *NeuroImage*, *53*(2), 718–724. https://doi.org/10.1016/j.neuroimage.2010.06.068

Silson, E. H., Steel, A. D., & Baker, C. I. (2016). Scene-Selectivity and Retinotopy in Medial Parietal Cortex. *Frontiers in Human Neuroscience*, *10*(412). https://doi.org/10.3389/fnhum.2016.00412

Smith, M. L., & Milner, B. (1981). The role of the right hippocampus in the recall of spatial location. *Neuropsychologia*, *19*(6), 781–793. https://doi.org/10.1016/0028-3932(81)90090-7

Spiers, H. J., & Maguire, E. A. (2006). Thoughts, behaviour, and brain dynamics during navigation in the real world. *NeuroImage*, *31*(4), 1826–1840. https://doi.org/10.1016/j.neuroimage.2006.01.037

Stalleicken, J., Mukhida, M., Labhart, T., Wehner, R., Frost, B., & Mouritsen, H. (2005). Do monarch butterflies use polarized skylight for migratory orientation? *Journal of Experimental Biology*, *208*(12), 2399–2408. https://doi.org/10.1242/jeb.01613

Steck, K., Hansson, B. S., & Knaden, M. (2009). Smells like home: Desert ants, Cataglyphis fortis, use olfactory landmarks to pinpoint the nest. *Frontiers in Zoology*, *6*, 5. https://doi.org/10.1186/1742-9994-6-5

Strange, B. A., & Dolan, R. J. (1999). Functional segregation within the human hippocampus. *Molecular Psychiatry*, *4*(6).

Sulpizio, V., Boccia, M., Guariglia, C., & Galati, G. (2016). Functional connectivity between posterior hippocampus and retrosplenial complex predicts individual differences in navigational ability. *Hippocampus*, *26*(7), 841–847. https://doi.org/10.1002/hipo.22592

Sulpizio, V., Committeri, G., Lambrey, S., Berthoz, A., & Galati, G. (2013). Selective role of lingual/parahippocampal gyrus and retrosplenial complex in spatial memory across viewpoint changes relative to the environmental reference frame. *Behavioural Brain Research*, *242*, 62–75. https://doi.org/10.1016/j.bbr.2012.12.031

Takahashi, N., Kawamura, M., Shiota, J., Kasahata, N., & Hirayama, K. (1997). Pure topographic disorientation due to right retrosplenial lesion. *Neurology*, *49*(2), 464–469. https://doi.org/10.1212/WNL.49.2.464

Taube, J. S. (1998). Head direction cells and the neurophysiological basis for a sense of direction. *Progress in Neurobiology*, *55*(3), 225–256. https://doi.org/10.1016/S0301-0082(98)00004-5

Taube, J. S. (2007). The Head Direction Signal: Origins and Sensory-Motor Integration. *Annual Review of Neuroscience*, *30*(1), 181–207. https://doi.org/10.1146/annurev.neuro.29.051605.112854

Timmann, D., Drepper, J., Frings, M., Maschke, M., Richter, S., Gerwig, M., & Kolb, F. P. (2010). The human cerebellum contributes to motor, emotional and cognitive associative learning. A review. *Cortex*, *46*(7), 845–857. https://doi.org/10.1016/j.cortex.2009.06.009

Tolman, E. C. (1948). Cognitive maps in rats and men. *Psychological Review*, *55*(4), 189.

Transport for London. (2018, April 23). Learn the Knowledge of London. Retrieved April 23, 2018, from https://www.tfl.gov.uk/info-for/taxis-and-private-hire/licensing/learn-the-knowledge-of-london

Tversky, B. (1992). Distortions in cognitive maps. *Geoforum*, *23*(2), 131–138. https://doi.org/10.1016/0016-7185(92)90011-R

Valerio, S., & Taube, J. S. (2012). Path integration: how the head direction signal maintains and corrects spatial orientation. *Nature Neuroscience*, *15*(10), 1445–1453. https://doi.org/10.1038/nn.3215

Vann, S. D., & Aggleton, J. P. (2004). Testing the importance of the retrosplenial guidance system: effects of different sized retrosplenial cortex lesions on heading direction and spatial working memory. *Behavioural Brain Research*, *155*(1), 97–108. https://doi.org/10.1016/j.bbr.2004.04.005

Vann, S. D., Aggleton, J. P., & Maguire, E. A. (2009). What does the retrosplenial cortex do? *Nature Reviews Neuroscience*, *10*(11), 792–802. https://doi.org/10.1038/nrn2733

Vogt, B. A., Absher, J. R., & Bush, G. (2000). Human retrosplenial cortex: where is it and is it involved in emotion? *Trends in Neurosciences*, *23*(5), 195–196. https://doi.org/10.1016/s0166-2236(00)01579-4

Vogt, B. A., Nimchinsky, E. A., Vogt, L. J., & Hof, P. R. (1995). Human cingulate cortex: surface features, flat maps, and cytoarchitecture. *Journal of Comparative Neurology*, *359*(3), 490–506.

Vogt, B. A., Vogt, L. J., Perl, D. P., & Hof, P. R. (2001). Cytology of human caudomedial cingulate, retrosplenial, and caudal parahippocampal cortices. *Journal of Comparative Neurology*, *438*(3), 353–376.

Vogt, B. A., Vogt, L., & Laureys, S. (2006). Cytology and functionally correlated circuits of human posterior cingulate areas. *NeuroImage*, *29*(2), 452–466. https://doi.org/10.1016/j.neuroimage.2005.07.048

Wagner, A. D., Shannon, B. J., Kahn, I., & Buckner, R. L. (2005). Parietal lobe contributions to episodic memory retrieval. *Trends in Cognitive Sciences*, *9*(9), 445–453. https://doi.org/10.1016/j.tics.2005.07.001

Walcott, C. (1996). Pigeon homing: observations, experiments and confusions. *Journal of Experimental Biology*, *199*(1), 21–27.

Wehner, R. (2003). Desert ant navigation: how miniature brains solve complex tasks. *Journal of Comparative Physiology A: Sensory, Neural, and Behavioral Physiology*, *189*(8), 579–588. https://doi.org/10.1007/s00359-003-0431-1

Wittlinger, M., Wehner, R., & Wolf, H. (2006). The Ant Odometer: Stepping on Stilts and Stumps. *Science*, *312*(5782), 1965–1967. https://doi.org/10.1126/science.1126912

Wittlinger, M., Wehner, R., & Wolf, H. (2007). The desert ant odometer: a stride integrator that accounts for stride length and walking speed. *Journal of Experimental Biology*, *210*(2), 198–207. https://doi.org/10.1242/jeb.02657

Wolbers, T., & Büchel, C. (2005). Dissociable Retrosplenial and Hippocampal Contributions to Successful Formation of Survey Representations. *Journal of Neuroscience*, *25*(13), 3333–3340. https://doi.org/10.1523/JNEUROSCI.4705-04.2005

Woollett, K., & Maguire, E. A. (2009). Navigational expertise may compromise anterograde associative memory. *Neuropsychologia*, *47*(4), 1088–1095. https://doi.org/10.1016/j.neuropsychologia.2008.12.036

Woollett, K., & Maguire, E. A. (2010). The effect of navigational expertise on wayfinding in new environments. *Journal of Environmental Psychology*, *30*(4), 565–573. https://doi.org/10.1016/j.jenvp.2010.03.003

Woollett, K., & Maguire, E. A. (2012). Exploring anterograde associative memory in London taxi drivers. *Neuroreport*, *23*(15), 885–888. https://doi.org/10.1097/WNR.0b013e328359317e

Xu, Y., & Chun, M. M. (2006). Dissociable neural mechanisms supporting visual short-term memory for objects. *Nature*, *440*(7080), 91–95. https://doi.org/10.1038/nature04262

Yakusheva, T. A., Shaikh, A. G., Green, A. M., Blazquez, P. M., Dickman, J. D., & Angelaki, D. E. (2007). Purkinje Cells in Posterior Cerebellar Vermis Encode Motion in an Inertial Reference Frame. *Neuron*, *54*(6), 973–985. https://doi.org/10.1016/j.neuron.2007.06.003

Zhang, S., & Li, C. R. (2012). Functional connectivity mapping of the human precuneus by resting state fMRI. *NeuroImage*, *59*(4), 3548–3562. https://doi.org/10.1016/j.neuroimage.2011.11.023

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