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Neural network dynamics during the generation and reinstatement of mnemonic representations

by

Aiden Arnold

A THESIS

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Abstract

The capacity to generate, reinstate, and mentally simulate mnemonic representations is a fundamental aspect of the human mind. It allows us to internally experience other places and moments of time, abstracting away from the present moment into past experiences or hypothetical future states of the world. Theoretical models posit that this capacity is afforded by a neural network distributed across the brain that codes features from our environment and experiences into neural representations that can be reinstated or flexibly combined in a goal oriented manner. Central to this network is the hippocampus, a region of the medial temporal lobes that putatively indexes both the spatial composition of a mental scene and the pattern of hippocampal-cortical interactions that represent feature details. Despite decades of research on hippocampal function during memory processes, our understanding of how this neural network operates dynamically remains limited. This thesis aim to assist in resolving this by investigating patterns of network reconfiguration that occur as a mnemonic representation of a virtual city is generated and reinstated to guide mental simulations of movement through the city. Chapter 2 provides evidence for a general encoding mechanism where the brain transitions from a state of information integration to localized processing based on encoding demands. These results are extended by showing that the hippocampus demonstrates flexibility in how it interacts with other brain regions to actively reinstate and bind features into a holistic representation that is used for mentally simulating movement. Chapter 3 investigates regional effects associated with the task as a validity check. Chapter 4 uses network reconfiguration processes to show that the default mode network, a putative task-negative system, also demonstrates flexibility by altering the functional interactions between its components and regions of the mental simulation network to facilitate feature integration during mnemonic reinstatement. Collectively, these results provide a

schematic for extending existing theoretical models on memory function into a dynamic perspective based on the adaptability of neural networks and the flexibility of network components to alter patterns of functional interactions across the brain to process information in a contextual, goal oriented manner.

Keywords: memory, hippocampus, navigation, prospection, mental simulation, graph theory

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Chapter 1

1.1 The self in time and space

The world is composed of a myriad of colours, shapes, and geometries that weave themselves into the tapestry of sensory information from which we derive our experience of the external environment. Through millennia of evolutionary pressures, the human brain has developed elaborate systems for parsing this sensory information into meaningful constituents that can be encoded, combined, and manipulated in a manner that optimizes the recall of past experiences and predictions about the future (Friston, 2010; Friston & Price, 2001; Schacter, Addis, & Buckner, 2007). The generation of mental models of the world motivating humans towards action is a central tenant of cognitive psychology (Markman & Dietrich, 2000), delineating the stages of one's mental development in childhood (Marshall & Meltzoff, 2015; Piaget & Cook, 1952; Zelazo, 2004), and shaping how we reason about conflicting sources of information as an adult (Byrne, 2002). Moreover, the capacity to imagine a world within one's own mind has led to the proliferation of our cultural and social world (Damasio, 2010), where learned and newly synthesized mental representations find expression in the urban architectures we inhabit, the forms of art we appreciate, and the choices we make to organize our lives in a personally meaningful manner.

Mental representations can be implicit in nature (Squire & Zola-Morgan, 1991), such as motor efferent copies allowing predictions of intended movement sequences, that are not immediately accessible to introspection of the conscious mind. However, the term will be used here to refer to mnemonic representations of a more specific form, in which environmental information and intended action sequences can be combined and rehearsed to both relive past experiences and make predictions about how we might interact with the world at some point in

the future. Therefore, a mnemonic representation will be defined as a mental model that is (1) accessible to conscious introspection, (2) declarable, and (3) situated in a spatiotemporal context. Although implicit and consciously accessible mnemonic representations may share overlapping cognitive and neural mechanisms (Pfeifer, Iida, & Lungarella, 2014), such that more basic sensory-motor interactions between a person and their environment provide a computational basis for higher-order cognitive processes, more research on the neural and computational basis of mental representations at each level is still needed before a comprehensive account of such embodied processing can be developed. One of the aims of this thesis is to assist in this process by integrating insights from both cognitive and neuroscientific perspectives on memory function into a theoretical perspective of how general mechanisms of brain function allow for the complex, multi-featural representations that pervade most of our conscious thought.

Akin to the revolution in physics at the beginning of the 20th century, the division of space and time in human cognition has recently been challenged (Eichenbaum, 2013), with important implications to understanding how humans generate and use mnemonic representations of the world. Early research attempting to resolve how mnemonic representations are coded by neural mechanisms focused on understanding the cellular basis of spatial memory. The *cognitive map theory* of hippocampus (HC) function was based largely on the discovery of *place cells* (O'Keefe & Dostrovsky, 1971; O'Keefe & Nadel, 1978), a type of pyramidal neuron located primarily in the HC that codes for one's location relative to spatial locations in an environment. This theory proposed that *place cells* handled the spatial computations necessary to generate map-like mental representations of an environment by encoding and reinstating spatial information about the layout and organization of environmental features. Expanding upon this view, behavioural and cognitive neuroscientists began to articulate a perspective on memory

function in which discrete aspects of the external world are encoded and represented in the mind (Kosslyn, Ball, & Reiser, 1978), putatively by dynamical activity of populations of neurons (Squire, 2004).

Early work on temporal memory was conducted primarily by neuropsychologists working to extend the discovery by Milner and colleagues (Penfield & Milner, 1958; Scoville & Milner, 1957) that damage or resection of the HC could lead to impairments of memory function and an inability to access information from past experiences or form new mnemonic representations of the world. Termed retrograde and anterograde amnesia, respectively, this finding led to an enormous body of research on understanding human memory function and its neural correlates (Squire, 2009). However, an equally important implication from Milner and colleagues later work (Milner, 1962) was the hypothesis that multiple memory systems operate in the brain, allowing for the preservation of certain forms of learning (e.g. motor) when there was selective damage to only one system. The *multiple memory systems hypothesis* provided the foundation for researchers to delineate taxonomies of memory systems that were distinguished by the classes of information they operated on and how brain lesions affected memory performance.

Over the following decades, the *multiple memory systems hypothesis* led to critical new insights on the organization of memory and how it relates to the brain. An influential perspective first articulated by Endel Tulving (1972; 1983) proposed that human memory can be divided into a semantic system, which allows encoding and retrieval of factual and abstract information about the world, and an episodic system that encodes and retrieves events in relation to oneself. Episodic memory is posited to rely on regions of the medial temporal lobe, primarily the HC, which has a unique anatomical structure consisting of dense recurrent connections (Yassa &

Stark, 2011) and interregional connectivity (Mišić, Goñi, Betzel, Sporns, & McIntosh, 2014) that allow it to reinstate patterns of neural activity representing environmental and episodic details from past experiences. Importantly, episodic memory theory provided a central framework to study how humans mentally move through time and access experiences from the past.

Although there has been extensive research to understand the neural basis of episodic memory, until recently neurocognitive models on temporal aspects of memory had yet to provide a computational mechanism akin to the *place cell hypothesis* of spatial memory. Place cells provide a specific and measurable cellular mechanism to understand how difference environmental features are coded and combined in the HC to generate the spatial context of a mnemonic representations. The representational format of temporal information remained unknown, however, despite being widely associated with HC function. The sequential ordering of events, a fundamental aspect of episodic memory (Tulving, 1983), had been shown to involve the HC through processes such as sequence disambiguation (Kumaran & Maguire, 2006), which allowed overlapping sequences of information to be categorized into different event streams. This suggested that neural codes in the HC represent the timelines of experience, and use pattern separation mechanisms to represent discrete events that shared common features, similar to how overlapping representations of space are disambiguated by neural codes in the HC (Brown, Ross, Keller, Hasselmo, & Stern, 2010; Kyle, Stokes, Lieberman, Hassan, & Ekstrom, 2015). The first cellular mechanism for understanding the temporal aspect of episodic memory was provided by the discovery of *time cells* in the HC, ensembles of neurons that temporally organize event sequences and disambiguate overlapping event features over delay periods (Eichenbaum, 2013; MacDonald, Lepage, Eden, & Eichenbaum, 2011). This finding showed that the HC encodes both the spatial and temporal features of a mnemonic representation through activity of neural

ensembles and can apply processes such as pattern separation to generate unique spatiotemporal contexts.

Importantly, however, the activity of HC neurons showing properties of *time cells* was found to be most strongly modulated by a combination of both temporal ordering and spatial location, indicating that these neural ensembles allow for conjunctive representations of both time and space (Eichenbaum, 2013). Although more research is needed to clarify the convergence and divergence of temporal and spatial processing in HC neurons, the identification of *time cells* and their modulation by spatial factors indicates that the fundamental neurocognitive function of the HC may be to allow one to abstract away from the present moment and situate oneself in a different time and place by generating mental representations of the world that are both consciously accessible and able to be manipulated in a goal-directed manner. To understand how this might occur requires a more comprehensive account of the taxonomy memory systems in the human brain and how interregional interactions between brain regions providing specialized processing allows for the generation and utilization of holistic mnemonic representations of the world.

1.2 Models of memory function

While a review of the complete taxonomy of memory systems is beyond the scope of this chapter, I will provide a more detailed overview of theoretical models on episodic memory and how it relates to other forms of memory. One of the most influential theories on episodic memory systems in the 20th century, termed *the standard model*, was proposed by Squire and Zola-Morgan (Squire & Zola-Morgan, 1991). Under this model, human memory is delineated into two broad categories of declarative and non-declarative memory. Declarative (explicit) memory is defined by memories that can be spoken about, encompassing both memories for

facts and memories for events. Non-declarative (implicit) memory encompasses all forms of memory systems that are not communicable via speech, such as motor learning, priming, and basic forms of classical conditioning. The declarative memory system at a cognitive level largely resembles Tulving's proposed distinction between episodic (events) and semantic (facts) memory. In Squire and Zola-Morgan's theory, regions in the medial temporal lobe are critical in forming neural representations underlying episodic memory by binding together different elements of an experience using associative learning mechanisms such as long-term potentiation. More specifically, the HC is theorized to be central to the medial temporal lobe memory system, creating 'summary sketches' of neocortical patterns of activity that can then be reinstated via activation of HC neurons. This reinstatement process allows a person to re-experience an event through the coordinated reactivation of cortical areas specialized to process the types of environmental and episodic features that were originally experienced, essentially creating a mental movie (i.e. a memory) of a past event that can be introspected upon. In its original proposal, this model viewed the inclusion of the HC in generating neural representations of events as transitory, only being involved in the encoding of a representation and its reactivation over limited timeframe of a few weeks while the memory becomes consolidated. Long-term, more stable memories, did not require HC activity for reinstatement, instead relying on changes to synaptic weights between areas of the neocortex coding for the episodic features of a memory.

The advent functional magnetic resonance imaging (fMRI) in the mid 1990s provided cognitive neuroscientists with a powerful methodology to study the hypotheses put forward in Squire and Zola-Morgan's theory (1991). Together with neuropsychological research on retrograde amnesia, evidence refuting claims of the *standard model* began to increase, suggesting that the two forms of declarative memory were subject to different effects of retrograde amnesia,

and therefore putatively relied on different components of the medial temporal lobe system (Nadel & Moscovitch, 1997; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). Critically, the view of *the standard model* that the HC was only involved in retrieval of recently encoded memories was not supported by research on the temporal gradient of retrograde amnesia on autobiographical memories, where damage to the HC could impact retrieval of memories that occurred 10-30 years previously (Nadel & Moscovitch, 1997). Additionally, initial fMRI evidence began to accumulate showing that level of activity in the HC or areas of the neocortex did not differ when retrieving memories recently acquired compared with those acquired decades ago (Ryan et al., 2001).

Building on the general perspective from *the standard model* of neocortical activity being sparsely indexed by neural representations in the HC, Nadel and Moscovitch (Nadel et al., 2000; Nadel & Moscovitch, 1997) proposed the *multiple trace theory* (MTT) of memory function. This theory attempted to accommodate the emerging evidence that the HC was critical for retrieval of remote memories by proposing that reinstatement of neocortical activity patterns associated with an event always necessitates activity of the HC. Similar to the *standard model*, MTT posited that environmental and episodic features processed across the brain are bound through associative learning mechanisms to a spatial context generated by the HC. Critically, MTT posits that the spatial context of a memory is always generated by the HC, and therefore even memories of events in the remote past require HC-neocortical interactions to be properly recalled. This view borrows partially from the cognitive map theory of spatial memory outlined previously (O'Keefe & Nadel, 1978), where place cells in the HC provide a neural computational mechanism to understand the spatial relationships between objects in an environment. Importantly, MTT suggests that spatial contexts are uniquely coded by the HC and that these spatial contexts

provide the scaffold upon which other features from memory (e.g. landmarks, objects, people, inter-personal interactions) are bound into a coherent representation. This proposal makes several predictions about hippocampal function, indicating that cognitive processes involving the generation of spatial contexts, and not the retrieval of previously experienced spatial contexts *per se*, requires the HC to provide a spatial context upon which neocortical information can be integrated into a holistic representation.

Aside from MTT, other prominent theories on the function of HC for memory retrieval have been developed in the wake of the *standard model*. Using results primarily from research using animal models, Eichenbaum (Eichenbaum, 2000a) proposed the *relational network theory* that posits the HC is able to disambiguate overlapping memories that share a common event or spatial location through a pattern separation mechanisms, while also being capable of binding together sequences of places or events into specific episodes. In this view, the HC acts as the crux of a memory system that facilitates associative representations, organizes them sequentially, and embeds them in relational networks so that episodes appear as a holistic representation, and elements from one memory can prime the retrieval of another (Eichenbaum, 2004). An important distinction here relative to MTT is that the HC provides neural mechanisms to bind and disambiguate environmental and episodic features that are encoded into memory, providing a more generalized mechanism for episodic memory formation and retrieval than the spatial context hypothesis of MTT. Additionally, this model predicted that both temporal and spatial information of a mnemonic representation is generated through relational processing in the HC, a prediction confirmed by the discovery of *time cells* (MacDonald et al., 2011).

1.3 Mental time travel

One of the most pervasive features of the human mind is our ability to re-experience the past in vivid detail. However, we are equally able to project ourselves forward into future, anticipating different hypothetical states of the world. We spend upwards of 30% of our day thinking about past experiences and anticipating future scenarios (Fox, Nijeboer, Solomonova, Domhoff, & Christoff, 2013; Killingsworth & Gilbert, 2010). For much of the 20th century, thinking about the past and the future were treated separately, with the majority of empirical work attempting to delineate the cognitive and neural processes involved in remembering past experiences (Moscovitch, Cabeza, Winocur, & Nadel, 2016). By the end of the century, scientists began to speculate that episodic projections into the past or future may share a similar neurocognitive basis, in which overlapping cognitive and neural systems allow for the experiencing of non-present timeframes (Schacter et al., 2012).

One early theory suggested that mentally traveling through time represented a unique form of awareness, termed autonoetic consciousness, that allow for conscious experiences outside of the present moment (Wheeler, Stuss, & Tulving, 1997). This theory formulated the *shared systems hypothesis*, predicting that the episodic memory system was also utilized to think about the future. The initial proposal by Wheeler and colleagues (1997) centralized the neural mechanisms of future thinking on areas of the prefrontal cortex, positing that autonoetic consciousness required elaborate and complex control of other systems in the brain, such as those supporting episodic memory, to generate, maintain, and simulate interaction using mental representations. However, more recent theoretical proposals (Atance & O'Neill, 2001) and empirical work (Addis, Wong, & Schacter, 2007; Szpunar, Watson, & McDermott, 2007) suggested that PFC was only one region in a wider network distributed across the brain that

allows for the generation and simulation of mental episodes based outside of the present moment.

The *shared systems hypothesis* represented a pivotal moment in the study of episodic memory, opening our understanding of the future to the theoretical and methodological advances that had been made in the decades before on memory research. Under this perspective, Hassabis and colleagues (Hassabis, Kumaran, Vann, & Maguire, 2007b) reported that patients with bilateral HC damage were impaired in both recalling past events and envisioning new scenarios that had never been experienced. Notably, the researchers observed that the primary deficit when making these mental projections outside the present moment was a reduced ability to generate a coherent spatial context in which to simulate experiences. This finding had two important implications. First, it shifted the potential loci of episodic future thinking to the HC, while giving credence to the overlap in neural mechanisms between episodic recall and future thinking. Second, it suggested that the primary function of the HC in recalling past events or anticipating new ones was to provide and organize spatial information into a task-oriented context that could be used to mentally simulate events, akin to the proposal of MTT.

The neural overlap between experiencing events in the past and future was further investigated by two brain imaging studies. A study by Szpunar and colleagues (Szpunar et al., 2007) used event-related functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms associated with thinking about past or future episodic events. Comparing differences in neural activity between the past and future, the researchers noted that future thinking involved increased functional activity in premotor and posterior parietal cortices, putatively through the simulation of novel action sequences rather than remembered ones. Additionally, they observed that thinking in both timeframes showed similar levels of

engagement in the medial PFC, bilateral parahippocampal gyrus, posterior cingulate cortex (PCC), occipital cortex, and the cerebellum. The researchers interpreted this pattern of results by drawing comparisons between autobiographical memory tasks and mental navigation of familiar routes, suggesting that each cognitive task involved the reactivation of a visuo-spatial context. Similarly, a study by Addis and colleagues (Addis et al., 2007) had participants generate and elaborate on episodic events at different time points in the past or the future. Using a conjunction analysis, the researchers observed similar increases in functional activity within the left HC, as well as within visual and associative regions of occipital and posterior parietal cortices when participants generated mnemonic representations in either temporal direction. However, the researchers also found differences in neural activity between the past and future, with the right HC and areas within PFC and the medial temporal gyrus showing increased levels of functional activity during the generation of mnemonic representations in a future timeframe.

Notably, the study by Addis and colleagues (2007) provided a critical insight in relation to the default mode network (DMN), a network of hub regions in the brain that display increased functional activity and inter-regional connectivity when a person is not overtly engaged in a task (Raichle et al., 2001). The DMN network is composed of medial PFC, PCC, and both the left and right lateral parietal cortex. Importantly, the DMN is theorized to comprise a task-negative network that displays attenuations in neural activity when a person is engaged in a cognitive task (Fox et al., 2005) and failure to suppress regions of the DMN has been shown to adversely impact behavioural performance (Fox, Snyder, Vincent, & Raichle, 2007; Weissman, Roberts, Visscher, & Woldorff, 2006). However, during the elaboration phase of the study in which participants attempted to increase the amount of detail of a generated mental representation, Addis and colleagues (2007) observed that both past and future elaborations robustly engaged

medial PFC and PCC (see Figure 2 in Addis et al., 2007), both primary components of the DMN. Although the authors did not discuss this finding in the context of DMN research, it suggested that the shared system supporting the elaboration of episodic events in the past and the future showed marked overlap brain regions posited to underlie the spontaneous, self-referential thought that characterizes the resting-state periods typically used to study the DMN (Andrews-Hanna, Smallwood, & Spreng, 2014).

Considering the overlap in neural activity associated with episodic projections, mental navigation, the DMN, and tasks involving theory of mind, Buckner and Carroll (Buckner & Carroll, 2007) proposed a theoretical model in which a core neurocognitive system allowed people to mentally project themselves outside of their present moment, egocentric awareness. Similar to *shared systems hypothesis* (Wheeler et al., 1997), the model by Buckner and Carroll drew parallels between cognitive tasks eliciting similar patterns of neural activity by attempting to find a common psychological function. The network topology they proposed consisted of regions of the medial PFC, PCC and surrounding areas (retrosplenial cortex, precuneus), and regions of the medial temporal lobe, including the HC. They posited that this network afforded a core ability of projecting a first-person perspective into different places, perspectives, and points of time. This function was also characterized as adaptive, in that the core network could flexibly alter its topology and output function to accommodate different task demands. Moreover, the authors suggested that the existence of such a network in the brain supported the idea of prospective coding (Schacter et al., 2007) in which the function of episodic memory is not only to recall the past, but also to supply the mental resources needed to make mental simulations of potential future states of the world.

Closely after the publication of Buckner and Carroll's model (2007), Hassabis and Maguire proposed a revised perspective entitled the *scene construction hypothesis* (Hassabis & Maguire, 2007). Borrowing the insight of a shared system between episodic projections and mental navigation, the authors developed a theoretical model in which the core function of the network was not self-projection, but the generation and elaboration of a spatial context, similar to the proposals by Szpunar and colleagues (Szpunar et al., 2007), and Addis and colleagues (Addis et al., 2007). In their model, Hassabis and Maguire additionally included the capacity to mentally simulate self-referential imagined events, not strictly future scenarios that a person believes may occur. Using the finding on spatial context from their earlier work on patients with HC damage (Hassabis, Kumaran, Vann, & Maguire, 2007b), the authors articulated a perspective in which neural ensembles in the HC generate and organize spatial information into a framework upon which additional episodic details can be bound, allowing for mental simulations of past, future, and hypothetical episodic events. The key distinction here compared to the model by Buckner and Carroll (2007) is that the amount of spatial information and its degree of organization in a mental simulation is posited to associate with HC function, as the processes of constructing mental scenes, not the amount of self-projection, necessitates HC activity in a cognitive task. This perspective was substantiated by reference to their previous study on amnesic patients (Hassabis, Kumaran, Vann, & Maguire, 2007b) where they found deficits in constructing the spatial context of hypothetical scenarios.

A following study on K.C., a patient with severe retrograde and anterograde amnesia, provided a critical test for the core function of HC-based neural networks (Rosenbaum, Gilboa, Levine, Winocur, & Moscovitch, 2009). To test whether HC function was associated deficits in recalling details from autobiographical memory, or constructive/reconstructive processes during

the generation of a mental scene in a non-present timeframe, the authors devised a clever task design that had K.C. construct fictional events and recall details of well-known fairy tales and bible stories. The authors found that K.C. displayed impairments in both recalling events from his past, as well as generating imaged scenarios that were never personally experienced. Although K.C. could generate the gist and some information about both the personal and non-personal narratives, the narratives displayed a lack of detail generation and coherent narrative structure. Intriguingly, K.C. had a persevered capacity for theory of mind (Rosenbaum, Stuss, Levine, & Tulving, 2007), suggesting that the forms of amnesia observed in K.C. were not related to his capacity to reason about the state of another's mind, providing further evidence the function of the core episodic network was not specific to self-projection. The researchers also observed that the impairment of detail generation in K.C. extended beyond the spatial domain, suggesting that the basic tenants of the *scene construction hypothesis* were viable, but non-spatial aspects of mental representations also need to be generated and organized through HC-based processes. This process of detail generation and organization could occur through mechanisms of relational binding (Eichenbaum, 2004) and suggested that the HC is necessary for the integration of environmental and episodic features occurring during the generation and elaboration of mental representations.

1.4 The mind's chimera: multi-featural models of the world

As noted by the both the *scene construction* (Hassabis & Maguire, 2007) and *detail generation and binding* (Rosenbaum et al., 2009) hypotheses, the mental representations of the world we generate and introspect upon are composed of a multitude of environmental (i.e. places, landmarks, paths) and episodic (i.e. action sequences, inter-personal interactions) features. These features are posited to be dynamically reinstated, combined, and organized in a

constructive manner, where elements of past experiences can be flexibly integrated into a task-oriented mental representation used to simulate or relive experiences in a spatiotemporal context (Arnold, Iaria, & Ekstrom, 2016; Schacter et al., 2007). While much more research is needed to develop a taxonomy of the classes of information that can be mentally represented and holistically combined, brain imaging studies using intracranial electrodes, as well as recent advances in multivariate statistical techniques and algorithms borrowed from machine learning, have begun to identify different categories of information contained in a mental representation can be decoded based on patterns of brain activity.

The *cognitive map theory* of HC function posited that spatial representations of environmental information, such as landmark location and distance estimates between landmarks, are coded and represented by activity of view-point invariant *place cell* ensembles (O'Keefe & Nadel, 1978). Research in rodents widely supported this perspective, showing that the location of a rodent at any point in time can be decoded based on the patterns of activity in *place cell* ensembles (Wilson & McNaughton, 1993). Place responsive cells have also been demonstrated in the human HC (Ekstrom et al., 2003), suggesting that the neural code for spatial locations is similarly represented by HC *place cell* dynamics in humans. However, conjunctive coding of current and goal locations has also been found, indicating that task contexts are able to modify neural codes for a spatial layout, putatively through remapping processes that allow for alterations to the location sensitivity of *place cell* neurons that anticipate trajectories through an environment (Brown et al., 2010). The study be Ekstrom and colleagues (Ekstrom et al., 2003) additionally found evidence for *place cells* in both parahippocampal region and frontal lobes, albeit to a lower degree than in the HC, providing one of the first indications that the neural code

for spatial environments is not specific to the HC in humans and that a more distributed network of brain regions may be coding spatial information.

If *place cells* provide the neural code of the spatial layout of an environment, it is reasonable to speculate that the spatial context of a mental representation is also coded by the coordinated activity of place sensitive HC neurons, similar to the proposal of HC function in MTT. This type of decoding within a mental representation of an environment was first shown by Brown and colleagues (Brown et al., 2016). The researchers asked participants to mentally simulate navigating to a target location from a starting point in a recently learned environment. Using a classifier, they showed that both current location (i.e. each trial starting point) and the goal location were represented in distributed patterns of HC activity. Further, they also showed that intervening landmarks along the simulated route could be decoded, indicating that HC neural activity was associated with representing and organizing spatial locations within a mental representation of the environment. Above chance future goal decoding was also found in the parahippocampal, perirhinal, and retrosplenial cortex, showing that imagined spatial locations were also represented in these regions. Importantly, the strength of goal representation in the HC was also correlated with activity in the parahippocampal, retrosplenial, and occipital frontal cortex, indicating that these regions participated in a functional network that together enabled the multi-featural representation of a spatial environment that was used to mentally simulate behavior.

The sensitivity of *place cells* is posited to vary based on the allocentric (i.e. landmark-based) information of environmental features independent of heading direction and distance estimates between a navigator and environmental features (Burgess, 2008). However, a second spatial coding system is hypothesized to exist in humans, which represents egocentric (i.e. body-

centric) heading and allows for a sense of direction when a person is situated in an environment (Ekstrom et al., 2003; Vass & Epstein, 2013). In a recent study, Marchette and colleagues (Marchette, Vass, Ryan, & Epstein, 2014) showed that patterns of neural activity in the retrosplenial cortex can decode both location and direction information when participants imagined mentally navigating a recently learned environment. Critically, the researchers showed that decoded location and direction in retrosplenial cortex was always relative to environmental features, thereby providing a neural basis for the complementary, egocentric system hypothesized to interact with place cell allocentric representations during navigation.

The outlined studies demonstrate that mental representations include spatial information about environmental features and egocentric perspectives that are coded by neural activity in a distributed set of regions across the brain. Similarly, temporal information derived from previous experiences is also coded in mental representations. Comparing the amount of time to navigate paths through a virtual city with mental simulations of navigating such routes, Arnold and colleagues (Arnold et al., 2016) showed that both virtual and mental navigation had correlated durations, although the duration of mental navigation was temporally compressed such that it was experienced at ~2.4x the rate at which it took to physically navigate the same route in the virtual city. Intriguingly, the duration of a mentally simulating a route was also inversely related to both the vividness of visual imagery and the spatial coherence of environmental features during mental simulations. This finding provided support for the constructive nature of memory (Schacter et al., 2007), and indicates that phenomenological qualities of mental simulations can serve as proxies for neurocognitive processes underlying the reinstatement and integration of multi-featural mental representations (Arnold et al., 2016).

The process of feature reinstatement and integration is not specific to spatial tasks, but appears to be a general mechanism subserved by the core network of regions outlined in the previous section. Paradigms engaging episodic memory process have shown that reinstatement of neural activity while recalling an episodic event is mediated through HC pattern completion mechanisms that coordinate the selective reactivation of neocortical areas representing features from the recalled event (Horner, Bisby, Bush, Lin, & Burgess, 2015; Leiker & Johnson, 2015). A study by Horner and colleagues (Horner et al., 2015) using a novel associative memory paradigm provided compelling evidence for this process. Investigating differences in HC activity when encoding overlapping pairs of stimuli (i.e. people, places, objects) in either an open-loop (A-B, B-C, C-D pairs) or closed-loop (A-B, B-C, A-C pairs) conditions, the researchers observed increased HC activity during the third encoding trial in the closed-loop condition (and therefore completed the three-way association) that was predictive of subsequent memory. This was interpreted as evidence for pattern completion by the HC, where the HC putatively bound each stimuli type into a holistic representation based on associative memory processes. The researchers also showed that neocortical areas displaying increased functional activity during encoding of each stimuli type (parahippocampal cortex for places, medial parietal for people, and lateral occipital cortex for objects) were reactivated during the retrieval task, which cued a specific stimulus and asked if it was previously associated with another stimulus. Critically, they showed increased neocortical reinstatement for the closed-loop condition in each of the three stimuli-specific areas, even though only two stimuli types were presented during the retrieval trial (e.g. a landmark cued with a person target still reactivated lateral occipital cortex representing the associated object). These findings support central tenants of MTT and *scene construction*, where the HC provides the contextual framework for the reinstatement and

integration of different feature types, and suggests that HC-cortical interactions code for the associative structure of a holistic, multi-featural representation (Buchel, Coull, & Friston, 1999). Collectively, the studies outlined in this section indicate that the encoding, generation, and manipulation of mental representations operates through the functional interactions of multiple brain regions, centered on the HC, and suggest that variability in both the topology and dynamics of this network are critical for effectively utilizing such representations.

1.5 Network interactions underlying mental representations

Each of the aforementioned models of memory function theorize that hippocampal-cortical functional interactions are necessary to bind multi-featural information into a mental representation about a past or, in the case of the *scene construction* and *detail generation and binding hypotheses*, a future experience. Empirical work investigating memory function in the context of these models has generally relied on bivariate statistical techniques that allow for evaluation of region-to-region changes in functional interactions (e.g. Brown et al., 2016; Horner et al., 2015). While bivariate techniques provide a wealth of information in regards to cognitive processes that are generated and modified by dynamical interactions between two sets of regions, they fail to capture more complex forms of regional information processing and network participation in topological structures consisting of a large set of connected components (Bassett, Nelson, Mueller, Camchong, & Lim, 2012). In the context of memory function, such a perspective is critical given that the reinstatement of vivid, multi-featural representations requires reinstatement of cortical activity across a multitude of brain regions (Brown et al., 2016; Horner et al., 2015), including associative regions which may perform certain types of information integration prior to feeding information forward to the HC. Multivariate techniques such as graph theoretical analysis allow for quantification of various measures of network function and

regional participation that are inclusive of numerous sets of functional interactions, and are therefore more adept at characterizing contextual changes in network states and regional roles in information processing and integration (Bullmore & Sporns, 2009; Rubinov & Sporns, 2010).

The network interactions underlying the retrieval of mental representations has recently been investigated in a set of studies using graph theoretical measures. Watrous and colleagues (Watrous, Tandon, Conner, Pieters, & Ekstrom, 2013) used phase synchrony between intracranial electrodes in lateral PFC, parietal cortex, and the parahippocampal gyrus to test the hypothesis that global connectivity, rather than regional processes, contributed to accurate retrieval of spatial and temporal information from a past experience. The researchers showed that correct retrieval of each type of information was associated with increases in the number of pair-wise connections between electrodes showing inter-regional functional coupling, and that this measure of global connectivity was a better predictor of correct retrieval than changes in regional activity. This finding was also replicated using fMRI data (Schedlbauer, Copara, Watrous, & Ekstrom, 2014). The researchers also investigated the frequency range of functional interactions within the global network during correct recall of spatial versus temporal information, finding that accurate retrieval of spatial information was best characterized by network interactions in the 1-4 Hz band. Conversely, retrieval of temporal information displayed a preferred frequency range of 7-10 Hz. Considered together, these results provided some of the first evidence that global state changes in functional interactions across the brain are associated with correctly recalling information from past experiences, and that multiple classes of information bound in a mnemonic representation of a past experience are able to be processed by the same network using different spectral fingerprints.

The finding that accurate memory retrieval is associated with increases in global functional connectivity across the brain suggest that the capacity of a network to distribute and integrate information may explain individual differences in memory function. To test this, Arnold and colleagues (Arnold, Protzner, Bray, Levy, & Iaria, 2014b) identified a core network of regions, including areas in PFC, the parahippocampal gyrus, parietal cortex, and posterior cingulate cortex, engaged by all participants in a study when retrieving spatial representations of a virtual city and making orientation decisions based on those representations. The topology of this network was then used to assess its global efficiency using resting-state fMRI data that had been collected previously to performing the orientation task used to identify regions in the retrieval network. Functional interactions in resting-state data provide a putative measure of the functional architecture of the brain (Biswal et al., 2010), allowing for an assessment of the information processing capacity of neural networks. The researchers found that the global efficiency of the identified network was strongly predictive of which participants made a high number of correct orientation decisions. This suggests that memory networks vary in how efficiently they integrate and distribute information, and that an increased capacity to do so allows for more accurate generation of the spatial context of a mnemonic representation.

Considered together, these studies provide initial support for dynamical network interactions underlying the reinstatement spatial and temporal features of a mnemonic representation. In light of this, a recent theoretical model was proposed that posited the spatiotemporal context of a mental representation is generated through a non-aggregate processing stream, where partially shared computations between network regions affords the capacity to mentally represent an episodic event (Ekstrom, Arnold, & Iaria, 2014). Under this view, the generation of spatiotemporal contexts does not occur through the additive summation

of specialized processes in each network region (i.e. each region contributes one specific component of a mental representation, which is sequentially added together into a representation), as some theoretical models have proposed (Burgess, 2008). Rather, mental representations are generated through complex and dynamical patterns of functional interactions that provide context specific changes to regional computations and allow for the preservation of specific cognitive processes in the presence of lesions affecting putatively specialized brain regions. Versions of a non-aggregate model of brain function have been proposed elsewhere (Bassett & Gazzaniga, 2011), such as the *neural context hypothesis* put forward by McIntosh (McIntosh, 2000), positing that the brain expresses functional plasticity in which the output function of a particular region is contingent upon the set of other regions it is functionally coupled with, and the process-specific alliance model by Cabeza and Moscovitch (Cabeza & Moscovitch, 2013), where brain regions that are functionally coupled provide a specific computation, but the output of the alliance is a complex phenomenon that cannot be explained by summating each specialized process.

The model proposed by Ekstrom and colleagues (Ekstrom et al., 2014) makes several predictions about putative dynamical network interactions involved specifically in generating and reinstating mnemonic representations based on a spatiotemporal context. First, it shifts the explanatory emphasis from how a region produces a cognitive function to how a region participates in a broader network from which a complex cognitive function emerges. In the case of generating the spatial context of mental representation, it suggests that the HC is involved in facilitating the exchange of information between regions of a network supporting memory reinstatement, rather than solely providing the spatial computations necessary for it. This leads to the prediction that the HC involvement in a task-oriented network is dynamic, changing based on

current task demands, rather than fixed, which would be predicted from models such as *cognitive map theory*, where the HC is posited to provide all allocentric based spatial computations (O'Keefe & Nadel, 1978). If it were the case that the HC provided critical spatial computations to generate mental representations, its contribution (and therefore neural activity) should be relatively fixed across tasks requiring those computations. Similarly, the model predicts that the topological structure of memory networks involves dynamic reconfigurations that are used to optimize performance, as components of the task-oriented network adapt to information processing demands by altering their functional interactions with other components. In additive models of mental representations, the topological structure is predicted to be fixed, as each component of the network contributes a specialized function that is required to generate a specific output behavior. As such, this model departs from both MTT and the *scene construction hypothesis* insofar as it suggests that the spatial context of a mnemonic representation can be instantiated (at least partially) by spatial computations occurring outside the HC. Rather, the HC is posited to play a principle role in coordinating information exchange and integration of reinstatement episodic features distributed throughout the cortex, akin to the *detail generation and binding hypothesis* (Rosenbaum et al., 2009) and the *relational network theory* (Eichenbaum, 2004) of HC function.

1.6 Predictions

The primary aim of this thesis is to investigate the neural mechanisms that allow environmental features to be encoded, reinstated, and manipulated to subserve prospection. It uses the perspective articulated by Ekstrom and colleagues (Ekstrom et al., 2014) as a guiding framework to organize the hypotheses and associated analytical approaches. It attempts to resolve and inform discrepancies between MTT (Nadel & Moscovitch, 1997), *scene construction*

(Hassabis & Maguire, 2009), *detail generation and binding* (Rosenbaum et al., 2009), and the network model of allocentric representations (Ekstrom et al., 2014). Moreover, in doing so it attempts to provide empirical insights into dynamical network processes that are often posited by theoretical models of memory function, but have yet to be quantified based on multivariate techniques suitable for describing complex network computations.

The secondary aim is to evaluate various hypotheses about HC function and the neural basis of mnemonic representations using an ecologically valid paradigm. Traditional approaches to studying the generation and reinstatement of mnemonic representations typically involve experimental tasks using basic forms of stimuli, such as pictures or words/labels, that are used as proxies for their real world counterparts (Cabeza & Moscovitch, 2013). Although informative in understanding the basis of associative memory processes related to mental mnemonic representations, they fail to capture the richness, detail, and complexity of information processing that occurs in the brain when we interact with the world. As such, they may underestimate dynamical network processes allowing humans to encode and reinstate multi-featural mnemonic representations (Ekstrom et al., 2014). Here, a large-scale virtual city was constructed, and experimental tasks developed, to mimic stimuli and naturalistic behavior experienced in daily life. While still a proxy to behavior in the real world, spatial navigation paradigms such as those utilized here are posited to be a model system for cognitive neuroscience, due to the complex and multi-component cognitive processing that reflects experiences outside the laboratory (Chersi & Burgess, 2015).

Chapter 2 addresses the issue of dynamical network processes during spatial encoding. The spatiotemporal context of a mental representation requires the encoding and organization of spatial and temporal information derived from experience (Arnold et al., 2016; Schacter et al.,

2012). Here, participants explore and encode the spatial layout of a virtual city using a simple spatial navigation task. Dynamical network processes are assessed at the topological level, as well as the changing role of the HC within local community and global networks while a mnemonic representation of the virtual city is being encoded.

Chapter 3 extends the findings of the previous chapter and evaluates detail generation during the reinstatement and manipulation of a mnemonic representation using a novel mental simulation paradigm. After encoding the city layout, participants first mentally simulate a route between landmarks and then subsequently navigate it through the virtual city. Global and local network states are compared, and measures of vividness and spatial coherence of environmental features during mental simulations are used to operationalize feature integration to test hypotheses pertaining to how the HC contributes to scene construction.

Chapter 4 departs somewhat from traditional models of memory function to explore hypotheses about the DMN and its role as a task-negative network. The topology of the DMN is compared at different levels of detail generation during mental simulations to rest, attempting to resolve how components of the DMN are associated with task-active networks supporting the reinstatement of mnemonic representations. The results are discussed in the context of both DMN theory and theoretical models that assume a shared system between memory processes and DMN activity (e.g. *scene construction*).

Chapter 5 attempts to integrate the findings across the three previous chapters into a cohesive theoretical perspective. The aim here is not to develop a unique, self-contained model of memory function, but to inform and build upon existing models through providing observations on complex network functions that have been sparsely investigated using suitable statistical techniques. The results are considered through the framework of MTT (Nadel &

Moscovitch, 1997), *scene construction* (Hassabis & Maguire, 2009), *detail generation and binding* (Rosenbaum et al., 2009), and the network basis of allocentric representations (Ekstrom et al., 2014). The chapter concludes with proposals for future research for experimental and clinical research areas.

Chapter 2

2.1 Abstract

Mnemonic representations based in a spatiotemporal context allow humans to re-experience the past or mentally simulate anticipated future scenarios by integrating environmental and episodic features in a constructive manner. Theoretical models post that this occurs through the dynamic interplay between the hippocampus, a region providing a putative neural index of environmental features, and areas of the cortex providing specialized information processing. While past work has generally supported these models during memory reinstatement, how environmental features are encoded and used to generate mnemonic representations is less well understood. Here, using spatial navigation as a model cognitive process, we investigate the dynamic nature of memory networks while a mnemonic representation of a virtual city is generated. We find that the brain reconfigures from a state of information integration, quantified by high global efficiency and low modularity values, when encoding demands are highest, to a state of localized processing once representations are formed. This reconfiguration is associated with changes in hippocampal centrality at the intra- and inter-module level, decreasing its role as a connector hub between modules and within a hippocampal neighborhood as integrative demands lessen. Together, the results provide a novel view of how mnemonic representations are generated through dynamical network processes.

2.2 Introduction

One of the most striking features of the human mind is our ability to re-experience the past in vivid detail. Memories pervade daily life, allowing us to develop a sense of self, find new and familiar locations, and identify more effective strategies for interacting with the world. The ability to encode and retrieve complex mnemonic representations by binding features from previous experiences is thought to be the primary function of an episodic memory system in humans (Tulving, 2002). These representations are hypothesized to be conjunctive in nature, integrating a myriad of sensory features from the environment – such as people, places, and objects – into holistic representations that can be used to guide behavior into the future (P. Byrne, Becker, & Burgess, 2007; Chersi & Burgess, 2015; Davachi, 2006). Theoretical and computational models suggest that these mnemonic representations are formed by integrating information processed throughout the neocortex in convergence zones (Burgess, 2008; Damasio, 1989; Marr, 1971; Meyer & Damasio, 2009; Nadel & Moscovitch, 1997), most notably the hippocampus (HC), where processes such as pattern completion allow representations to then be reinstated using a partial set of input features (Marr, 1971; Norman & O'Reilly, 2003; Rugg & Vilberg, 2013). Recent research has provided support for these models, showing that the architecture of the brain is structured to concentrate information flow to the HC (Mišić et al., 2014), and that the HC acts as a convergence zone during associative memory tasks (Backus, Bosch, Ekman, Grabovetsky, & Doeller, 2016; A. M. Gordon, Rissman, Kiani, & Wagner, 2014a), allowing different types of information processed in the neocortex to be reinstated and integrated into a holistic representation (Horner et al., 2015; Staresina, Cooper, & Henson, 2013).

Although there is preliminary empirical evidence for hippocampal-based information integration during memory retrieval (Backus et al., 2016; A. M. Gordon et al., 2014a; Horner et al., 2015; Iaria et al., 2014; Robin et al., 2014; Schedlbauer et al., 2014), key questions remain about how mnemonic representations are encoded in the real world. A critical but untested component of theoretical models is that when encoding occurs, there is a heightened demand to integrate information processed in sensory and first-order association cortices into neural patterns within memory structures that form the basis of a mnemonic representation (Damasio, 1989; Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Meyer & Damasio, 2009; Nadel & Moscovitch, 1997; Squire & Zola-Morgan, 1991). Recent work using functional Magnetic Resonance Imaging (fMRI) analyses has shown that encoding associations between sensory features (i.e. people, places, and objects) depends on neural activity in areas of the cortex specialized to the specific feature (Horner et al., 2015), and that hippocampal-cortical functional interactions increase when stimuli features need to be combined into a single associative representation (Gordon et al., 2014a; Staresina et al., 2013; Zeithamova, Dominick, & Preston, 2012). Surprisingly though, how regions distributed throughout the brain interact dynamically as a network during encoding and whether the forms of interaction change as representations are encoded and subsequently utilized remains unknown despite its critical importance to understanding memory function in humans (Chrastil, 2012; Ekstrom et al., 2014).

An important characteristic of brain network topology is modularity (Bertolero, Yeo, & D'Esposito, 2015). Modular systems are sub-networks or communities defined by dense interconnections between intra-module components, with sparse or weak inter-module connections (Newman, 2006). Of importance here, the dynamic formation and interaction of modules and their components defined using functional interactions between brain regions has

been proposed to provide a mechanism for adaptability in the brain (Ghosh, Rho, McIntosh, Kotter, & Jirsa, 2008; Meunier, Lambiotte, & Bullmore, 2010; Werner, 2010), putatively through a reduced cost to rapidly change network configurations in response to environmental demands (Kashtan & Alon, 2005; Kirschner & Gerhart, 1998). Dynamic shifts in modularity have been associated with motor learning tasks (Bassett et al., 2011) and working memory paradigms such as the n-back task (Cohen & D'Esposito, 2016; Stanley, Dagenbach, Lyday, Burdette, & Laurienti, 2014). In the present study, we use spatial navigation as a behavioural model to extend the line of research on network modularity to more complex cognitive processes, suggesting that the dynamic reconfiguration of module systems across the brain provides a general mechanism for encoding and reinstating mnemonic representations based on the degree to which environmental features needs to be integrated and associated over time.

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

To test these three predictions, we constructed a large-scale virtual city and calculated graph theoretical measures using fMRI data acquired while people encoded the spatial layout of landmarks in the city using a simple navigation task. Spatial navigation is a model system for understanding how mnemonic representations are encoded and reinstated to guide behavior and inform decision making processes (Arnold et al., 2016; Chersi & Burgess, 2015), with past research demonstrating that the topology of resting-state (Arnold et al., 2014b) and task-active networks facilitate the accurate reinstatement of spatial representations (Arnold, Burles, Bray, Levy, & Iaria, 2014a; Schedlbauer et al., 2014; Watrous et al., 2013). Here, for the first time, we used navigation to study dynamic network reconfiguration while encoding mnemonic representations and the role of putative memory structures underlying changes in network topology. For the global integration hypothesis, we calculated the modularity index *Q*, global efficiency, and global flow of distributed networks, and compared trials where participants were unsure about landmark locations to trials in which they were highly confident of knowing the landmark location. Next, we calculated the betweenness centrality, participation, and flow coefficient for the HC, graph theoretical metrics that assess the centrality of the HC at the global, inter-module, and local network level, respectively. Third, we calculated the local efficiency of the hippocampal networks to identify whether localized network processing increased as the need to integrate environmental information decreased.

2.3 Methods

2.3.1 Participants

Fourteen right handed undergraduates (9 female; mean age = 21.64, SD = 2.56) recruited through the University of Calgary research participation pool participated in the study. Prospective participants were pre-screened to exclude anyone who reported previously

experiencing nausea while playing a videogame. All participants provided informed consent prior to scanning, received $50 reimbursement whether they completed the experiment or not, and were debriefed after the experiment.

2.3.2 Environment design

The virtual city was designed using Unity3D (version 4.6; https://unity3d.com). The city was composed of an interconnecting series of roads lined with buildings (see Figure 7.1a). The configuration of the roads was constructed to be nearly symmetric across the city to minimize the potential to derive location information based on global geometrical cues. The city buildings consisted of target landmarks and non-target buildings. The non-target buildings were variations of three architectural styles that were repeated throughout the city and selected to be visually similar in order to reduce their use as spatial cues during navigation trials. Five target landmarks were selected to be visually unique relative to the rest of the city (Figure 7.11b). The location of the target landmarks was selected by applying a 10x10 grid over the city layout and randomly selecting grid locations to place the landmarks. Numerous shortcuts were created by placing walkable paths between the buildings and a series of back alleyways. We also included two blockades on the main roads to ensure that the shortest path between any two target landmarks was only available by taking shortcuts. Movement speed was capped at 6 virtual m/s, which approximates to a 4.47x increase over an average real world walking speed of 1.34 m/s given the relative scale of the virtual city. Post-experiment interviews suggested that participants primarily used relative orientation of target landmarks to one another to guide navigation. Aside from the exposure phase (see section 2.3.3), participants viewed the city by projecting it on a mirror in the scanner and moved using four buttons coded to forward and backward movement, and left and right rotation.

2.3.3 Task design

The task was divided into three phases: an exposure, encoding, and simulation phase. Prior to entering the scanner, participants were given an overview of the task and completed the exposure phase. The overview consisted of giving participants instructions on the mechanics of the task in each phase and provided time for them to ask the experimenter any questions. The exposure phase consisted of watching a video of first person movement along the perimeter of the city (see Figure 7.1a). The video stopped for 5 seconds at each of the target landmarks and the experimenter pointed to the landmark on the screen and verbally confirmed that the participant had seen it before proceeding. The video started at the same point it had started, which was a randomly selected point along the perimeter and was consistent across participants. The exposure phase was designed to give the participants a sense of scale of the city and a baseline knowledge of the target landmark identities and locations.

Once inside the scanner, participants completed the encoding phase. This phase consisted of a sequence of fixation, reinstatement, and navigation blocks (see Figure 7.1c). It began by placing participants at a random starting point in the city (randomized once and held consistent across participants), showing them an image of one of the target landmarks, and asking them to rate on a scale of 1-4 their confidence in knowing the location of the landmark (1: not at all, 4: very well). Afterward, the participants were instructed to find the cued landmark as quick as possible. Once located, the participants walked into the front of the building which prompted the next rest/reinstatement/navigation block sequence. We also included a helper arrow that was initiated once participants had taken more than 90 seconds to locate the landmark. The helper arrow always pointed in the cardinal direction of the cued landmark, requiring the participants to still make decisions on how best to navigate to it. The helper arrow was included based on results

from an initial pilot study that showed trials where participants took longer than 90 seconds frequently resulted in getting lost. Optimal path time between each landmark pair was calculated by taking the quickest possible path between landmarks using available shortcuts (mean path time for optimal routes = 24.85 seconds, *SD* = 7.15; mean number of turns = 5.9, *SD* = 2.33). As with the starting point, the order of starting-goal landmark pairs was randomized once and held consistent across participants. The encoding phase lasted for 23 minutes and had an upper limit of 21 possible trials consisting of all pairwise combinations of landmarks in both directions, as well as the initial starting trial. At the end of the 23 minutes, scanning stopped irrespective if they had completed all the trials or not.

2.3.4 Functional MRI data acquisition

All MRI data were collected using a 3T GE Discovery MR750w scanner with a 32-channel head coil. A single shot EPI sequence was used during the encoding phase, consisting of 38 interleaved T2*-weighted slices per volume (total volumes: 685, flip angle: 77°, TR: 2000 ms, TE: 30 ms, 3.6 isotropic voxel size, 64x64 matrix size). The first five volumes were discarded to allow for T1 equilibrium. Additionally, a T1-weighted three dimensional FSPGR anatomical image using 1mm isotropic voxels was collected to assist with normalization of the EPI data.

2.3.5 Functional MRI preprocessing

All fMRI data from the encoding phase were preprocessed through Nipype (Gorgolewski et al., 2011) using FSL (version 5.0.9; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/) and Advanced Normalization Tools (ANTs; https://github.com/stnava/ANTs). Data were first realigned with MCFLIRT, smoothed using a 7mm FWHM Gaussian filter, intensity normalized, and temporally filtered using a 90 second high-pass filter. Next, data were denoised using MELODIC to remove non-hemodynamic components based on inspection of the time course and power spectrum for

each component. Anatomical and EPI data were then normalized into MNI152 space and resliced into 2mm voxel space using ANTs by first computing a transformation matrix for registering each participant's anatomical image to the MNI152 2mm template, and then applying a linear transform of each EPI volume using the computed matrix.

2.3.6 Node definition

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

2.3.7 Graph construction

Correlation matrices for all network analyses were calculated using the conn toolbox inside SPM12. To further minimize non-BOLD signal from the data, anatomical images were segmented into grey matter, white matter, and cerebral spinal fluid (CSF) estimates. These tissue classes were then used to apply the CompCor noise correction method (Behzadi, Restom, Liau, & Liu, 2007) by regressing out principle components obtained from each participant's white matter and CSF estimates from signal located in grey matter. Next, a series of general linear models (GLM) were constructed by binning reinstatement and navigation periods at the trial level based on the confidence rating for each trial. That is, for each participant we binned their reinstatement and navigation blocks into four levels by how confident the participant was in knowing the target landmark location (1: not at all, 4: very well). Each GLM was then convolved

with the canonical hemodynamic response function in SPM12 and used to calculate 335x335 correlation matrices using Fisher transformed *r*-values.

2.3.8 Graph analysis

Calculation of all graph metrics was done using the brain connectivity toolbox for Python (version 0.4; https://github.com/aestrivex/bctpy). Briefly, a graph $G(N,E)$ is characterized as a set of N nodes (here, 335 ROIs) and E edges (here, Fisher transformed *r*-values) representing the relationship between time varying data in any pairwise combination of nodes. Graphs are represented as a correlation matrix C_{ij} where i, j is defined by the number of nodes being analyzed.

Each graph metric was calculated across a range of density levels by thresholding each correlation matrix C_{ij} based on a series of cost values (k). Cost thresholds are applied to isolate a fixed percentage of edges (i.e. connections) between nodes in a graph. For the present study, we investigated each graph metric across a k value range of 0.1-0.25 at .05 increments representing the top 5% to 25% edges in each graph, a similar range used to identify developmental (Khundrakpam et al., 2013) and clinical (Bassett et al., 2008) changes in network topology. Each thresholded correlation matrix was then binarized by setting all supra-threshold edges to 1 and all sub-threshold edges to 0 to produce an adjacency matrix used for calculating different graph metrics.

2.3.9 Global network metrics

We calculated three metrics to investigate reorganization of global network topology: modularity, global efficiency, and global flow. Modularity was calculated using a spectral community detection algorithm developed by Newman (2006). Modules are defined as a subset of nodes in a graph $G(N,E)$ such that nodes within a module are more densely connected than

between modules. Partitioning of a graph into modules is done by maximizing the modularity index Q by iterating over possible sub-divisions of a network. Q is obtained by first calculating a modularity matrix B_{ij} using the formula:

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

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

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

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

Global efficiency is the inverse characteristic path length in a graph (i.e. the average shortest path length between any two pairs of nodes; (Watts & Strogatz, 1998)). In functional brain networks, it represents the minimum number of statistical associations required to link any two brain regions and is indicative of the integrative and communicative capacity of a network to share information (E. Bullmore & Sporns, 2009; Sporns, Honey, & Kötter, 2007; van den Heuvel & Pol, 2010). Its inclusion in the present analysis is to provide a metric of global integration across all nodes in the network. Global flow is the average flow coefficient (Honey, Kötter, Breakspear, & Sporns, 2007) across all nodes in a graph and represents the degree to which, on

average, nodes act as hubs within local neighborhoods. Its inclusion here is quantify integration at a local scale.

2.3.10 Node centrality metrics for left and right HC

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

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

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

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

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

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

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

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

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

Local efficiency is defined by Latora and Marchiori (Latora & Marchiori, 2001) as the efficiency of a subgraph G_i composed centered on the *i*th node, where the subgraph is composed solely of nodes that are immediate neighbors of *i*. It is calculated using the formula

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

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

2.4 Results

2.4.1 Behavioral performance

The experiment began with an exposure phase in which participants viewed a video of passive first person movement along the perimeter of the city (Figure 7.1a). Following that, participants completed the encoding phase in the scanner (Figure 7.1b). Each trial began by cueing a target landmark and asking participants to rate their confidence in knowing its location within the city (termed the reinstatement block), after which they were asked to navigate to the cued landmark as quickly as possible (Figure 7.1c). Participants completed on average 13.14 trials (*SD* = 4.91) of 21 possible trials during the encoding phase. Mean path time was 82.7 seconds (*SD* = 69.24) and the average length of time during the reinstatement period was 2.85 seconds (*SD* = 2.09). Confidence ratings were negatively correlated with observed path time (r =

-0.32, $p < 0.001$) and path efficiency ($r = -0.31$, $p < 0.001$), indicating that higher confidence in knowing landmark locations was associated with more efficient navigation.

2.4.2 Global network reorganization during encoding

To test the hypothesis that functional networks across the brain demonstrate dynamic reorganization as mnemonic representations are encoded, we calculated and compared three network-level graph metrics by binning trial-level navigation and reinstatement blocks based on the confidence rating for knowing the target landmark location and compared them across a range of density thresholds. Confidence ratings of memory retrieval has been shown to engage a population of memory-selective in the HC posited to underlie the retrieval of mnemonic features within declarative memory systems (Rutishauser et al., 2015).

The first graph metric analyzed was the modularity index Q (Newman, 2006), a measure of the amount of modularity observed in a network. We calculated Q for both navigation and reinstatement blocks separately. In both cases, we found support for our prediction that higher encoding demands relates to lower modularity. For the navigation blocks, there was a statistically significant difference using paired-samples t-tests at different density thresholds of $k = 0.15$ ($t(13) = -2.57$, $p = 0.023$), $k = 0.2$ ($t(13) = -2.63$, $p = 0.021$), and $k = 0.25$ ($t(13) = -2.5$, $p = 0.026$). We also computed a summary metric by collapsing across all density thresholds and comparing differences of Q. There were also statistically significant differences in Q using this summary metric, ($t(55) = -4.87$, $p < 0.001$). For the reinstatement blocks, we additionally found support for our prediction with increased modularity in high confidence trials across all density thresholds, $k = 0.1$ ($t(13) = -2.57$, $p = 0.047$), $k = 0.15$ ($t(13) = -2.44$, $p = 0.03$), $k = 0.2$ ($t(13) = -2.6$, $p = 0.022$), $k = 0.25$ ($t(13) = -2.57$, $p = 0.023$), and as well as the summary metric, ($t(55) = -5.01$, $p < 0.001$). Figure 7.2a summarizes these results.

Next, to complement our modularity analysis, we computed the global efficiency values for each graph across the different density thresholds. Global efficiency represents the integrative and communication capacity of a network by indicating, on average, how interconnected nodes in a network are (Bullmore & Sporns, 2009; Sporns et al., 2007; van den Heuvel & Pol, 2010). As with modularity, our prediction here was that higher encoding demands would require more integration of information processed across the brain and therefore be related to higher levels of global efficiency. We found support for this prediction in both the navigation and reinstatement blocks across all density thresholds. For the navigation blocks, there were statistically significant differences at $k = 0.1$ ($t(13) = 2.5$, $p = 0.027$), $k = 0.15$ ($t(13) = 2.64$, $p = 0.02$), $k = 0.2$ ($t(13) = 2.66$, $p = 0.02$), $k = 0.25$ ($t(13) = 2.65$, $p = 0.02$), and for the summary metric ($t(55) = 5.23$, $p < 0.001$). This pattern of results was consistent for the reinstatement blocks at $k = 0.1$ ($t(13) = 3.07$, $p = 0.009$), $k = 0.15$ ($t(13) = 3.02$, $p = 0.01$), $k = 0.2$ ($t(13) = 2.94$, $p = 0.01$), $k = 0.25$ ($t(13) = 2.89$, $p = 0.01$), and for the summary metric ($t(55) = 5.97$, $p < 0.001$).

Thus far our data suggest that as encoding occurs, brain networks reorganize into a more modular structure with a reduced need of global information integration. Another important aspect of information flow in networks is based on the topological structure of local neighborhoods. In the context of encoding mnemonic representations, it is plausible to suggest that higher encoding demands are also associated with increased need for processing within local networks early on. That is, as features of an environment are encoded into a representation, there may be a higher demand placed on not only integrating between, but also processing within task-relevant systems such as the visual, somatosensory, and attentional subnetworks. To quantify and compare this, we calculated the global flow coefficient (Honey et al., 2007). This metric is the average flow coefficient across all nodes within a network, which represents how efficiently

information flows between neighboring nodes and is therefore representative of integration at a local level. Here, our prediction was that higher values of global flow (and therefore more information integration) would be associated with lower confidence trials due to the increased need to process different types of sensory information within different subnetworks. As with modularity and global efficiency, we found support for our hypothesis. For the navigation blocks, we found statistically significant differences at $k = 0.1$ ($t(13) = 2.32$, $p = 0.038$), $k = 0.15$ ($t(13) = 2.54$, $p = 0.024$), $k = 0.2$ ($t(13) = 2.69$, $p = 0.019$), $k = 0.25$ ($t(13) = 2.72$, $p = 0.018$), and for the summary metric ($t(55) = 5.28$, $p < 0.001$). This was consistent for the reinstatement blocks with statistically significant differences at $k = 0.1$ ($t(13) = 3.04$, $p = 0.009$), $k = 0.15$ ($t(13) = 3.03$, $p = 0.01$), $k = 0.2$ ($t(13) = 2.92$, $p = 0.012$), $k = 0.25$ ($t(13) = 2.91$, $p = 0.012$), and for the summary metric ($t(55) = 6.12$, $p < 0.001$).

2.4.3 Hippocampal centrality during encoding

The HC plays a putative role in pattern completion and neocortical reinstatement during memory retrieval (Horner et al., 2015). Therefore, we sought to ask whether the HC would additionally act as a network hub during encoding of mnemonic representations and how its role relates to the reorganization of global brain networks while representations are formed. To address this, we calculated four node-based metrics that quantify different aspects of hubness in a network. The first metric was betweenness centrality, a common measure of global network centrality that quantifies the number of shortest paths between nodes that pass through a given node. Figure 7.3a summarizes these results. Here, we found no statistically significant differences during navigation blocks for the right ($k = 0.1$ ($t(13) = 0.32$, $p = 0.75$), $k = 0.15$ ($t(13) = 0.5$, $p = 0.63$), $k = 0.2$ ($t(13) = 0.07$, $p = 0.95$), $k = 0.25$ ($t(13) = 0.25$, $p = 0.81$), summary statistic ($t(13) = -0.38$, $p = 0.7$)) or left HC ($k = 0.1$ ($t(13) = 0.07$, $p = 0.95$), $k = 0.15$ ($t(13) =$

1.13, $p = 0.28$), $k = 0.2$ ($t(13) = 0.66$, $p = 0.52$), $k = 0.25$ ($t(13) = 0.85$, $p = 0.41$), summary statistic ($t(13) = -1.12$, $p = 0.27$)). Similarly, for the reinstatement blocks we found no statistically significant differences for the right HC ($k = 0.1$ ($t(13) = 0.15$, $p = 0.89$), $k = 0.15$ ($t(13) = 0.48$, $p = 0.64$), $k = 0.2$ ($t(13) = 0.05$, $p = 0.96$), $k = 0.25$ ($t(13) = 0.52$, $p = 0.61$), summary statistic ($t(13) = 0.31$, $p = 0.76$)). For the left HC, there were no statistical differences across density thresholds, however there were increased values for the summary statistic during high confidence reinstatement ($k = 0.1$ ($t(13) = 1.58$, $p = 0.14$), $k = 0.15$ ($t(13) = 1.28$, $p = 0.22$), $k = 0.2$ ($t(13) = 1.22$, $p = 0.25$), $k = 0.25$ ($t(13) = 1.13$, $p = 0.28$), summary statistic ($t(13) = 2.31$, $p = 0.025$)).

Next, we calculated the flow coefficient (Honey et al., 2007). As outlined in the previous section, the flow coefficient indicates the centrality of a node within a local neighborhood. See figure 7.3b for the results. For the navigation blocks, we found statistically significant differences across all density thresholds for the right ($k = 0.1$ ($t(13) = 3.08$, $p = 0.009$), $k = 0.15$ ($t(13) = 3.15$, $p = 0.008$), $k = 0.2$ ($t(13) = 3.26$, $p = 0.006$), $k = 0.25$ ($t(13) = 3.07$, $p = 0.009$), summary statistic ($t(13) = 6.45$, $p < 0.001$)) and left HC ($k = 0.1$ ($t(13) = 2.44$, $p = 0.03$), $k = 0.15$ ($t(13) = 3.05$, $p = 0.009$), $k = 0.2$ ($t(13) = 3.42$, $p = 0.005$), $k = 0.25$ ($t(13) = 3.09$, $p = 0.009$), ($t(13) = 6.45$, $p < 0.001$)). However, for the reinstatement blocks we found no statistically significant differences at the individual density thresholds, although the summary statistic was significantly different for both the right ($k = 0.1$ ($t(13) = 0.81$, $p = 0.43$), $k = 0.15$ ($t(13) = 1.26$, $p = 0.23$), $k = 0.2$ ($t(13) = 1.41$, $p = 0.18$), $k = 0.25$ ($t(13) = 1.63$, $p = 0.13$), summary statistic ($t(13) = 2.56$, $p = 0.013$)) and left HC ($k = 0.1$ ($t(13) = 0.78$, $p = 0.45$), $k = 0.15$ ($t(13) = 1.78$, $p = 0.1$), $k = 0.2$ ($t(13) = 1.74$, $p = 0.1$), $k = 0.25$ ($t(13) = 1.95$, $p = 0.07$), summary statistic ($t(13) = 2.98$, $p = 0.004$)).

The two analyses so far suggest that the HC displays increased centrality within local, but not global, networks during navigation when encoding demands are high. However, given that we observed shifts in modularity associated with encoding demands, it is plausible that the HC is acting as a connector hub integrating information across these modules rather than as a hub across a singular whole brain network. To investigate this, we calculated the participation coefficient (Guimerà & Amaral, 2005). The participation coefficient quantifies the amount of inter-module connections of a node compared to the amount of intra-module connections, and is representative of the degree to which a node participates in and integrates across different subnetworks. These results are summarized in figure 7.3c. For the navigation blocks, we found increased participation coefficients when encoding demands were high across most of the density thresholds and the summary statistic for the right HC (k = 0.1 (t(13) = 1.97, p = 0.07), k = 0.15 (t(13) = 2.79, p = 0.015), k = 0.2 (t(13) = 2.92, p = 0.01), k = 0.25 (t(13) = 1.45, p = 0.17), summary statistic (t(13) = 4.54, p < 0.001)) but only with the summary statistic for the left HC (k = 0.1 (t(13) = 0.77, p = 0.46), k = 0.15 (t(13) = 1.65, p = 0.12), k = 0.2 (t(13) = 1.9, p = 0.08), k = 0.25 (t(13) = 1.31, p = 0.21), summary statistic (t(13) = 2.85, p = 0.006)). Similar to the flow coefficient, for the reinstatement periods we observed no statistical differences at the individual density thresholds, although there were statistical differences for the summary measure for the right (k = 0.1 (t(13) = 0.4, p = 0.7), k = 0.15 (t(13) = 0.83, p = 0.42), k = 0.2 (t(13) = 1.95, p = 0.07), k = 0.25 (t(13) = 1.44, p = 0.17), summary statistic (t(13) = 2.4, p = 0.02)) but not the left HC (k = 0.1 (t(13) = 0.55, p = 0.59), k = 0.15 (t(13) = 0.64, p = 0.54), k = 0.2 (t(13) = 1.6, p = 0.13), k = 0.25 (t(13) = 0.72, p = 0.48), summary statistic (t(13) = 1.74, p = 0.088)).

Lastly, we calculated the local efficiency for hippocampal subnetworks. As outlined previously, our prediction was that as encoding occurs and representations are formed, there

should be reconfiguration of network topology during navigation from a state supportive of global integration to one based on local processing. We found support for this prediction (see Figure 7.3d) with increased local efficiency in high confidence navigation blocks for the right (k = 0.1 (t(13) = -3.76, p = 0.002), k = 0.15 (t(13) = -3.15, p = 0.008), k = 0.2 (t(13) = -3.25, p = 0.006), k = 0.25 (t(13) = -3.08, p = 0.009), summary statistic (t(13) = -6.76, p < 0.001)) and across the majority of density thresholds for the left HC (k = 0.1 (t(13) = -1.04, p = 0.32, k = 0.15 (t(13) = -2.58, p = 0.022), k = 0.2 (t(13) = -3.36, p = 0.005), k = 0.25 (t(13) = -3.04, p = 0.01), summary statistic (t(13) = -4.21, p < 0.001)). For the reinstatement periods, we observed no statistical differences for the right (k = 0.1 (t(13) = 0.07, p = 0.94), k = 0.15 (t(13) = 1.12, p = 0.28), k = 0.2 (t(13) = 1.32, p = 0.21), k = 0.25 (t(13) = 1.59, p = 0.14), summary statistic (t(13) = 1.55, p = 0.126)) or left HC subnetworks (k = 0.1 (t(13) = 0.01, p = 0.99), k = 0.15 (t(13) = 1.73, p = 0.11), k = 0.2 (t(13) = 1.69, p = 0.11), k = 0.25 (t(13) = 1.94, p = 0.07), summary statistic (t(13) = 1.65, p = 0.105)).

2.5 Discussion

Theoretical and computational models of memory function posit that mnemonic representations are generated by integrating sensory features processed across the neocortex into neural patterns within memory structures, and the retrieval of these representations involves reinstatement of feature-specific activity in the neocortex via pattern completion mechanisms in the HC (Damasio, 1989; Marr, 1971; McClelland, McNaughton, & O'Reilly, 1995; Meyer & Damasio, 2009; Nadel & Moscovitch, 1997; Norman & O'Reilly, 2003). While there is increasing evidence for these models during memory retrieval (Backus et al., 2016; Gordon et al., 2014a; Horner et al., 2015; Schedlbauer et al., 2014; Staresina et al., 2013; Watrous et al., 2013), empirical evidence for how brain networks interact dynamically during encoding has been lacking. Here,

using confidence ratings as an index of processing demands within memory networks (Rutishauser et al., 2015), we demonstrate for the first time that the topological structure of brain networks reconfigures from a state of global integration to localized processing based on the degree of environmental information that needs to be integrated into a representation, and that the HC flexibly changes its role as an inter- and intra-module connector hub in response to these integrative demands.

Adaptability of complex networks is thought to operate in part through the dynamic formation and interaction of different network communities (Bassett et al., 2011; Ghosh et al., 2008; Meunier et al., 2010; Werner, 2010), allowing the network to optimize its output based on relevant environmental demands. Using 335 ROIs distributed across the brain, we found support for network adaptability during the encoding and retrieval of mnemonic representations. In navigation trials where participants had low confidence in knowing the target landmark location, we observed lower values of the modularity index *Q* compared with trials in which they had high confidence in knowing the landmark location. This suggests that the brain displays an increasingly stable modular topology as the need to integrate environmental features lessens and can dynamically reconfigure its community organization based on changing task demands. We extended this result at the global and local network level, finding that in low confidence navigation trials there was increased values of global efficiency and global flow across the brain. This pattern of results provides empirical support at the network level for the long held but sparsely tested hypothesis that encoding features into mnemonic representations increases the integration of information processed in a distributed set of systems across the brain (Damasio, 1989; Marr, 1971; McClelland et al., 1995; Meyer & Damasio, 2009; Nadel & Moscovitch, 1997; Squire & Zola-Morgan, 1991). Building on the perspective of Bassett and colleagues

(Bassett & Gazzaniga, 2011), we suggest that adaptability in network topology underlies changes in how domain-specific information is integrated into holistic representations in a manner that allows the contents of a specific representation to become more stable over time.

In the context of episodic theory, mnemonic representations are believed to be generated through learned associations between environmental features (Horner et al., 2015; Tulving, 2002). Over time, as associations are encoded, neural responses in domain-specific brain regions decrease (Buchel et al., 1999; Epstein, Higgins, & Thompson-Schill, 2005), a phenomenon known as repetition suppression. Importantly, changes in neural responses are coupled with increases in connectivity between brain regions (Buchel et al., 1999; Gordon et al., 2014a). This suggests that the associative structure of a mnemonic representation is coded in part by the functional interactions between different brain regions (Bassett & Gazzaniga, 2011; Eichenbaum, 2000b). This view is in line with perspectives on spatial memory, where theoretical models suggest that generating spatial representations of an environment requires the interaction of multiple neural systems across the brain (Byrne et al., 2007; Ekstrom et al., 2014) allowing both incidental and associative learning mechanisms (Doeller & Burgess, 2008), and that neural responses in spatial processing areas change as representations are formed (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003). Here, using principles of adaptability, we provide a putative mechanism for these processes, where the dynamic reconfiguration of network communities is posited to vary the degree of local and global interaction to accommodate changing in incidental and associative encoding demands. Our finding that global flow decreases as representations are encoded suggests that changes to the efficiency of different systems across the brain may impact on the degree of neural responses to specific environmental features. Further, decreases in global efficiency and increases in hippocampal community local efficiency indicate that as a

representation is formed, there is a decreased need to integrate across sensory and associative systems in the brain and an increased need to rapidly propagate information within the hippocampal sub-network. Although more research is needed, these findings provide a tentative experimental framework for understanding the neural basis of the dynamic formation of networked representations (Eichenbaum, 2000b).

The HC has long been thought to be a primary convergence zone (Backus et al., 2016; Eichenbaum, 2000b; Meyer & Damasio, 2009; Mišić et al., 2014), receiving multisynaptic inputs from both sensory cortices and associative systems in the perirhinal and parahippocampal cortex. This allows for conjunctive coding of high-level sensory and associative environmental features, such as spatial information to specific locations (Ekstrom et al., 2003; O'Keefe & Nadel, 1978) and the temporal sequence of places and events that form the basis of episodic memories (Davachi, 2006; Eichenbaum, 2004; 2013; MacDonald et al., 2011). Although the results of the current study are in line with the role of the HC as a convergence zone, our findings extend past results by showing that the HC demonstrates flexibility during representational encoding by changing the degree to which it acts as a connector hub within local networks, as well as between network modules. On low confidence trials where encoding demands are highest, we observed increased values of the flow coefficient, indicating that the centrality of the HC within its local network is associated with the need to integrate sensory and associative information. Importantly, we also observed increased values of the participation coefficient on low confidence trials in the right HC, supporting its role as an inter-module hub, combining information processed within different modules across the brain into a putative mnemonic representation. Conversely, on high confidence trials, we found evidence for increased levels of local efficiency within a hippocampal sub-network. Considered together, these results suggest that the

convergence of information into the HC is mediated in part by associative demands during the encoding of a representation, and operates dynamically by changing the functional interactions within and between network modules. As representations are formed, the centrality of the HC decreases while the efficiency of information flow within hippocampal sub-networks increases. This finding builds upon past work positing that the learned associations composing a mnemonic representation are coded in the functional interactions between brain regions (Buchel et al., 1999; Eichenbaum, 2000b), putatively through the reconfiguration of hippocampal interactions that initially allow sensory and associative information to be bound into a holistic representation that is subsequently coded by the functional interactions between components of a hippocampal based sub-network.

Although the primary focus of the current study was on encoding mnemonic representations, we included an analysis of graph theoretical measures during the period where participants reinstated their memories of target landmark locations. This was done to facilitate comparisons to the larger body of research on retrieval processes, and because navigation and reinstatement of spatial representations display different patterns of localized activity (Spiers & Maguire, 2006) and therefore may be subject to different patterns of network interactions. At the whole brain level, we found consistent results during reinstatement blocks, where decreased values of *Q*, and increased values of both global efficiency and global flow were associated with low confidence trials. However, for the hippocampal node metrics we found no statistical differences between high and low confidence reinstatement across the individual density thresholds. We did observe statistical differences in the summary statistic for the left hippocampal betweenness centrality values, the right HC participation coefficient, and the flow coefficient for both hippocampal ROIs. These effects were in line with the results of the

navigation blocks, where there were no observed statistical differences for betweenness centrality. A potential explanation for these findings is that reinstatement of a representation operates via pattern completion processes centered primarily on the HC (Horner et al., 2015; Norman & O'Reilly, 2003), which requires similar levels of hippocampal centrality at the local and inter-module level, resulting in more subtle differences that only emerged statistically when collapsing across all density thresholds. Conversely, at the whole brain level, the weaker associative structure of a mnemonic representation may be compensated for by increases in global and local connectivity, such that environmental features that are reinstated are more actively combined at the polysensory level before being input to the HC (Bird, Keidel, Ing, Horner, & Burgess, 2015; Wagner et al., 2015).

In conclusion, the present study provides novel empirical support for critical predictions by theoretical models on how mnemonic representations are formed. We show that when encoding demands are highest, the topological structure of the brain is organized to facilitate global and local information flow. As representations are formed, the HC flexibly changes its functional interactions across the brain, decreasing its role as connector hub within its local sub-network and across network modules, while the information flow within the hippocampal community increases in efficiency. This provides a tentative experimental framework to understand the dynamic nature of representational encoding and retrieval, through assessing changes in topological structure across global and hippocampal based brain networks. Future research will be able to use this framework to understand how the pathology of cognitive and neurodegenerative disorders impacts the topological structure of global and local brain networks during memory encoding and retrieval, and how neurostimulation methods enhance the ability to form accurate mnemonic representations.

Chapter 3

3.1 Abstract

Theoretical models on the constructive nature of memory posit that mnemonic representations based in a spatiotemporal context are reinstated by actively combining encoded features from past experiences. This process is thought to occur through neural indexes in the hippocampus that represent the spatial composition of features and hippocampal-cortical interactions that code feature details. However, the dynamic basis of information processing across the brain during the reinstatement and goal directed utilization of mnemonic representations remains obscure. To provide insight on this, we investigated network processes associated with feature integration while participants made mental simulations of movement through a virtual city. Our data show that the hippocampus increases functional interactions with portions of lateral occipital cortex and the angular gyrus to assist in organizing spatial information and increasing perceptual fidelity during mental simulations. Additionally, dynamic changes in the topology of a hippocampal network were observed in relation to perceptual fidelity, suggesting that information flow vis-à-vis the hippocampus is critical for high perceptual fidelity, but can be compensated for by increased functional interactions between other regions connected to the hippocampus that provide a more schematic like representation of environmental features.

3.2 Introduction

The ability to use past experiences to predict and mentally simulate future events is a fundamental aspect of human cognition. It underlies flexible goal planning during navigation (Burgess, 2008) and is a central aspect to the constructive nature of episodic memory (Boyer, 2008; Moulton & Kosslyn, 2009; Schacter et al., 2012; Suddendorf, Addis, & Corballis, 2009). Research over the past decade using mental simulation has revealed new aspects of mnemonic processing, including the ability to recapitulate details from past experiences into novel contexts (Hassabis, Kumaran, & Maguire, 2007a; Szpunar, Addis, McLelland, & Schacter, 2013) and how these anticipatory future simulations can motivate and guide behavior (Boyer, 2008; Suddendorf & Busby, 2005). Many of these studies have cumulated into a growing consensus (Buckner & Carroll, 2007; Hassabis & Maguire, 2009; Moulton & Kosslyn, 2009; Schacter et al., 2012; Schacter & Addis, 2007; Szpunar et al., 2013) that mental simulation involves a dynamic neurocognitive system dedicated to encoding experiences, extracting features (i.e. people, places, objects, and interactions) from those memories, and actively combining those features into representations, or mental 'scenes', that are used to optimize behavior. This has led to new perspectives on how aging influences memory, prospection, and mental imagery (Addis, Wong, & Schacter, 2008; Personnier, Kubicki, Laroche, & Papaxanthis, 2010; Schacter, Gaesser, & Addis, 2013), and how these processes are affected by cognitive and neurodegenerative disorders (Addis, Sacchetti, Ally, Budson, & Schacter, 2009; Hassabis, Kumaran, Vann, & Maguire, 2007b; Irish & Piolino, 2015; Kwan, Carson, Addis, & Rosenbaum, 2010).

Prospection is theorized to rely on a set of brain regions that encompass the episodic memory system in humans (Buckner & Carroll, 2007; Hassabis & Maguire, 2009; Schacter et al., 2012). The hippocampus (HC) is central to this system, using mechanisms of pattern separation

and completion (Stokes, Kyle, & Ekstrom, 2014; Yassa & Stark, 2011) to reinstate mnemonic representations through interactions with sensory and associative regions across the brain. Past work has demonstrated that HC activity codes for goal-directed spatial sequences in both rodents and humans, primarily through a set of location-sensitive neurons termed *place cells* (O'Keefe & Nadel, 1978), providing a putative neural mechanism for reinstatement of the spatial context underlying prospection. Rodents demonstrate prospective firing (i.e. pre-play) of HC place cell sequences in different maze types, allowing researchers to accurately predict subsequent behavior at critical spatial decision points (Pfeiffer & Foster, 2013). In humans, recent work has shown that goal-specific trajectories and intervening locations can be decoded during prospection using patterns of hippocampal activity (Brown et al., 2016), further supporting the role of the HC in coordinating the neural codes underlying the spatial context for mental simulations.

Although there is increasing support for the role of the HC in prospection, fundamental questions remain about how the HC interacts with other regions across the brain, and whether these interactions vary based on how environmental features encoded in memory are integrated into a holistic representation subserving prospection. Central theories on the constructive basis of memory and prospection posit that simulating future experiences involves the active reinstatement and integration of features from past experiences into novel contexts (Buckner & Carroll, 2007; Hassabis & Maguire, 2009; Schacter et al., 2012). Feature reinstatement involves the reactivation of functionally specialized regions of the brain (Horner et al., 2015; Janzen & van Turennout, 2004), putatively controlled through pattern completion mechanisms in the HC. The strength of location coding in the HC during prospection has also been shown to correlate with spatial coding in the prefrontal, medial temporal, and medial parietal cortex (Brown et al.,

2016), suggesting that hippocampal-cortical interactions are critically important for feature integration and maintenance of goal-directed representations. However, there has yet to be a direct empirical investigation of how HC network interactions operate during prospection. Further, although mental simulations preserve spatial and temporal information (Arnold et al., 2016; Bonasia, Blommesteyn, & Moscovitch, 2015; Kosslyn et al., 1978) from past experiences, the fidelity of simulations varies based on visual qualities and how orderly spatial information is during the simulation (Arnold et al., 2016). Variability in simulation fidelity has been proposed as a measure of feature integration (Arnold et al., 2016), providing a quantifiable metric of how task-oriented mnemonic representations are generated through multi-feature reinstatement. Of relevance to the present study, this suggests that variance in simulation fidelity may be associated with the degree of functional interactions within the hippocampal-cortical networks supporting prospection.

In the present study, we sought to provide the first empirical evaluation of network topology during mental simulation, looking at global network state shifts between simulating and experiencing an event, how the HC interacts with other brain regions during mental simulations, and whether differences in network topology are associated with variability in simulation fidelity. To this end, we formulated three research questions based on current theoretical models and previous empirical work. First, we asked whether there were any differences in global network topology between simulating a route through a virtual environment and subsequently navigating the same route. Theoretical models suggest a large degree of overlap between networks supporting prospection, navigation, and episodic memory (Buckner & Carroll, 2007; Hassabis & Maguire, 2009; Schacter et al., 2012). However, there has yet to be an empirical investigation of whether simulating and experiencing an event share similar network states. Due

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

3.3 Methods

3.3.1 Participants

As in chapter 2, 14 right handed undergraduates (9 female; mean age = 21.64, SD = 2.56) recruited through the University of Calgary research participation pool participated in the study.

Participants were prescreened to exclude persons previously experiencing nausea while playing a video game. All participants were provided $50 reimbursement regardless if they completed the study or not, and were debriefed following scanning.

3.3.2 Task design

The task environment, exposure phase, and encoding phase are described in detail in chapter 2 section 2.3.3 (pg. 33-34). Briefly, the task environment consisted of a large scale virtual city with five visually salient landmarks that acted as target locations. During the exposure phase, which occurred outside the scanner, participants viewed a video of passive first-person movement along the perimeter of the city. The video stopped for 5 seconds at each landmark location, during which the experimenter pointed to the landmark on the screen and verbally confirmed that the participant had seen it. After the video, participants entered the scanner and completed the encoding phase. The encoding phase lasted for 23 minutes and had participants try to locate a target landmark using the quickest route possible. Each trial began by cueing a target landmark and asking participants to rate their confidence in knowing where the landmark was within the city. Participants then tried to find the landmark as fast as possible. There was an upper limit of 21 trials consisting of all pairwise combinations of target landmarks.

After the encoding phase, participants completed the simulation phase (Figure 7.4c). All participants conducted two practice trials prior to entering the scanner to ensure they properly understood the task instructions and provide them with the opportunity to ask the experimenter questions. Participants were instructed that the simulation portion would begin with the word ‘Simulation’ on the center of the computer screen. Afterwards, they would be shown two images of the five target landmarks – one on the left and one on the right. Once the landmarks disappeared from the screen, they were instructed to mentally simulate in as much detail as

possible moving through the city from the landmark on the left to the one on the right. The experimenter emphasized that it was important to mentally immerse themselves in the city and to take as much time as they needed to properly navigate the route. Participants were instructed to mentally navigate the quickest route between landmarks rather than trying to specifically recall the route they had previously taken.

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

Inside the scanner, each trial of the simulation phase began with a fixation period for 12 seconds in which a white fixation cross was placed on top of a black background. Next, the word 'Simulation' displayed on the screen for two seconds. Following that, images of the starting and target landmark appeared for three seconds. Immediately afterwards, the screen turned to black and the participants began to mentally simulate the route. The simulation period lasted for 15 seconds. After the simulation, participants complete a 14 item post-simulation questionnaire (PostSQ). Table 6.1 outlines the wording for each question/response and how they were grouped into different factors for analysis. The PostSQ included items modified from the Memory Characteristics Questionnaire (Johnson, Foley, Suengas, & Raye, 1988), as well as novel items, and was intended to probe qualitative aspects of the simulation experience. This included

questions about spatial and temporal coherence, vividness, fractionation, confidence in knowing the starting/target locations, and perceived accuracy of their memory for the route. Each item was rated on a scale of 1-4. Immediately following the questionnaire, participants were placed within the virtual city facing the starting landmark and navigated to the target landmark as quick as possible. Once there, a post navigation questionnaire (PostNQ) was displayed where they rated two items on a scale of 1-4 assessing how well they simulated the route and how well the simulation matched their navigation experience. In total, 10 routes were included in the simulation phase. The starting-destination landmark pairs were pseudo-randomly selected such that each of the five landmarks were included as a starting point and destination only once.

3.3.3 fMRI data analysis

Details of the fMRI data acquisition and preprocessing are described in chapter 2 section 2.3.4 and 2.3.5, respectively (pg. 34-35). Briefly, fMRI data from the simulation phase were realigned using MCFLIRT, smoothed using a 7mm FWHM Gaussian filter, intensity normalized, and run through a 60 second high-pass filter. Data were then denoised using MELODIC. Anatomical and EPI scans were normalized to MNI152 space using ANTs. Data were then further denoised by segmenting anatomical images based on tissue classes and applying the CompCor noise correction method (Behzadi et al., 2007) inside conn and SPM12.

To address the outlined hypotheses, fMRI data were analyzed at the bivariate level using generalized psychophysical interaction (gPPI) models and at the multivariate level using graph theoretical measures. Generalized PPI models allow for the assessment of context-specific changes in functional connectivity between a seed region and sets of voxels across the brain (McLaren, Ries, Xu, & Johnson, 2012). Models are constructed by taking the interaction between the time course of the seed region and a general linear model describing a task context,

and searching for sets of voxels with a time course that correlates to the interaction model. Here, we use right and left hippocampal seeds defined using subject-specific segmentations generated using the FIRST algorithm in FSL to investigate context-specific changes in functional connectivity between simulation and navigation periods, as well as between simulation periods with different levels of reported vividness and spatial coherence. All gPPI analyses use the standard corrections for multiple comparisons with a voxel height threshold of $p < 0.001$ and a cluster threshold of $p_{FWE} < 0.05$.

Correlation matrices for the graph analyses were calculated using the same procedure described in chapter 2 section 2.3.7 (pg. 35). Hippocampal ROIs segmented with FIRST and the set of 333 ROIs from Gordon and colleagues (Gordon et al., 2014b) were used to define nodes and Fisher transformed *r*-values to define edges in each graph. Calculation of graph theoretical measures used the same set of equations described in chapter 2 section 2.3.9 and 2.3.10. At the network level, differences in the modularity index *Q* and global efficiency between conditions of interest were assessed, and at the node level the betweenness centrality, participation coefficient, and flow coefficient of hippocampal nodes were compared.

3.4 Results

3.4.1 Behavioural performance

All 14 participants completed the simulation phase. Participants completed an average of 7.79 trials ($SD = 2.26$) out of 10 possible trials and spent an average of 1112.37 seconds (approximately 18 minutes and 30 seconds; $SD = 84.2$ seconds) completing the simulation phase. Simulation vividness and spatial coherence were significantly correlated ($r = 0.52$, $p < 0.001$), suggesting that highly vivid mental simulations are also spatially ordered.

3.4.2 Network topology during navigation and mental simulation

Navigation, prospection, and episodic memory are theorized to rely on similar neural systems (Brown et al., 2016; Buckner & Carroll, 2007; Hassabis & Maguire, 2009), with limited differences in regional activity when simulating spatial experiences in the past, present, or future (Nyberg, Kim, Habib, Levine, & Tulving, 2010). To test whether simulation and experiencing a spatial event also share similar network states, we calculated and compared graph theoretical measures previously shown to have behavioural relevance to encoding and retrieving spatial contexts from memory (Arnold et al., 2014b; chapter 2). First, we tested for differences in the modularity index Q (Newman, 2006), a measure of robustness of the modular structure in a network. Across a range of density thresholds, there were no statistically significant differences between the simulation and navigation blocks (Figure 7.5a), $k = 0.1$ ($t(13) = -0.7$, $p = 0.45$), $k = 0.15$ ($t(13) = -0.58$, $p = 0.57$), $k = 0.2$ ($t(13) = -1.9$, $p = 0.85$), $k = 0.25$ ($t(13) = -0.35$, $p = 0.73$). Next, we compared the global efficiency of whole brain networks between the two block types. Here, we only observed statistically significant differences using at the highest density threshold (Figure 7.5b), $k = 0.1$ ($t(13) = -0.7$, $p = 0.48$), $k = 0.15$ ($t(13) = -1.7$, $p = 0.11$), $k = 0.2$ ($t(13) = -2.13$, $p = 0.053$), $k = 0.25$ ($t(13) = -2.3$, $p = 0.038$). However, further investigation of this effect showed only a minor difference in global efficiency values between the simulation ($M = 0.612$, $SD = 0.005$) and navigation ($M = 0.615$, $SD = 0.004$) blocks.

3.4.3 Hippocampal-cortical interactions during mental simulation

Retrieval and integration of environmental features from memory into the spatiotemporal context of a mental simulation is believed to operate through the reinstatement of regional activity in sensory and associative areas of the cortex, coordinated primarily through pattern completion and separation mechanisms in the HC (Horner et al., 2015; Norman & O'Reilly,

2003; Stokes et al., 2014). Based on this perspective, we hypothesized increased functional coupling between the HC and areas of visual cortex during simulations with high visual and spatial fidelity. To test this, we binned simulation blocks based on how participants rated the simulation vividness and spatial coherence in the post-simulation questionnaire (PS-Q). We then used the binned simulation blocks to construct generalized psychophysiological (gPPI) models (McLaren et al., 2012) by multiplying the time course of BOLD signal in the left and right HC with general linear models denoting trials with low (PS-Q rating value of 1) and high (PS-Q rating value of 4) vividness and spatial coherence.

During highly vivid simulation blocks, we found evidence for increased functional connectivity between the right HC and the superior portion of the left lateral occipital cortex ($t(13) = 4.81$, $p < 0.001$; 128 voxels; peak MNI coordinates: -46, -64, 46) (Figure 7.6a; Table 6.2). For spatial coherence, high ratings for spatial coherence during simulations were associated with increased functional connectivity between the left HC and areas within the left angular gyrus and the superior division of the left lateral occipital cortex ($t(13) = 4.34$, $p < 0.001$; 118 voxels; peak MNI coordinates: -40, -56, 42) (Figure 7.6b; Table 6.2). There were no statistically significant increases in functional connectivity with the right or left HC in low vividness or spatial coherence simulation blocks. Considered together, these results support our hypothesis that increased hippocampal-cortical functional coupling is associated with a high degree of simulation fidelity, putatively through more effective feature integration coordinated by the HC through selective functional coupling with areas of the brain associated with visual processing.

3.4.4 Network topology and simulation fidelity

In the next analysis, we sought to extend our findings of changes in hippocampal-cortical functional coupling based on simulation fidelity by testing our hypothesis that high simulation

fidelity would be associated with hippocampal-based network states conducive to information integration. While bivariate techniques such as gPPI can elucidate the functional coupling between a seed region and a cluster of voxels sharing similar BOLD response patterns, multivariate techniques such as graph theory allow for the assessment of more complex patterns of information communication and integration by considering the functional interactions between more than two sets of regions in the brain (Bassett et al., 2012; Rubinov & Sporns, 2010; Sporns et al., 2007). Of importance here, graph theoretical measures allow for assessment of network dynamics in local neighborhoods (i.e. sub-networks characterized by shared patterns of functional interactions), and how a particular region (e.g. the HC) coordinates the information flow between multiple sets of regions. To assess how hippocampal network topology relates to simulation fidelity, we calculated node-based graph theoretical measures of betweenness centrality, flow coefficient, and local efficiency for the right and left hippocampal nodes. These measures quantify the centrality of the HC at the global and local network level, and assess the communication efficiency of local HC networks, respectively.

The first measure we calculated was the betweenness centrality of the right and left HC. Betweenness centrality quantifies the degree to which the shortest paths between any two nodes in a graph pass through a specific node and is considered a measure of centrality at the global network level irrespective of the modular composition of a network (Rubinov & Sporns, 2010). Comparing high and low vividness simulations (Figure 7.7a), we observed no statistically significant differences between betweenness centrality values in the right, $k = 0.1$ ($t(13) = 1.91$, $p = 0.08$), $k = 0.15$ ($t(13) = 0.43$, $p = 0.67$), $k = 0.2$ ($t(13) = 0.34$, $p = 0.74$), $k = 0.25$ ($t(13) = -0.32$, $p = 0.76$), or left HC, $k = 0.1$ ($t(13) = 1.7$, $p = 0.11$), $k = 0.15$ ($t(13) = 1.02$, $p = 0.33$), $k = 0.2$ ($t(13) = 1.23$, $p = 0.24$), $k = 0.25$ ($t(13) = -0.17$, $p = 0.87$). Similarly, comparing high and

low spatial coherence simulations, there were no statistically significant differences in the right, $k = 0.1$ ($t(13) = 0.7$, $p = 0.5$), $k = 0.15$ ($t(13) = 0.37$, $p = 0.71$), $k = 0.2$ ($t(13) = 1.58$, $p = 0.14$), $k = 0.25$ ($t(13) = 0.11$, $p = 0.91$), or left HC, $k = 0.1$ ($t(13) = -0.1$, $p = 0.92$), $k = 0.15$ ($t(13) = 0.39$, $p = 0.71$), $k = 0.2$ ($t(13) = 0.22$, $p = 0.83$), $k = 0.25$ ($t(13) = 1.02$, $p = 0.33$).

Next, we calculated the flow coefficient for the left and right hippocampal nodes (Figure 7.7b). The flow coefficient quantifies the degree to which a node conducts information flow between neighboring nodes and is representative of centrality within local neighborhoods (Honey et al., 2007). Here, there were statistically significant increases in flow coefficients during high vividness simulations at the higher density thresholds for the right, $k = 0.1$ ($t(13) = -1.31$, $p = 0.21$), $k = 0.15$ ($t(13) = -3.21$, $p = 0.007$), $k = 0.2$ ($t(13) = -3.45$, $p = 0.004$), $k = 0.25$ ($t(13) = -3.34$, $p = 0.005$), and left HC, $k = 0.1$ ($t(13) = -1.51$, $p = 0.16$), $k = 0.15$ ($t(13) = -2.73$, $p = 0.017$), $k = 0.2$ ($t(13) = -3.12$, $p = 0.008$), $k = 0.25$ ($t(13) = -3.22$, $p = 0.007$). Comparing high and low spatial coherence trials, we found no statistical differences for the right, $k = 0.1$ ($t(13) = -0.77$, $p = 0.46$), $k = 0.15$ ($t(13) = -0.99$, $p = 0.34$), $k = 0.2$ ($t(13) = -0.74$, $p = 0.47$), $k = 0.25$ ($t(13) = -0.88$, $p = 0.4$), or left HC, $k = 0.1$ ($t(13) = -0.5$, $p = 0.62$), $k = 0.15$ ($t(13) = -1.06$, $p = 0.31$), $k = 0.2$ ($t(13) = -1.54$, $p = 0.15$), $k = 0.25$ ($t(13) = -1.88$, $p = 0.08$).

Thus far our data show that there are no differences between the centrality of the HC at the global network level in mental simulations with high vs low vividness and spatial coherence. However, we did find evidence for increased hippocampal centrality within its local neighborhood during mental simulations with high vividness. Next, we sought to evaluate information flow within hippocampal neighborhoods. As previously outlined, the HC is theorized to coordinate the selective reactivation of sensory and associative areas of the cortex through pattern completion mechanisms to reinstate environmental features from memory and

integrate them into a representation used during mental simulation. A plausible prediction from this is that in trials with low hippocampal centrality (i.e. low vividness simulations), the coordination of feature reinstatement and integration is compensated by increases in functional interactions between other regions of the memory system supporting mental simulations (Fornito, Harrison, Zalesky, & Simons, 2012). To evaluate this, we calculated the local efficiency of hippocampal networks. Local efficiency represents the efficiency of information flow in a subnetwork composed only of immediate neighbors of a specific node. Comparing simulations of high and low vividness (Figure 7.7c), we found statistically significant decreases in local efficiency values for high vividness simulations in the right hippocampal neighborhood, $k = 0.1$ ($t(13) = 2.19$, $p = 0.047$), $k = 0.15$ ($t(13) = 3.76$, $p = 0.002$), $k = 0.2$ ($t(13) = 3.69$, $p = 0.003$), $k = 0.25$ ($t(13) = 3.42$, $p = 0.005$), and across higher density thresholds in the left hippocampal neighborhood, $k = 0.1$ ($t(13) = 1.42$, $p = 0.18$), $k = 0.15$ ($t(13) = 2.66$, $p = 0.02$), $k = 0.2$ ($t(13) = 3.07$, $p = 0.009$), $k = 0.25$ ($t(13) = 3.21$, $p = 0.007$). We also investigated differences in local efficiency values of hippocampal networks between simulations with high and low spatial coherence. Here, we found no statistically significant differences for the right, $k = 0.1$ ($t(13) = 0.73$, $p = 0.48$), $k = 0.15$ ($t(13) = 0.86$, $p = 0.41$), $k = 0.2$ ($t(13) = 0.69$, $p = 0.5$), $k = 0.25$ ($t(13) = 0.87$, $p = 0.4$) or left hippocampal neighborhoods, $k = 0.1$ ($t(13) = 0.74$, $p = 0.47$), $k = 0.15$ ($t(13) = 1.12$, $p = 0.28$), $k = 0.2$ ($t(13) = 1.48$, $p = 0.16$), $k = 0.25$ ($t(13) = 1.86$, $p = 0.09$).

3.5 Discussion

Prospection allows humans to mentally simulate future events based on past experiences and is central to the generation and implementation of goal-directed behavior. Current theoretical models on prospection posit that it operates using a neural system shared with episodic memory,

allowing features encoded from previous experiences to be flexibly combined into a novel spatiotemporal context (Buckner & Carroll, 2007; Hassabis & Maguire, 2009; Nadel et al., 2000; Schacter et al., 2012). Past research has demonstrated the role of the HC in representing spatial information pertaining to target destinations and intermediate locations along a route, and has suggested that the HC coordinates mnemonic representations with other brain areas during prospection, including regions within the prefrontal cortex, medial temporal lobes, and medial parietal lobes (Brown et al., 2016).

Here, for the first time, we investigate fundamental questions on the topological structure and dynamics of whole brain and hippocampal networks during prospection. Our data show that simulating and experiencing an event share a similar network state defined using measure of communication efficiency, extending previous findings on patterns of regional activity between simulating and experiencing events (Brown et al., 2016; Nyberg et al., 2010). Critically, our results also show that mental simulations display variability in representational fidelity, varying in both the vividness and coherence of spatial information, putatively through differences in feature integration (Arnold et al., 2016). During highly vivid and spatially coherent simulations, the HC was shown to increase functional interactions with areas of the brain associated with object recognition, manipulation of mental imagery, and awareness of intended action sequences. Highly vivid simulations were also shown to increase hippocampal centrality in local memory networks, indicating that the HC is vital for supporting multi-regional integration of visual information during prospection.

Theoretical models on prospection commonly employ a *shared systems hypothesis* in which simulating future experiences is posited to rely on similar neural mechanisms as episodic memory (Schacter et al., 2012). Conjunctive analyses comparing regional activity between the

recall and simulation of experiences show the common engagement of a neural system involving regions of the medial temporal lobes, medial prefrontal cortex, and posterior parietal cortices (Hassabis, Kumaran, & Maguire, 2007a; Nyberg et al., 2010). This system is theorized to coordinate the selective reactivation and integration of information processed in sensory and associative areas into a unified mnemonic representation (Horner et al., 2015). Our data extend these findings by showing that simulating and experiencing events share a similar network state. Our analysis of network topology showed no statistical differences in the modular structure or the global efficiency of the whole brain network between the two task conditions. Crucially, this shows that the two processes broadly share levels of communication capacity based on patterns of functional interactions between regions, which are posited to code the associative structure of features composing the spatiotemporal context of a mnemonic representation (Buchel et al., 1999; Ekstrom et al., 2014).

Mental simulations are not a singular construct, however, varying in how orderly and vivid spatial information appears subjectively. Variability in simulation fidelity is theorized to be associated with how effectively environmental features from previous experiences can be recapitulated into a mnemonic representation underlying prospection (Arnold et al., 2016). Based on this and other outlined theoretical perspectives (Hassabis & Maguire, 2009; Schacter et al., 2012), we hypothesized that the representational fidelity of a mental simulation would require increased coordination between the HC and visual areas of the brain, as the neural codes of the spatial context in the HC putatively coordinates the recapitulation of environmental features needing to be integrated in a task oriented manner. Our data provide support for this hypothesis by showing that highly vivid and spatially coherent simulations involve increased functional coupling between the HC and cortical areas associated with object representation and the

manipulation of mental simulations. Comparing simulations with high and low vividness ratings using gPPI models, we observed increased functional connectivity during highly vivid simulations between the right HC and the superior division of the left lateral occipital cortex and the left angular gyrus. Similarly, we found increased functional connectivity during simulations with high ratings of spatial coherence between the left HC and the left angular gyrus and the superior division of the left lateral occipital cortex, similar to the area identified in the vividness analysis. Lateral occipital cortex has previously been implicated in representing high-level visual features of objects and how they are localized in spatial contexts (Kourtzi & Kanwisher, 2001; Silk, Bellgrove, Wrafter, Mattingley, & Cunnington, 2010; Y. Xu & Chun, 2006). Additionally, this area has been found to uniquely increase activity during mental simulations that involve self-referential processes in non-present timeframes (i.e. past, future, and imagined) (Nyberg et al., 2010). Angular gyrus has more widespread functional roles, acting as a multi-modal hub integrating multisensory information to allow for the manipulation of mental representations (Seghier, 2013) and subjective awareness of intended action sequences and their consequences in spatial contexts (Arnold et al., 2014b; Farrer et al., 2008). Considered together, these functional interactions suggest that the neural codes in the HC representing the spatial context of a location interact with visual and associative areas of the cortex to reinstate and organize environmental features from memory into a non-present timeframe, and generate prospective action sequences. Critically, the degree of these functional interactions relate to how effectively environmental features can be reinstated, integrated, and manipulated during simulation of movement within a spatial context.

Prospection is theorized to rely on functional interactions between a multi-regional network across the brain (Brown et al., 2016; Hassabis, Kumaran, & Maguire, 2007a; Schacter et

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

A comparison of the neural patterns associated with variability in the vividness and spatial coherence of a mental simulation reveals important differences. In both cases, there was increased functional connectivity between the HC and left lateral occipital cortex and angular gyrus, providing evidence that neural codes in the HC requires interaction with associative areas in order to mentally simulate movement through a spatial context. However, differences in network topology were specific to variability in simulation vividness. This suggests that the HC plays a more principled role in organizing the spatial context of a mnemonic representation and the locations composing that context, while the visual fidelity of a representation requires more widespread interactions across the brain. Although we did not formulate specific hypotheses on this, it provides support for theoretical models positing the organizational, but not purely representational, nature of spatial features in the HC (Eichenbaum, 2000a; Milivojevic & Doeller, 2013).

In summary, the current study builds on the role of the HC in prospection by addressing fundamental questions on network topology. Simulating and experiencing an event were found to share similar global network states based on measures of communication efficiency, providing support for a central tenants of theoretical models on prospective coding and memory function (Buckner & Carroll, 2007; Hassabis & Maguire, 2009; Schacter et al., 2012). However, mental simulations were found to vary in the vividness and coherence of spatial information. As predicted, both aspects of representational fidelity were related to increased functional coupling between the HC and visual and associative areas of the brain, putatively allowing for more effective feature integration during mental simulation. Highly vivid simulations were also found to be associated with both increased hippocampal centrality and decreased local efficiency within a hippocampal sub-network, suggesting that the visual basis of a mental simulation requires

coordination of information processing via the HC into high-resolution mnemonic representations (Rosenbaum et al., 2009; Yonelinas, 2013). Critically, this provides the first direct empirical evidence that the neural representations underlying prospection are generated and manipulated through hippocampal-cortical functional interactions rather than neural codes in the HC alone.

Chapter 4

4.1 Abstract

The default mode network is a putative neural system characterized by task related attenuations in functional activity when a person is engaged in a cognitively demanding task. Theoretical models on the constructive nature of memory posit that the default mode network shares a similar network composition with a putative construction network that allows for the reinstatement of mnemonic representations to re-experience the past or simulate potential future events. Here, we investigate the commonalities in network topology between the default mode network and the construction network by comparing measures of functional associations between network components and communication efficiency during resting periods and mental simulations of movement through a virtual city. Our data show that while there is a degree of overlap, mental simulations are characterized by increased functional coupling between regions of the default mode network and the hippocampus. Differences in interactions between network components were also tentatively associated with the spatial coherence of environmental features during mental simulations, with posterior cingulate cortex demonstrating an increased amount of functional coupling with the hippocampus during highly coherent simulations relative to rest. These results provide empirical support for theoretical models on the constructive nature of memory, and suggest revisions to the models based on dynamic network processes.

4.2 Introduction

The brain is composed of numerous neural networks characterized by a high degree of intra-network connectivity with limited inter-network connectivity (Sporns, 2011; van den Heuvel, Kahn, Goñi, & Sporns, 2012). In the early 2000s, Raichel and colleagues (Raichle et al., 2001) observed the operation of a neural network composed of critical convergence zones that displayed robust correlations of functional activity during rest. Termed the default mode network (DMN), this network has since been researched in extensive detail and is posited to provide the neural basis of spontaneous and unconstrained thought that occurs when people are not overtly engaged in a mental task. Although a complete taxonomy of the types of thought and their underlying cognitive processes has yet to be articulated, past research has provided evidence for the association between DMN integrity and multiple interacting types of thought, including self-referential processing, prospection, and retrospection, often characterized by their emotional and personal significance (see Andrews-Hanna et al., 2014 for a review of self-generated thought and DMN activity).

In their original proposal, Raichle and colleagues (Raichle et al., 2001) defined a DMN composed of medial prefrontal cortex (mPFC), posterior cingulate cortex/precuneus (PCC), and lateral parietal cortex (LP), based on cortical areas showing task-related attenuations of neural activity in a meta-analysis of brain imaging data. This topological distribution has generally been supported by more recent studies using larger samples and more robust parcellation strategies (Andrews-Hanna, Reidler, Sepulcre, Poulin, & Buckner, 2010; Yeo et al., 2011). A pivotal study on understanding the dynamics of the DMN was published Fox and colleagues (Fox et al., 2005), suggesting that the brain is organized into anti-correlated networks that are associated with either task and resting states. Under this view, the DMN was theorized as a task-negative network,

showing decreased functional activity with a high degree of intra-network connectivity when a person is engaged in a specific cognitive task. Conversely, a task-positive network composed primarily of areas associated with a dorsal attentional system displays a large degree of anti-correlations with activity in regional components of the DMN. This perspective of competition between the DMN and task-active networks was empirically supported by studies showing that attentional lapses interfering with task performance are associated with failure to suppress activity in the DMN (Weissman et al., 2006) and that variability in motor performance is associated with the degree of anti-correlations between the task-positive and task-negative networks (Fox et al., 2007).

Although the division of the brain into competitive task-positive and task-negative networks provided an intuitive heuristic to understand how the brain switches between an exogenous and endogenous locus of attention, research in certain areas of cognitive neuroscience has shown the reliable activation of DMN regions during tasks (Spreng, Mar, & Kim, 2009). The PCC, for example, had previously been implicated in supporting spatial navigation (Grön, Wunderlich, Spitzer, Tomczak, & Riepe, 2000) and in recalling and imagining episodic details in the past and future (Szpunar et al., 2007). Additionally, research on episodic memory has shown that activity in PCC reliably couples with the hippocampus (HC) during rest and recall tasks, indicating that reinstatement of self-referential memories involves the coordination of memory processes in the HC and information processing in PCC (Vincent et al., 2006). Furthermore, systems neuroscience models of spatial navigation posit a central role for PCC and surrounding areas, including precuneus and retrosplenial cortex (RSC), in integrating location and direction information from allocentric and egocentric representations of space into a task-oriented representation of where one is within an environment (Burgess, Maguire, Spiers, & O'Keefe,

2001; Byrne et al., 2007; Marchette et al., 2014). These findings suggest that regions in the DMN are not exclusively task-negative, but rather are critical components of networks supporting fundamental aspects of human cognition.

Using these and similar studies as a framework, two important theories were formulated to explain the overlap between the topological distributions of the DMN and networks underlying spatial navigation and episodic memory to resolve why information processing in DMN regions are necessary for certain cognitive processes. The first, termed the *self-projection hypothesis*, was proposed by Buckner and Carroll (Buckner & Carroll, 2007) and suggests that the large degree of overlap in neural networks supporting episodic recall, prospection, theory of mind, and the spontaneous self-referential thought observed during resting periods, is due to a shared cognitive process of displacing one's perspective from a present moment, egocentric point of view to one centered on either other people, places, or moments of time . Building from this perspective, Hassabis and Maguire (Hassabis & Maguire, 2007) formulated the *scene construction hypothesis*, theorizing that the function of the shared network is to generate mental scenes with environmental and episodic detail that provide the basis for mental simulations about the past, future, or an alternative reality. One notable difference in the network composition identified by Hassabis and Maguire is the inclusion of the HC in the scene construction network, a region the authors suggest is functionally specialized to generate the spatiotemporal context of a mental representation. Critically, the *scene construction hypothesis* provides an important explanation of why activity in the DMN is observed during spontaneous thought, and how activity in related regions is essential for tasks requiring one to make a mental representation of a spatiotemporal context, such as in navigation and episodic recall. However, both its original formulation (Hassabis & Maguire, 2007) and its extension (Hassabis & Maguire, 2009) provide

limited discussion on similarities and difference between the DMN and the scene construction network, focusing rather on neural and cognitive similarities between remembering, future thinking, and imagining. Despite this, the scene construction hypothesis makes two important predictions pertaining to DMN composition and function. First, the DMN is not a task-negative network, as information processing in PCC and mPFC is posited to be vital to self-referential processing during scene construction. Second, the DMN is itself not a static system, but rather has a dynamic topology that allows for context driven changes in the functional interactions between regions.

Research published since the scene construction proposal supports the dynamic nature of the DMN. Forming a *flexible modulation hypothesis*, studies have shown that regions from the DMN – notably mPFC and PCC – are functionally coupled with regions in a frontal-parietal control network during autobiographical planning tasks (Spreng, Stevens, Chamberlain, Gilmore, & Schacter, 2010) and mental simulations of conducting autobiographical plans (Gerlach, Spreng, Gilmore, & Schacter, 2011). Fornito and colleagues (Fornito et al., 2012) have also shown that the functional coupling of regions in the DMN and the fronto-parietal component of an external attentional system is associated with more efficient memory recall, suggesting that the DMN is able to reorganize into different sub-networks depending on task contexts. The fractionation of the DMN is hypothesized to occur through the sub-division of the DMN into three components – a dorsal medial subsystem composed of dorsal mPFC, the temporo-parietal junction, and lateral temporal cortex; a medial temporal subsystem of the HC, parahippocampal cortex, inferior parietal lobe, and ventral mPFC; and a core sub-system of anterior mPFC and PCC (Andrews-Hanna et al., 2010). Each sub-system is theorized to contribute different component processes to self-generated thought, with the dorsal medial system performing social

and conceptual processing, the medial temporal system supporting autobiographical thought and contextual recall, and the core system bridging the two other subsystems through self-referential processing (Andrews-Hanna et al., 2014). In the context of scene construction, the *flexible modulation hypothesis* predicts that regions in the medial temporal subsystem – notably the HC – should dynamically change the degree of functional interactions with areas of the core subsystem depending on the amount of environmental and episodic detail used during scene construction. A similar prediction was made by Hassabis and Maguire (Hassabis & Maguire, 2009), and a recent analysis of similarities and difference in network topology between rest, recall, and future thinking shows that the HC is able to increase functional interactions with PCC and surrounding areas, as well as regions in LP and occipital cortex during recall and future thinking compared to rest (Bellana, Liu, Diamond, Grady, & Moscovitch, 2017). However, the experimental design by Bellana and colleagues (Bellana et al., 2017) did not measure the detail generation during recall and future thinking, and was therefore unable to directly test whether the degree of environmental and episodic details in a mental simulation is related to differences in HC connectivity with DMN regions.

To resolve this, we developed an experimental task requiring participants to make mental simulations of routes through a previously learned virtual city. This task allowed us to ask two important questions pertaining to DMN-HC functional connectivity and its relation to scene construction. First, we asked whether there were topological differences between resting state networks and those involved in mentally simulating the route. Our prediction here, based on indirect observations from Hassabis and Maguire (Hassabis & Maguire, 2009), is that there is a broad similarity in network topology between the two cognitive states. Second, by measuring the vividness and spatial coherence of environmental information during a mental simulation, we

asked whether differences in DMN-HC are related to the degree of detail generation in the mental scene used during the simulation. Our prediction here, based on the scene construction hypothesis and the component process model formulated by Andrews-Hanna and colleagues (Andrews-Hanna et al., 2014), was that more detail generation (i.e. higher vividness and spatial coherence) would be related to increased functional connectivity between the HC and PCC/mPFC as modules of the core subsystem interaction with HC and other regions to dynamically reorganize network topology during scene construction.

4.3 Methods

4.3.1 Participants

Data collected from the same sample of 14 undergraduates described in chapter 2 section 2.3.1 (pg. 31) was used for the following analyses.

4.3.2 Task design

All data analyzed were collected during the simulation phase described in chapter 3 section 3.3.2 (pg. 56-58) and presented in figure 7.4. Briefly, each trial began with a 12 second rest period in which participants attended to a white fixation cross overlaid on a black background, after which two landmarks were cued for 2 seconds. Following that, the screen when black and participants were instructed to mentally simulate navigating from the starting landmark to the destination landmark in as much detail as possible over a 15 second block. Once the simulation block ended, participants answered 14 questions from the post-simulation questionnaire (PSQ) that was designed to assess various qualitative aspects of the simulation (see Table 6.1 for list of questionnaire items and how they were grouped). Next, participants were placed in front of the starting landmark and navigated through the virtual city to the target landmark in the fastest route possible. Once there, they answered two additional questions from

the PSQ assessing how effectively they simulated the route and how close the navigation experience matched what they had mentally simulated. After, a new trial began using the target landmark from the previous trial as the starting point for the new trial.

4.3.3 Functional MRI data analysis

Data preprocessing followed the same pipeline described in chapter 2 section 2.3.5-2.3.10 (pg. 34-39). Correlation matrices from the 12 second fixation block and the 15 second mental simulation block were calculated in conn (Whitfield-Gabrieli & Nieto-Castanon, 2012) using the four DMN ROIs identified by Fox and colleagues (Fox et al., 2005) and the subject specific left and right hippocampal ROIs estimated using FIRST. Changes in DMN topology were assessed by computing Fisher transformed *r*-values for each pairwise connection in the network and comparing values between rest blocks to simulation blocks. Simulation blocks were initially binned together, then sorted and compared based on different levels of vividness and spatial coherence measured using the PSQ. A statistical threshold of $p_{FDR} < 0.05$ was used to assess significance of changes in DMN connectivity.

4.4 Results

4.4.1 Similarities between resting and mental simulation networks

To evaluate our first hypothesis, we investigated the network topologies of regions in the DMN and the HC during resting and mental simulation blocks using an ROI-to-ROI analysis. We observed no statistically significant differences in a direct comparison of network topology associated with each cognitive state. However, investigating the degree of functional connectivity between network nodes independently for each cognitive state showed that during rest (Figure 7.8a) the HC was functionally coupled bilaterally ($t(13) = 7.81$, $p_{FDR} < 0.001$) but did not have statistically non-zero correlations with all other nodes in the DMN, whereas seeding the

PCC, a common method to obtain DMN connectivity values (Andrews-Hanna et al., 2014), showed that the PCC had statistically non-zero correlations with left ($t(13) = 10.65$, $p_{FDR} < 0.001$) and right ($t(13) = 4.84$, $p_{FDR} < 0.001$) LP cortex, but not mPFC ($t(13) = 1.35$, $p_{FDR} = 0.12$). During mental simulation (Figure 7.8b), the contralateral HC ROI and all regions of the DMN showed positive, non-zero correlations with the left (right HC: $t(13) = 10.66$, $p_{FDR} < 0.001$; PCC: $t(13) = 5.44$, $p_{FDR} < 0.001$; mPFC: $t(13) = 2.08$, $p_{FDR} = 0.036$; left LP: $t(13) = 3.24$, $p_{FDR} = 0.003$; right LP: $t(13) = 1.87$, $p_{FDR} = 0.042$) and right HC (left HC: $t(13) = 10.66$, $p_{FDR} < 0.001$; PCC: $t(13) = 4.45$, $p_{FDR} < 0.001$; mPFC: $t(13) = 3.5$, $p_{FDR} = 0.003$; left LP: $t(13) = 2.37$, $p_{FDR} = 0.017$; right LP: $t(13) = 3.12$, $p_{FDR} = 0.004$). Using the PCC again as a seed region, we additionally observed closer functional coupling between all nodes of the DMN and both the left and right HC (left HC: $t(13) = 5.44$, $p_{FDR} < 0.001$; right HC: $t(13) = 4.45$, $p_{FDR} < 0.001$; mPFC: $t(13) = 2.38$, $p_{FDR} = 0.017$; left LP: $t(13) = 10.5$, $p_{FDR} < 0.001$; right LP: $t(13) = 4.94$, $p_{FDR} < 0.001$).

4.4.2 Network reconfiguration associated with detail generation

Next, we compared DMN and HC functional connectivity at different levels of vividness and spatial coherence reported during mental simulations. To do this, we used left and right HC seeds, as well as PCC, and calculated differences in ROI-to-ROI functional connectivity between all nodes in the network by comparing Fisher *z*-scores obtained from low and high vividness and spatial coherence simulations against rest. The results are presented in figure 7.9. For low vividness simulations relative to rest blocks, we observed increased functional connectivity between the right HC and the left (Figure 7.9a; $t(13) = 3.25$, $p_{FDR} = 0.003$) and right (Figure 7.9b; $t(13) = 2.41$, $p_{FDR} = 0.039$) LP. There were no statistically significant differences seeding the left HC or PCC. For high vividness simulations relative to rest blocks, we found increased functional

connectivity between the right HC and left LP (Figure 7.9a; $t(13) = 2.94$, $p_{FDR} = 0.029$), but not between left HC or PCC and the other network nodes. Similar to low vividness, for low spatial coherence we found statistical differences in connectivity between the right HC and the left (Figure 7.9c; $t(13) = 2.53$, $p_{FDR} = 0.037$) and right (Figure 7.9d; $t(13) = 2.44$, $p_{FDR} = 0.037$) LP, but not using the left HC or PCC as a seed region. For high spatial coherence simulations, we found no statistical differences using our seed regions, but found near significant differences between the right HC and left LP (Figure 7.9c; $t(13) = 2.61$, $p_{FDR} = 0.053$), and between PCC and the left (Figure 7.9e; $t(13) = 2.46$, $p_{FDR} = 0.065$) and right (Figure 7.9f; $t(13) = 1.91$, $p_{FDR} = 0.065$) HC, as well as the right LP (Figure 7.9g; $t(13) = 2.03$, $p_{FDR} = 0.065$).

4.5 Discussion

The DMN is a neural network reliably observed when a person is in a resting state, composed primarily of the mPFC, PCC, and left and right LP. Initially, the DMN was conceptualized as a cohesive network characterized by high intra-network functional connectivity that showed task-related attenuations in activity (Raichle et al., 2001), and anti-correlations in functional activity to task-activated brain regions (Fox et al., 2005). However, theories based on observations that components of the DMN are commonly engaged during cognitive tasks such as episodic recall, spatial navigation, and prospection, argue that those tasks share cognitive processes with the types of spontaneous thought that characterize conscious experience when not overtly engaged in a task. The *scene construction hypothesis* (Hassabis & Maguire, 2007) theorizes that each cognitive state (i.e. recalling the past, imaging the future, navigating, and mind wandering) involved the construction of mental scenes which were used to simulate past, anticipated future, or imagined experiences. It makes the explicit prediction that scene construction requires functional coupling of the HC with areas of the DMN, particularly

the mPFC and PCC (Hassabis & Maguire, 2009). Although research has begun to demonstrate that the DMN is not a static network that is reliably suppressed during cognitive tasks (Andrews-Hanna et al., 2014), also a prediction from the original *scene construction hypothesis*, there has yet to be an investigation of whether differences in HC and DMN functional connectivity relate to generating details of the spatiotemporal context used for mentally simulating an experience. Here, using a conventional spatial navigation paradigm that included a novel use of mental simulations, we show that the functional interactions between the HC and regions of the DMN, specifically PCC and the left and right LP, are increased relative to the patterns of functional connectivity at rest. This provides the first network-based evidence of a central prediction in the *scene construction hypothesis* and shows that the amount of detail generation relates, in part, to reconfiguration of functional connections between the HC and DMN regions.

Our initial analysis on similarities in network topology between rest and mental simulations revealed no differences using a direct statistical comparison. However, investigating the network topologies independently by testing whether each network edge was statistically non-zero, revealed that at rest, the left and right HC were strongly connected with each other, but did not have statistically above or below zero correlations with regions in the DMN. Conversely, during mental simulations, the functional interactions between the left and right HC with all regions of the DMN were statistically above zero. This finding is in line with the proposed scene construction network topology outlined by Hassabis and Maguire (Hassabis & Maguire, 2009), in which the HC functionally couples with DMN regions while generating the spatiotemporal context of a mental representation. However, this finding also shows that the HC is more transiently connected to DMN regions at rest, supporting conclusions by Bellana and colleagues

(2017) and others (e.g. Chen et al., 2016) that HC and DMN interactions are only required when episodic information needs to be retrieved and maintained over a period of time.

The fidelity of a mental simulation is theorized to relate to how well environmental and episodic features from memory can be flexibly combined into a task-oriented mnemonic representation (Arnold et al., 2016; Schacter et al., 2012; Schacter & Addis, 2007). Here, we use simulation vividness and the spatial coherence of environmental features as proxies for the fidelity of a mental simulation. These measures were used to test the prediction that greater detail generation while constructing mental scenes would require increased functional connectivity between the HC and the core subsystem of the DMN as proposed by Andrews-Hanna and colleagues (Andrews-Hanna et al., 2014). Although our hypothesis was not directly supported, the overall pattern of results has important implications and suggests that the general proposal in the *scene construction hypothesis* is correct, albeit with some differences in the specific patterns of network reconfiguration.

In the present study, we found that both mental simulations with both low and high vividness relative to rest showed increased functional connectivity between the right HC and left LP, as well as with the right LP in low vividness simulations. This pattern was similar for mental simulations with low spatial coherence, where we observed increased functional connectivity between the right HC and left and right LP. However, for high spatial coherence, we found no statistical differences using a false discovery rate threshold to control for multiple comparisons, but did observe near significant increases in functional connectivity between the right HC and left LP, as well as between PCC and the left and right HC, and right LP. Lateral parietal cortex is involved in numerous episodic recall and simulation paradigms (Benoit & Schacter, 2015), putatively through its role as a hub region allowing manipulation of multi-sensory mental

representations (Seghier, 2013; chapter 3) and participation in sequencing episodic details (Demblon, Bahri, & D'Argembeau, 2016) that involve transformations in subjective time (Nyberg et al., 2010). The observed increase of functional connectivity between LP and the right HC in mental simulations with different degrees of vividness suggests that it provides a general mechanism to assist in a task-oriented manipulation of the spatiotemporal context coded by the HC, rather than a dynamic role related to the level of detail generation. The PCC, however, had near significant increases in functional connectivity related to only simulations with a high degree of spatial coherence. Tentatively, as this interpretation is based on near statistically significant effects, this supports its role as a critical hub region during mental simulations, allowing the integration of direction and location information into a task-oriented representation (Burgess et al., 2001; Byrne et al., 2007; Marchette et al., 2014) through interactions with the HC, and the manipulation of these representations through interactions with LP [chapter 3]. Furthermore, it suggests that changes in the functional interactions of the core subsystem of the DMN are related to correctly ordering reinstated environmental and episodic features in relation to oneself, rather than in generating specific visual details about the features from memory being reinstated. In the context of the *scene construction hypothesis*, these findings collectively indicate that generating more visual detail in a mental scene is not related to the degree of functional interactions between the HC and components of the DMN *per se*, but that the dynamic reorganization of DMN regions into task-oriented networks underlies the reinstatement, integration, and ordering of environmental and episodic information during the construction and manipulation of a mental scene.

There are two main limitations to the present study. First, the topology of the DMN is still being researched, and has been suggested to include more regions subdivided into different

components than the ROIs utilized here (Andrews-Hanna et al., 2010). However, the shared topological overlap between the DMN and functional networks supporting episodic memory has only recently been investigated (Bellana et al., 2017), and there has yet to be a direct investigation of mental simulations that are primarily spatial in nature, a critical aspect of the hypothesis that episodic recall, prospection, and spontaneous thought at rest share the common cognitive process of generating mental scenes (Hassabis & Maguire, 2009). As such, we selected standard DMN ROIs for our initial assessment and suggest that future studies look at more extensive parcellation strategies. Second, our sample size is smaller than is typical of studies using resting blocks to characterize the DMN (e.g. Andrews-Hanna et al., 2010). This is reflected in the near statistically significant results of the PCC in the high spatial coherence analysis. A larger sample size may be able to more precisely estimate effect sizes and support the speculations we make here.

In conclusion, the present study provides the first empirical investigation of the similarities between DMN topologies during rest and mental simulations that are primarily spatial in nature. Our results offer empirical support for speculations from a recent study on episodic recall and future thinking (Bellana et al., 2017) that HC-DMN interactions are necessary for the integration of episodic details into mental simulations. We add to a growing body of literature showing that the DMN is indeed a network with a dynamic topology, with inter-regional functional connections that are amenable based on cognitive demands. Our data support critical components of the *scene construction hypothesis*, and suggest that the functional coupling between the PCC, HC, and other areas allow for the accurate ordering of spatial information in relation to oneself during mental simulations.

Chapter 5

5.1 Summary of findings

The ability to generate and manipulate mental representations of the world is a fundamental aspect of the human mind, affording the capacity to abstract away from the present into different places and moments of time. It is a central tenant of episodic (Tulving, 2002) and prospective (Schacter et al., 2007) theories of memory function, where features (i.e. people, places, events) from past experiences are coded by neural patterns in the brain that can be reinstated through dynamically coordinated interactions between the HC and areas across the neocortex (Brown et al., 2016; Horner et al., 2015). Although theoretical models on memory function posit functional interactions between memory and sensory/associative regions in generating the spatial context of a mental representation and binding episodic/environmental features to it, empirical evidence for how this occurs dynamically across a multitude of regions has been sparse. The primary aim of this thesis is to evaluate the network basis of memory by investigating putative dynamical network processes underlying the generation, reinstatement, and simulation of mental representations that are (1) accessible to conscious introspection, (2) declarable, and (3) situated in a spatiotemporal context.

Chapter 2 provides an investigation of changes in network topology and the role of the HC in facilitating information exchange while mnemonic representations of a large-scale virtual city are encoded and periodically reinstated. Using confidence judgements, which serve as proxies for the engagement of memory-selective neuron ensembles (Rutishauser et al., 2015), we found evidence for a general encoding mechanism where functional networks across the brain reconfigure from a state of global information integration to localized processing as mnemonic representations are formed. This reconfiguration was accompanied by changes to the role of the

HC as a connector hub. In low confidence trials, the HC displayed increased centrality at the inter and intra-module level, as quantified by changes in the participation coefficient and flow coefficient values, respectively. Conversely, high confidence trials were characterized by decreased HC centrality and increased local efficiency within a HC-based neighborhood of regions. Collectively, this pattern of results suggests that when encoding demands are highest in low confidence trials, the HC increases its role as a convergence zone for information processing across the brain, putatively to assist in generating neural codes indexing both the spatiotemporal context of mnemonic representations and the pattern of HC-cortical interactions used for feature reinstatement and integration during memory retrieval.

Chapter 3 extends the findings on representation encoding by investigating the network dynamics associated with reinstating and manipulating a mnemonic representation during mental simulation of navigation between city landmarks. Measures of simulation vividness and spatial coherence were used as indexes of feature integration (Arnold et al., 2016), allowing for an assessment of putative topological reconfiguration based on how effectively environmental features are reinstated and integrated into a holistic representation. During simulations with high vividness and spatial coherence, the HC (right hemisphere for vividness; left hemisphere for spatial coherence) displayed increased functional coupling with a cluster of voxels extending through left lateral occipital cortex and angular gyrus. This finding suggests that the neural codes for the spatiotemporal context represented in the HC (Brown et al., 2016; Ekstrom et al., 2003) dynamically interacted with an area of the cortex previously associated with spatially localizing visual objects (Y. Xu & Chun, 2006), manipulation of mental representations (Seghier, 2013), and putatively providing unique computations underlying self-referential awareness in non-present timeframes (Nyberg et al., 2010). Increased levels of functional coupling between these

regions leads to better simulation fidelity, suggesting that reinstatement and binding of environmental features during simulated action sequences within a mnemonic representation is facilitated through this specific HC-cortical interaction. Further, at a theoretical level it suggests that the HC does not solely provide the spatial computations necessary to generate and elaborate on a spatial context during memory reinstatement, instead requiring functional interactions with cortical regions to effectively reinstate and organize environmental features.

The role of the HC in global and local networks during mental simulations of different representational fidelity was also assessed. Here, no differences in HC centrality or HC neighborhood communication efficiency were related to variance in spatial coherence. However, a high degree of representational vividness was associated with increased HC centrality and decreased local efficiency within a HC neighborhood. Considered together, these results suggest that the HC plays a more principled role in organizing environmental features within a mental representation (Eichenbaum, 2004), insofar as the information flow vis-à-vis the HC does not relate to the reinstatement of mnemonic representations with high or low ordering of spatial information. It is possible to interpret this null finding as the HC not being necessary for the ordering of spatial information in a mnemonic representation; however, given the extensive empirical data supporting the role of the HC in providing the spatial context of a representation (Ekstrom et al., 2003; Hassabis, Kumaran, Vann, & Maguire, 2007b; Rosenbaum et al., 2009; Wilson & McNaughton, 1993), this interpretation seems unlikely. Conversely, increased information exchange via the HC appears to assist in the reinstatement of the visual aspects of environmental features, as the HC had higher flow coefficients during simulations with high vividness. Decreased HC neighborhood centrality was associated with increases in information exchange between other components of the HC neighborhood during simulations with low

vividness, suggesting a putative compensatory mechanism that allows reinstatement of environmental features with lower visual fidelity.

Chapter 4 explores a more speculative issue tying components of the DMN, a putative task-negative network (Fox et al., 2005), with the HC, a brain region posited to be a central component of the network involved in mentally displacing oneself into different places or moments in time. In the first analysis, no differences were observed in a statistical comparison of the topological configuration of a network composed of four DMN components (mPFC, PCC, left and right LP) and the left and right HC during rest and mental simulation blocks. However, a follow up analysis revealed that during rest, the left and right HC displayed statistical non-zero correlations with each other, but no regions of the DMN. Conversely, during mental simulations, both the left and right HC had statistical non-zero correlations with the contralateral hemisphere, as well as with the PCC and the left and right LP. This suggests that during rest the HC displays stronger functional coupling bilaterally, and that reconfiguration of functional connections with regions of the DMN occurs to facilitate mental simulations, putatively due to retrieval and maintenance of episodic features from memory (Bellana et al., 2017). The lack of non-zero functional coupling between PCC and the HC during rest blocks may be due to the more varied content of thoughts occurring at rest (Andrews-Hanna et al., 2014) that place a lower demand in generating mental representations with a spatiotemporal context.

Potential DMN reconfigurations were also investigated in relation to simulation fidelity. In the case of simulations with low and high vividness ratings, increased functional interactions were observed between the right HC and the left LP (and right LP, in the case of simulations with low vividness) relative to rest. This suggests that DMN reconfiguration occurs during mental simulations, and that the recapitulation of environmental features from memory and the

subsequent manipulation of them during simulated navigation requires interactions between information processing in the HC and that occurring in LP. For spatial coherence, a similar effect was observed during simulations with low spatial coherence, with increased functional connectivity between the right HC and the left and right LP relative to rest. However, for simulations with high spatial coherence, a similar effect was found to be nearly statistically significant, with increased functional connectivity between the right HC and left LP. Additionally, near significant effects were observed when using the PCC as a seed ROI, showing increases in functional connectivity with the left and right HC, as well as right LP. The increases in PCC-based functional interactions during mental simulations with a high degree of spatial coherence is suggestive of an increased demand to integrate allocentric and egocentric spatial information into a holistic representation that can be used to mentally simulate movement (P. Byrne et al., 2007; Marchette et al., 2014). Together, these results add to a growing body of literature on the dynamic nature of the DMN (Andrews-Hanna et al., 2010; Bellana et al., 2017; Fornito et al., 2012), indicating that changes in the functional connections, particularly involving PCC, or either left or right LP, are necessitated by the cognitive processing demands of mentally simulating movement through a spatiotemporal context.

Comparing the functional interactions between the HC and regions of LP observed in chapter 3 and 4, it is plausible that the effects identified in chapter 3 better approximates the changes in network interactions during mental simulations of different visual fidelity. The gPPI analysis in chapter 3 was not constrained to *a prior* ROIs, instead identifying clusters of voxels across any region of the brain that were represented by the gPPI model. In chapter 4, the analysis was constrained to *a priori* LP ROIs, which bordered with the LP/angular gyrus cluster identified in chapter 3. As such, the observed increases of functional connectivity between the HC and LP

relative to rest periods, but not between mental simulations with high vs low vividness or spatial coherence, suggests that the functional coupling of HC and LP is necessitated by generating mental simulations, but that the specific neural mechanism associated with generating a higher representational fidelity was not properly captured by the LP seed in chapter 4.

5.2 Bridging results with models of memory function

The results from each chapter support the general perspective of the HC in generating and reinstating the spatiotemporal context of a mnemonic representation, and that HC-cortical interactions underlie feature reinstatement (Ekstrom et al., 2014; Hassabis & Maguire, 2007; Nadel & Moscovitch, 1997; Rosenbaum et al., 2009; Squire & Zola-Morgan, 1991). However, these findings also suggest an important extension to existing theoretical models by showing that the role of the HC in encoding and reinstating spatiotemporal information is flexible, varying in relation to encoding demands and how efficiently environmental and episodic features can be reinstated and organized into a mnemonic representation. This flexibility can provide critical insights into the functional role of the HC in relation to mnemonic representations, and more broadly suggests that the brain is able to adapt to task demands by reconfiguring patterns of functional interactions within and between neural networks.

The *standard model* (Squire & Zola-Morgan, 1991) and *multiple trace theory* (MTT) (Nadel & Moscovitch, 1997) of memory function both theorize that the HC is unique in its capacity to encode and represent the spatial context of a memory through patterns of neural activity. The two models differ in their prediction of HC involvement in remote memories, however. The *standard model* proposes that consolidation of cortical-cortical interactions over a long period of time leads to long term potentiation, resulting in a diminishing role of the HC in retrieving remote memories. Conversely, MTT predicts that the HC is always required to provide

the spatial context of a memory trace, regardless of memory age. Research on memory performance in both amnesic patients and healthy people has widely supported the proposal of MTT (Moscovitch et al., 2016). As such, the results of the analyses here will only be discussed in the context of MTT.

Although MTT posits the unique role of the HC in encoding and representing the spatial context of an episode, it also theorizes that gist, or schematic-like, spatial representations do not necessitate HC involvement. Schematic representations lack perceptual details but in some cases can provide sufficient spatial information for navigation (Kolarik et al., 2016; Winocur & Moscovitch, 2011). The data from chapter 2 provides a novel perspective on this dual-representation framework in MTT, suggesting that initial schematic representations of spatial features are formed through increased levels of functional interactions between regions across the brain. These distributed interactions are associated with an increased role of the HC as a connector hub at the inter- and intra-module level, where it putatively works to encode a neural pattern that indexes cortical processing relating to environmental features, as well as the spatial organization of such features. As encoding occurs, and these features are integrated into a mnemonic representation, the brain reconfigures into a more robust modular state, characterized in part by decreasing levels of global connectivity. This topological reconfiguration may be due to a decreased demand to integrate environmental information into existing features/representations, or, speculatively, may underlie a change in component processing (Cabeza & Moscovitch, 2013), where rather than attempting to integrate environmental information, the detail and organization of features encoded in a representation are monitored and contrasted against environmental information being experienced as a person navigates a route (Spiers & Maguire, 2008). In the context of MTT, these findings suggest that the role of the

HC in memory encoding and retrieval is not singular, as would be predicted from its original formulation (Nadel & Moscovitch, 1997), but varies based on integrative demands and is putatively associated with a more general mechanism across the brain that facilitates state shifts in network topology to encode and represent environmental and episodic features.

The results from chapter 3 are also informative to tenants of MTT. Here, it was observed in the gPPI analyses that HC-cortical interactions were associated with differences in representational fidelity. As such, it suggests that HC-cortical interactions, rather than HC functioning alone, are necessary for the reinstatement of highly visual and spatially coherent mnemonic representations. If it were the case that spatial computations in the HC alone indexed the organization of environmental features, there would be no predicted differences in the patterns of functional connectivity with the HC as those spatial computations would be required in all cases. While this finding emerged through an analysis of mental simulations, rather than mental representations *per se*, and therefore requires a higher degree of goal-oriented manipulation than the simple reinstatement of a representation, the degree of manipulation was consistent across trials as both high and low vividness/spatial coherence trials had the same task demands. As such, differences in neural processes between trials should be interpreted as differences in representational fidelity. To this extent, the findings indicate that HC-based functional interactions facilitate the reinstatement and organization of environmental features. However, at a broader network level, changes in HC centrality and neighborhood efficiency were only observed in the case of differences in vividness. This finding has two important implications: first, organizing spatial features into a coherent representation does not appear to require more widespread functional interactions outside of those identified in the gPPI analysis; second, the reinstatement of perceptual aspects of environmental features does require more

widespread functional interactions with the HC, supporting the proposal in MTT that a HC-based index facilitates reinstatement of environmental features processed outside of the HC, and that schematic (or low detail) representations can be reinstated through increased functional interactions between non-HC regions of the memory network.

Although the dual-representational framework of MTT accommodates variation in representational fidelity, both the *scene construction* (Hassabis & Maguire, 2009) and *detail generation and* binding (Rosenbaum et al., 2009) hypotheses provide a more comprehensive theoretical perspective to contextualize the results from chapter 3. *Scene construction* theorizes that the common cognitive function of the HC-cortical network observed in navigation and episodic memory tasks involves the construction of a mental scene. The constructive process of generating a mental scene is not the output of a single brain region such as the HC, but the result of network interactions occurring in PFC, PCC, HC, and parietal cortices (Hassabis & Maguire, 2009). However, research since its proposal has focused primarily on understanding component processes within regions of the network (e.g. Brown et al., 2016; Marchette et al., 2014) rather than how dynamical network processes associate with variability in the scene construction. The results from this thesis address this limitation and show that the reinstatement of perceptual details and the ordering of environmental features is accomplished through changes in network interactions. Specifically, increased levels of functional coupling between HC and LP/angular gyrus is associated with higher fidelity scene construction, putatively through better coordination between neural codes in the HC indexing representational information and processes in LP/angular gyrus allowing the elaboration, transformation, and manipulation of representational information. Further, increases in HC centrality and decreases in non-HC functional interactions within a HC-based neighborhood were related to more vivid mental scenes, indicating that HC-

mediated functional interactions are associated with constructing mental scenes with a high degree of perceptual detail. Intriguingly, and similar to the interpretation of schematic representations in MTT, it appears that low detail spatial representations can be generated, at least partially, through increased levels of non-HC interactions within a memory network. More specifically, if the HC singularly provides the computations needed to construct a mental scene with highly detailed environmental features, the prediction would be that high vividness representations are associated with increased levels of HC centrality within a memory network, as was found in chapter 3, but that the topological organization of non-HC interactions within the same network should remain stable between conditions. However, lower values of HC centrality in simulations with low levels of vividness were associated with increased local efficiency values, suggesting that the other regions of the memory network compensate for decreased HC involvement in coordinating information flow by increasing the degree to which they interact with other components of the network. In the context of *scene construction*, this confirms the prediction that cooperative dynamics in the memory network facilitate the generation of a mental scene, but extends it by showing that information flow within the memory network vis-à-vis the HC facilitates the construction of highly detailed mental scenes.

Although the *detail generation and binding* hypothesis shares many of the tenants of *scene construction*, it makes two important predictions that differ. First, it suggests that schematic representations are able to be generated without HC involvement. As previously outlined, this is supported by the data presented in chapter 3, where mnemonic representations with lower amounts of perceptual details were associated with lower levels of HC centrality. While the HC was still functionally coupled with other regions during low vividness simulations, and is therefore not a direct assessment of the schematic representation hypothesis, it does

support the general proposal that the HC contributes to a high resolution reinstatement of perceptual details in a mnemonic representation through increased levels of information coordination. Second, the *detail generation and binding* hypothesis predicts that the sequential binding of event components, rather than specifically the spatial context *per se*, is provided by HC computations. Given the spatial nature of the task, it would be improper to formulate conclusions in a spatial vs. non-spatial manner. However, the results in chapter 3 on spatial coherence provide some insight into how this process may occur. The findings that there were no differences in HC centrality or the local efficiency of a HC-network when comparing simulations with low and high spatial coherence suggests that the ordering of environmental features in the mnemonic representation is not accomplished through HC computations *per se*. If that were the case, the prediction would be higher levels of information flow vis-à-vis the HC should associated with increased levels of spatial coherence. Rather, the data suggest that the ordering of environmental features is accomplished though HC-cortical interactions focused primarily on LP/angular gyrus. In this view, the neural codes in the HC indexing spatial information of environmental features are more effectively organized through information exchange with LP/angular gyrus. Deficits in generating coherent narratives (Rosenbaum et al., 2009) or mental scenes (Hassabis, Kumaran, Vann, & Maguire, 2007b) observed in amnesic patients may therefore be due to a loss of neural codes that are typically manipulated and organized through HC-LP/angular gyrus interactions, rather than a loss of putative HC computations correctly ordering feature information in a representation.

The dynamic nature of neural systems supporting memory function identified in this thesis provide some of the first empirical support for the proposals by Ekstrom and colleagues (Ekstrom et al., 2014). As predicted, the information processing role of the HC adapted based on

encoding demands, changing from a more central component of intra- and inter-network modules when encoding demands were highest to a less central role as inter-regional information flow between components of the memory network increase. This suggests that the computations for the spatial context of a mnemonic representation are not isolated to the HC, but are at least partially distributed, such that encoding demands are associated with non-HC changes in functional interactions within the memory network. Additionally, in line with predictions from Ekstrom and colleagues (Ekstrom et al., 2014) and counter to the *scene construction* hypothesis, the composition of the neural networks supporting the generation of a mnemonic representation that is highly spatial appear to be dynamic, where the degree of functional interactions between network components adapts in a contextual manner based on current task demands. Although preliminary, these results suggest that mnemonic representations are indeed associated with dynamical systems in the brain, and that more complex forms of information integration occur rather additive forms of component processing.

Chapter 4 investigates that topological overlap between the putative scene construction network and the DMN. Here, the data suggest that the DMN is not a static network as had been previously proposed (Fox et al., 2005; Raichle et al., 2001), but one that also displays context dependent adaptability in terms of functional interactions between network components. During mental simulations which required the construction of elaborate mental scenes, the HC displayed statistically non-zero correlations with all regions of the DMN, whereas there were only statistically non-zero correlations between each HC ROI during rest. Moreover, HC-LP interactions were related to representational fidelity, increasing the degree of functional connectivity relative to rest during simulations with low and high vividness and spatial coherence, albeit the correlation in high spatial coherence simulations only approached the

statistical threshold. Together, these results suggest that the putative overlap between the DMN and the core network supporting the generation of mnemonic representations is limited and that contextual changes in DMN functional connectivity are associated with constructing mnemonic representations. In line with the *scene construction* hypothesis, this suggests that functional interactions between HC, PCC, and LP are necessary for generating the spatiotemporal context of a mnemonic representation.

5.3 A dynamical view of memory function

Collectively, the results presented in this thesis argue for a dynamical view of the neural systems supporting memory function, where adaptability in the configuration of functional interactions within and between neural networks allows for contextual changes underlying how environmental and episodic information is encoded and integrated into a holistic mnemonic representation, and then subsequently utilized in a goal-directed manner. While various tenants of the outlined theoretical models were supported, they provide limited hypotheses to explain how the configuration of neural systems adapts to provide contextual shifts in information processing. A plausible explanation for this is the theoretical models were formulated prior to a recent surge in theoretical and methodological advances to understand dynamical network processes in the brain. As such, each model applies a more ridged framework to understand component processes and output functions of the brain regions and networks subserving memory function. However, using the data presented in this thesis and recent empirical findings, it is possible to articulate a theoretical perspective that is more inclusive of the complex and dynamic basis of neural processes supporting the capacity to generate and manipulate mnemonic representations.

It is important to highlight the spatial nature of the tasks used in this thesis prior to developing theoretical insights. While spatial navigation has been proposed as a model system to study memory function (Chersi & Burgess, 2015), it is important going forward to investigate the following hypotheses using tasks that are inclusive of other categories of feature information composing episodic events. Given the overlap in neural systems identified during spatial navigation tasks and episodic memory/future thinking tasks (Buckner & Carroll, 2007; Hassabis & Maguire, 2009; Schacter et al., 2012), it appears reasonable that similar network dynamics would occur. However, this is speculative and must be evaluated empirically. In order to facilitate this process, the analytical pipeline and code for analyzing and visualizing datasets has been made freely available online (https://github.com/A2ed/network_reconfig).

When environmental and episodic features of an event need to be encoded, the topological structure of networks distributed across the brain reconfigure to a state allowing for a higher level of information integration. This is accomplished through increases in communication efficiency at the global and local neighborhood level, and increases in the intra- and inter-module centrality of critical hub regions such as the HC. This state shift allows for experienced environmental and episodic features represented in neural patterns across sensory and associative brain regions to be indexed by the HC. As the neural codes for mnemonic representation is formed and the spatiotemporal context generated, brain networks reconfigure to become more modular and decrease in global connectivity. This fractionation is coupled with decreases in HC centrality at the intra- and inter-module level, and increases in communication efficiency between components of a HC-based memory network, as a putative neural index of event features is stabilized. Similar to MTT and proposals elsewhere (e.g. Buchel et al., 1999), the featural basis of a mnemonic representation is proposed to be based on the interactions

between the HC and areas of the cortex, rather than the neural code in the HC alone. The state shift to modular, local mnemonic processing provides a putative protective mechanism against interference of competing memory traces, where pattern differentiation processes in the HC allow for a multitude of partially orthogonal neural codes using shared environmental features to be generated (Favila, Chanales, & Kuhl, 2016; Kyle et al., 2015).

In the context of the spatial task used here, it is plausible that unique route information (e.g. which way to turn) is encoded relative to shared environmental features such as landmarks or geometric cues (Brown et al., 2010), allowing for a composite mnemonic representation of the city layout to be assembled through integration of multiple, partially overlapping neural codes representing different aspects of the city layout (Derdikman & Moser, 2010). This process is proposed to occur largely within a modular HC-cortical memory network, where the information processing emphasis dynamically reconfigures from a state of global and inter-module information integration during the initial encoding of neural representations (here, low confidence trials), to one where the neural codes of overlapping multi-featural representations are differentiated based on patterns of information flow within a local HC neighborhood (here, high confidence trials). The local patterns of functional interactions between non-HC components of the memory network are posited to provide a schematic like representation of environmental features, whereas HC-mediated information processing allows for high fidelity neural representations (Rosenbaum et al., 2009; Yonelinas, 2013) that are modifiable based on task context.

The reinstatement and simulation of multi-featural mental representations is posited to be constructive, as proposed elsewhere (Addis et al., 2007; Arnold et al., 2016; Hassabis & Maguire, 2007; Rosenbaum et al., 2009). This process requires that feature information is

contextually reinstated based on task demands, allowing for holistic, goal-oriented mnemonic representations to be generated by binding together multiple, partially overlapping neural codes using shared feature information. This assembly process provides flexibility in the content and organization of feature information, allowing one to reconstruct past experiences, anticipate future scenarios in a familiar spatiotemporal context, or envision hypothetical world states due to novel assemblies of feature details. Critically, this process is not theorized to be additive, such that two neural codes are co-activated and their associated feature information added together (Ekstrom et al., 2014). Rather, the process is posited to be complex, allowing for a novel synthesis and binding of feature information that produces output behavior that is more than the sum of its parts. For example, novel routes between landmarks are theorized to occur by integrating route specific environmental features into a composite representation that allows for an inference on a possible new trajectory. The generation of a task-oriented representation derived from multiple, partially overlapping neural codes suggests that there will be variability in the degree to which feature information can be actively bound together. This variability has been previously demonstrated, where the degree of representational fidelity is predictive of how quickly a person can simulate an event such that high fidelity, and therefore more integrated representations, allow for quicker mental simulations (Arnold et al., 2016).

The reinstatement and organization of feature information occurs through functional interactions between the HC and LP/angular gyrus, as well as within a local HC neighborhood. LP/angular gyrus is theorized to allow for contextual organization of multiple neural codes in the HC that are bound into a holistic representation. That is, LP/angular gyrus provides a putative representational buffer to input and manipulate neural indexes in the HC. The sequential reinstatement of neural indexes in the HC simultaneously elicits reactivation in

sensory/associative regions of the brain that code for feature information bound within the mnemonic representation. While it is theorized to still be possible to generate task-oriented representations with limited HC coordination by increasing the functional interactions between other regions of the memory network, information flow vis-à-vis the HC allows for higher resolution reinstatement of perceptual details of feature information. This is because the HC is posited to uniquely index the neural pattern of activity in regions throughout the brain used for feature reinstatement, whereas with lower HC communication coordination, co-activation and feed forward/backward mechanisms for information flow between non-HC regions rely on less differentiated neural codes in other brain areas and are therefore subject to more interference, slower reaction times during reinstatement, and less perceptual detail. Critically, the removal of the HC interferes with both the organization and reinstatement of feature information, due to a loss of pattern differentiation (Kyle et al., 2015) and completion (Horner et al., 2015) processes allowing for multiple neural indexes to be organized through HC-LP/angular gyrus interactions, instead relying on feature reinstatement using more schematic and less differentiated neural indexes in other regions of the memory network.

5.4 Future research

While it is possible to articulate a theoretical perspective of memory function based in part on the findings from this thesis, it should be emphasized that much more research is needed to understand dynamical processes occurring during the generation and reinstatement of mnemonic representations. Given the breadth of past memory research, as well as its central role in human cognition, there are various additional research areas where modeling dynamical processes will be highly informative. Below are some of the more pertinent areas given the current findings.

Although the HC is putatively the primary brain region supporting information flow during memory functioning (Hassabis, Kumaran, Vann, & Maguire, 2007b; Mišić et al., 2014; Rosenbaum et al., 2009), other regions appear to act as additional convergence zones with important implications for dynamical network processes. In the context of spatial representations, another region of likely importance is the retrosplenial cortex (RSC). This region is part of the purported rich club of brain regions that are characterized by a high degree of inter-regional connectivity at the structural and functional level (Grayson et al., 2014). Past research has shown that RSC is involved in maintaining object locations relative to oneself during movement (i.e. spatial updating) (Burles, Slone, & Iaria, 2016), putatively through a capacity to anchor internal representations of an environment to local environmental features (Marchette et al., 2014). As such, RSC appears to be an important brain region, similar to the HC in hubness and spatial processing, that may provide critical insights into the integrative processes occurring during the generation and reinstatement of mnemonic representations based in a spatiotemporal context.

In terms of memory processes, perhaps the most important to investigate is the effect of consolidation on network dynamics. Consolidation is posited to alter the neural basis of mnemonic representations through an initial change in synaptic connections within the first few hours of memory formation, as well as more gradual, long term system changes to how memories are represented across different regions of the brain (Frankland & Bontempi, 2005). As such, it seems plausible that consolidation would alter how information is communicated and integrated both within and between network modules in relation to representation processing. Intriguingly, the angular gyrus has previously been implicated in converging multiple representations into a holistic one during short term consolidation (Wagner et al., 2015),

suggesting that the multitude of neural indexes, presumed to be dynamically operating in the spatial task used here, may consolidate over time into a more singular representation via HC-angular gyrus interactions. Additionally, the incorporation of new information such as environmental features into existing mnemonic representations has been shown to influence consolidation processes (Tse et al., 2007). Future research using a similar spatial navigation task will be able to evaluate the influence of both consolidation and prior environmental knowledge on network dynamics.

The theoretical perspective and analytical techniques developed in this thesis also have potential utility in applied and clinical frameworks. Neuro-stimulation studies using methods such as transcranial direct current stimulation have shown benefits on memory performance when cognitive training paradigms are coupled with cortical stimulation (Jones, Stephens, Alam, Bikson, & Berryhill, 2015). This suggests that the neural mechanisms are in some way enhanced through stimulation. An interesting area of future research is to evaluate the effects of neuro-stimulation on network dynamics by comparing pre- and post-stimulation communication efficiency measures to assess whether stimulation enhances the integrative capacity of global and local networks, as well as convergence zone regions such as the HC and RSC, and how stimulation induced topological changes relate to memory performance (Kim, Ekstrom, & Tandon, 2016).

Additionally, measures of communication efficiency and integration during the generation and reinstatement of mnemonic representations may be informative for understanding functional reorganization of memory networks after brain injury, in the presence of lesions to memory related regions of the brain, or in neuro-degenerative diseases such as Alzheimer’s Disease (Addis et al., 2009). Past work has shown that functional reorganization of semantic

memory networks is associated with the preservation of language skills in patients with medial temporal lobe epilepsy (Protzner & McAndrews, 2011), suggesting that there may be some degree of network reorganization associated with other memory impairments. Quantifying graph theoretical measures associated with putative long term changes in network dynamics may illuminate how functional reorganization of different neural systems allows for the partial preservation of memory function in some clinical cases.

Healthy aging has also been associated with functional changes in HC-based networks. Putatively, these network changes underlie age-related decreases on various memory tasks involving the reinstatement of spatiotemporal information (Addis et al., 2008). By evaluating the changing role of the HC within global and local networks, as well as the topology of HC-based neighborhoods, it may be able to precisely delineate how changes in network dynamics occur in relation to memory performance. One possible candidate for this is the adaptability of both global networks and the HC, where more ridged network and node topologies may underlie age-related changes in flexibly shifting to networks states (Mcintosh, Kovacevic, & Itier, 2008) that allow for optimization of encoding, reinstating, and manipulating feature information into goal-oriented mnemonic representations used to guide behavior into the future.

Chapter 6: Tables

Table 1. Post simulation questionnaire (PSQ) items listed by category

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

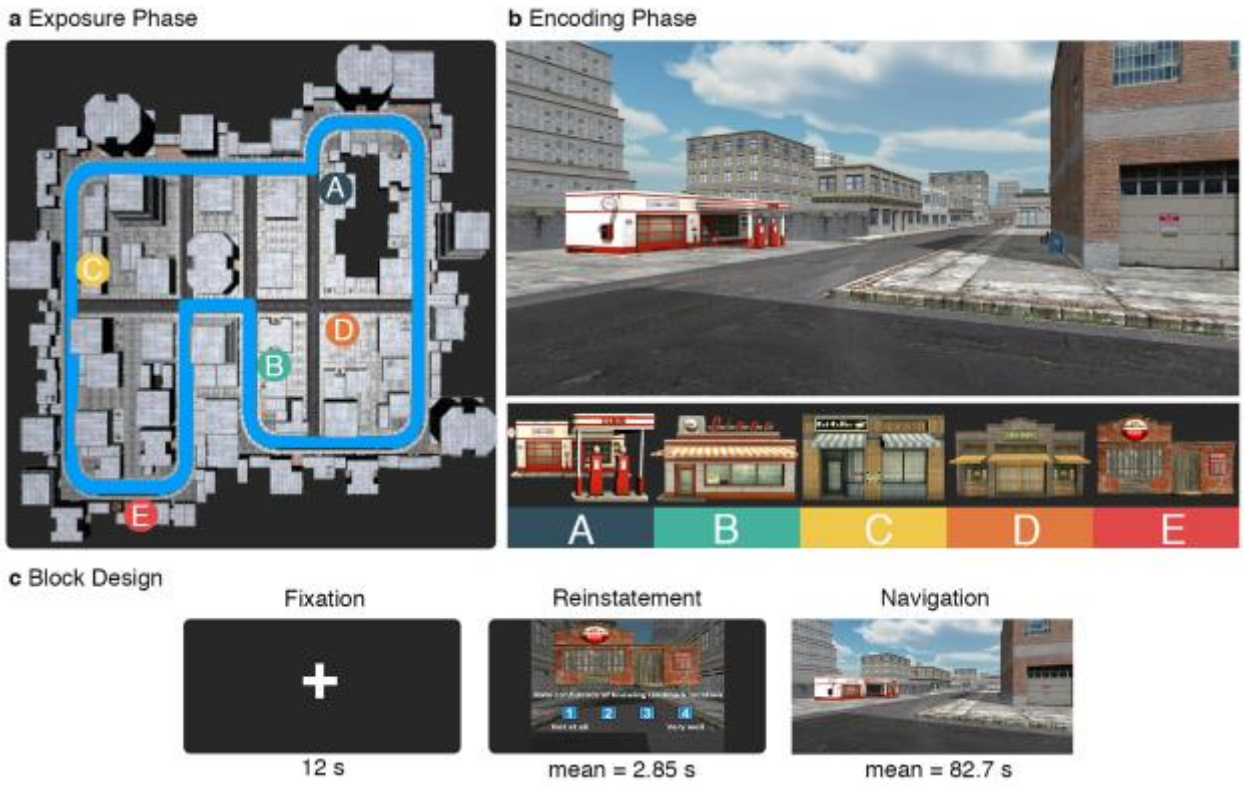
*indicates response that was inverted prior to analysis

Table 2. List of brain regions showing increased functional connectivity related to simulation fidelity

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

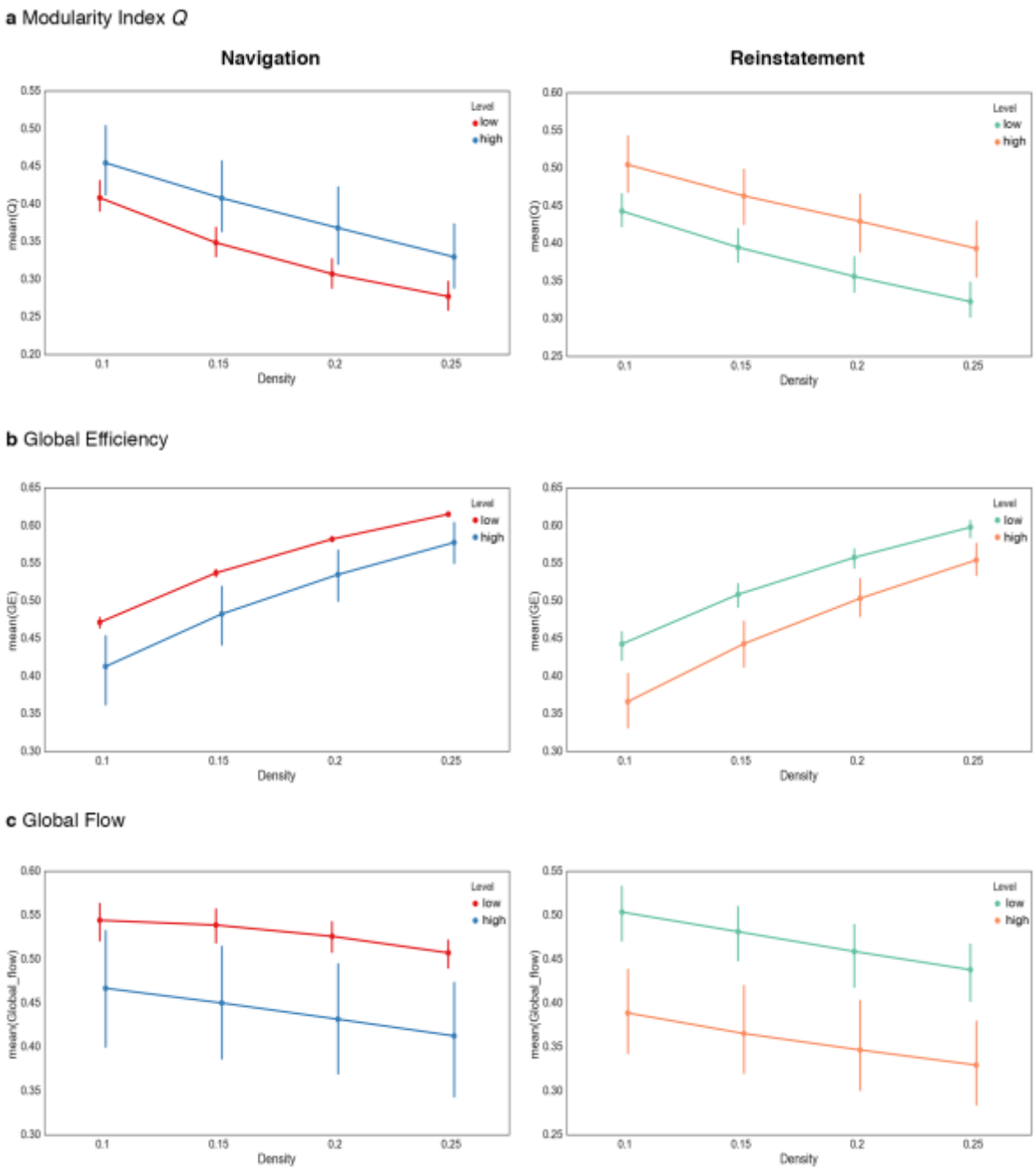
Table shows results for differences in functional connectivity between a source region and a multi-regional cluster. Anatomical regions for each cluster are listed by voxel size. All clusters were identified using a peak voxel threshold of $p < 0.001$ and a cluster correction threshold of $p_{FWE} <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

Chapter 7: Figures



7.1 Task design for encoding study.

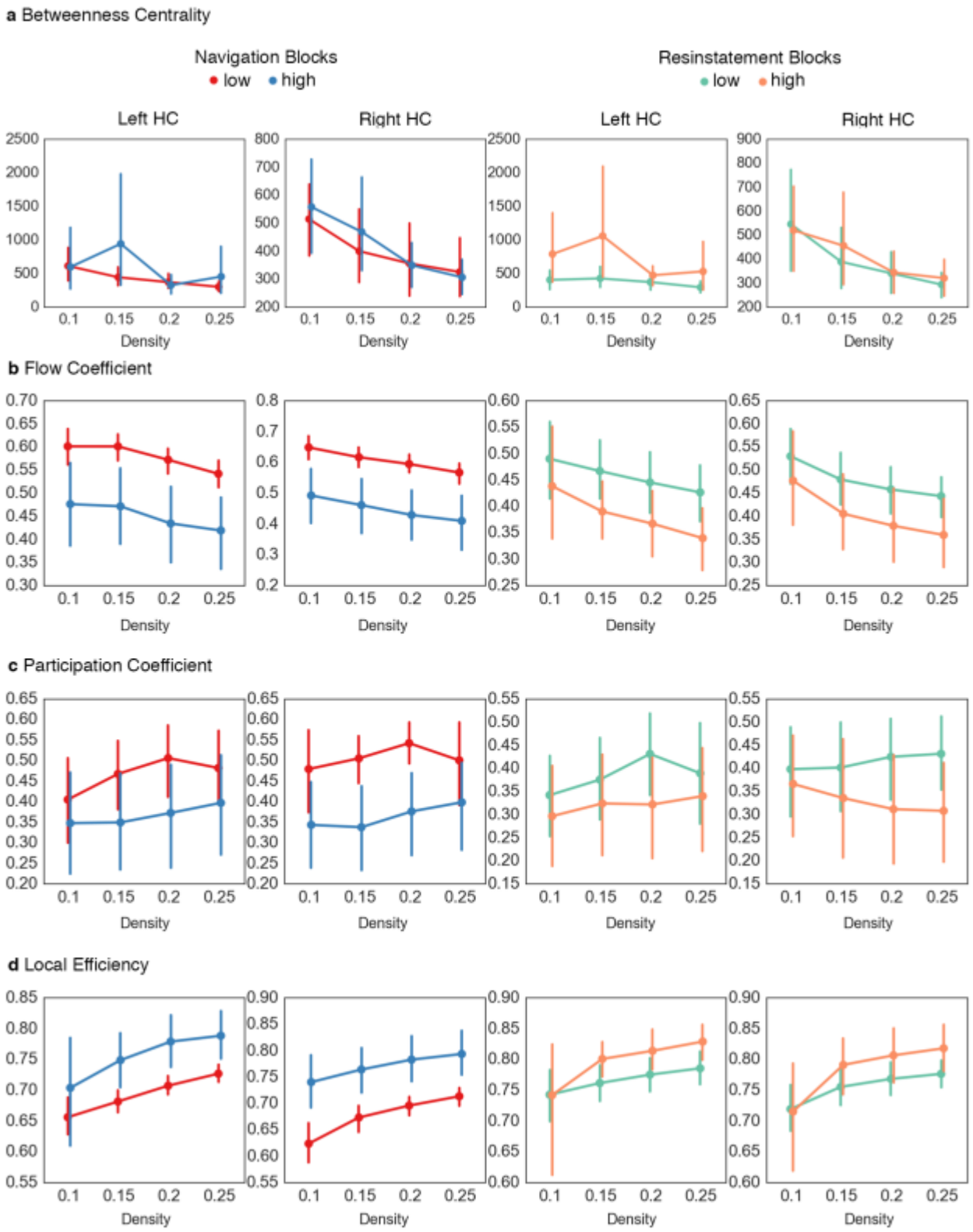
(a) Top-down view of the city. During the exposure phase, participants viewed a video of passive first-person movement along the city perimeter outlined in blue. Also displayed are the locations of the five target landmarks. (b) During the encoding phase, participants navigated between the five target landmarks. The city was composed of buildings using variations of three architectural styles, while the target landmarks were selected to be visually salient. (c) Block sequence order during scanning. Each trial began with a fixation cross, followed by a reinstatement block in which one of the target landmarks was displayed and participants rated on a scale of 1-4 their confidence in knowing its location. After, participants were instructed to navigate to the landmark as quick as possible.



7.2 Global network reconfiguration during representation encoding.

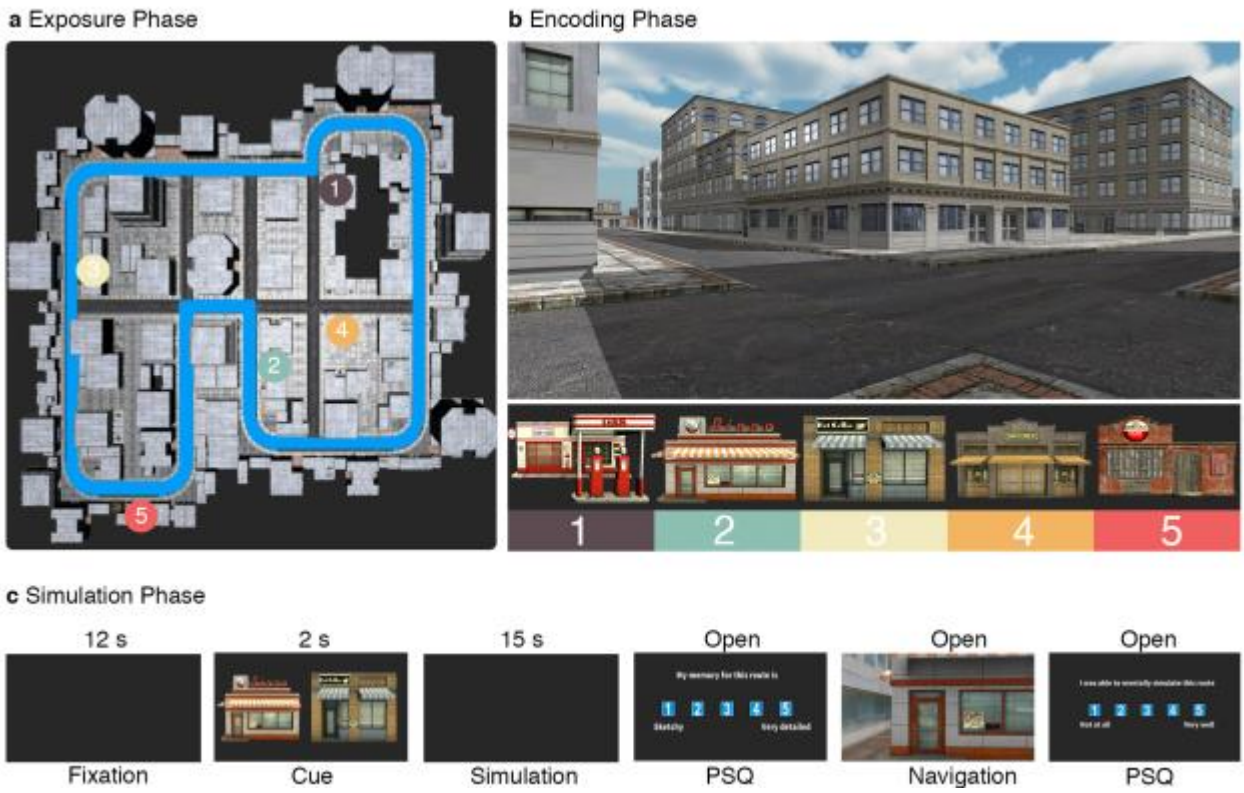
(a) Increases in the modularity index Q were observed across the whole 335 ROI network in both the navigation and reinstatement blocks across all the density thresholds (upper 10%-25% of connections in the network). (b) Similarly, there were increased global efficiency values during

the low confidence trials during navigation and reinstatement blocks. (c) This effect was also found for the global flow values in both the navigation and reinstatement blocks. Error bars represent 95% confidence intervals.


a Betweenness Centrality
Navigation Blocks
low
high
Resinstatement Blocks
low
high
Left HC
Right HC
Left HC
Right HC
Density
b Flow Coefficient
Density
c Participation Coefficient
Density
d Local Efficiency
Density

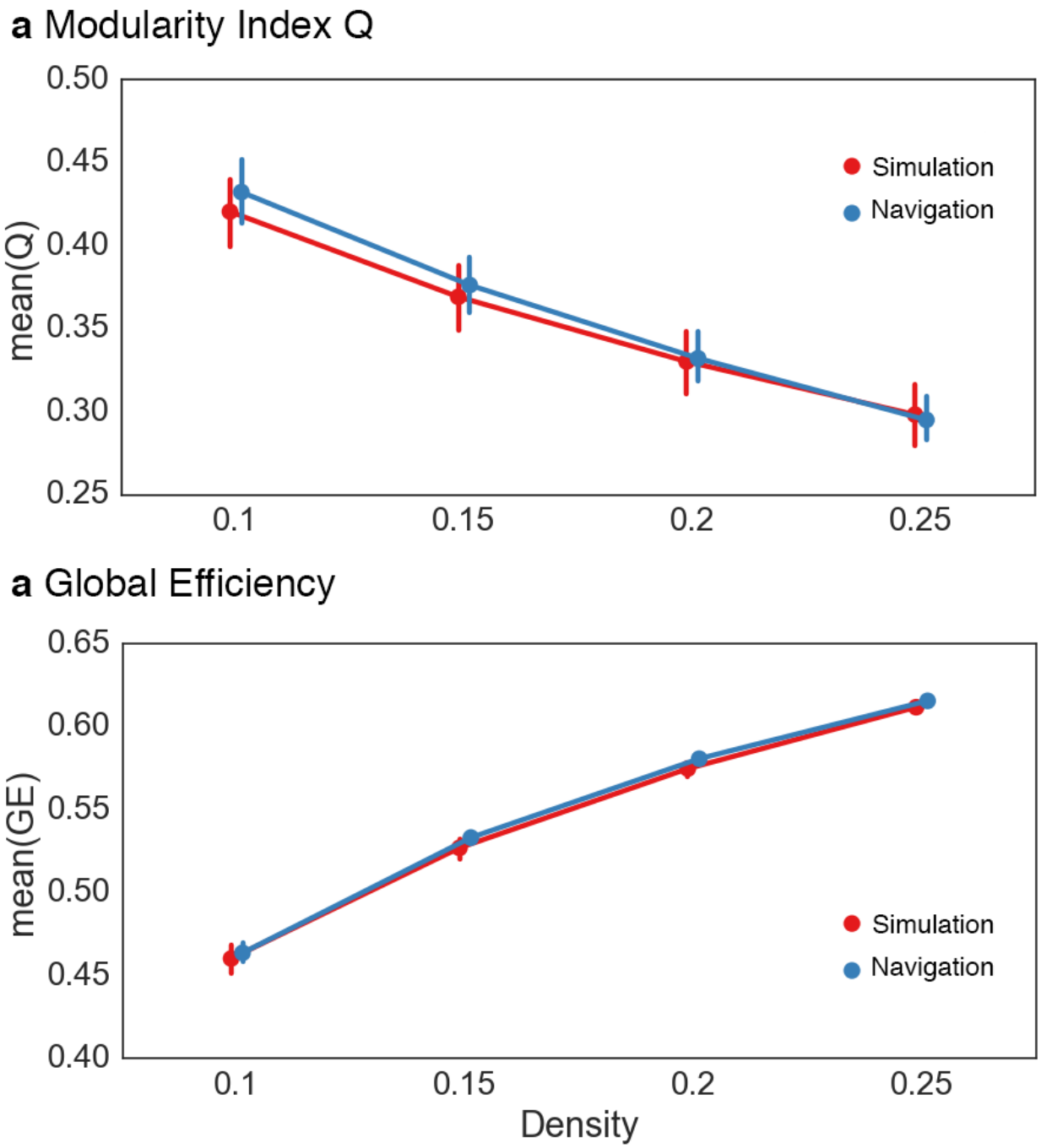
7.3 Centrality measures for hippocampal nodes during representation encoding.

(a) No differences were observed across the density thresholds for the betweenness centrality of the left and right hippocampus (HC) in either the navigation or reinstatement blocks. The summary statistic (betweenness centrality values averaged across density thresholds) was significantly increased during high confidence trials for the left HC during memory reinstatement. (b) Increased values of the flow coefficient were observed for both the left and right HC in low confidence trials during navigation blocks. Only the summary statistic for the left and right HC were significantly increased in low confidence trials during the reinstatement period. (c) Across the majority of density thresholds (0.15-0.25) there were increased participation coefficient values during low confidence trials for the right HC during navigation blocks, but only for the summary statistic in the left HC. The summary statistic was significantly increased in a similar manner for the right but not left HC. (d) Across all density thresholds in the right HC and for the majority (0.15-0.25) for the left HC, there were increased local efficiency values for the hippocampal sub-network during high confidence navigation blocks. There were no statistical differences during memory reinstatement. Error bars in all graphs represent 95% confidence intervals.



7.4 Overview of mental simulation task design.

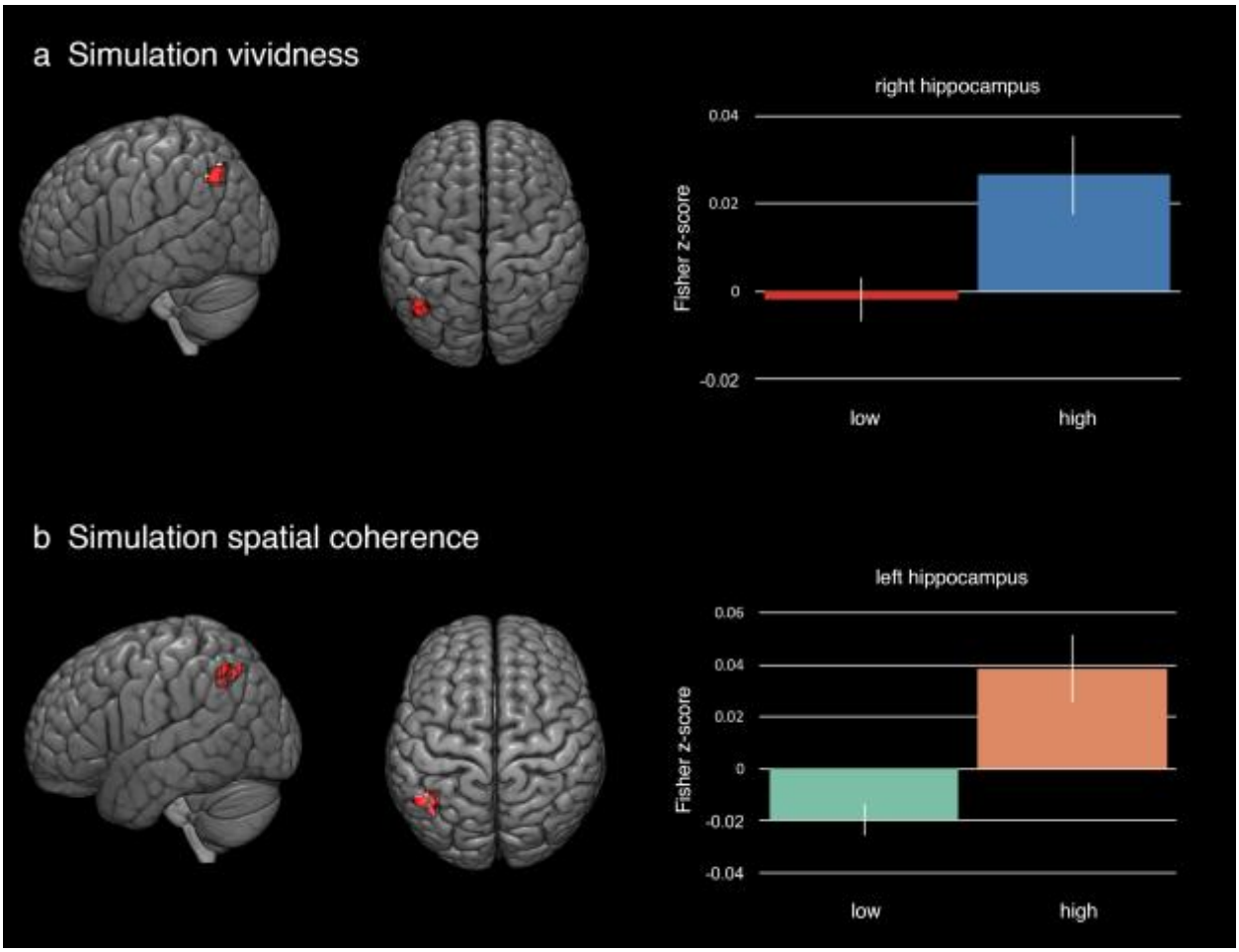
(a) The exposure phase was conducted outside of the scanner. Blue line indicates the path passive movement the participants viewed. Target landmark location denoted by circular icons. (b) Encoding phase occurred inside the scanner and lasted 23 minutes. Each trial cued a target landmark and participants navigated to it. Storefronts of five target landmarks shows their visual salience compared to the repeating architecture of the city. (c) Timing information for the simulation phase. After the initial 12s fixation period, participants were cued with a starting landmark (left) and a target landmark (right). They were given 15s to simulate movement between the two landmarks in as much detail as possible. Completion of the PSQ was open ended as was the subsequent navigation period between the two cued landmarks and the two remaining questions of the PSQ.



7.5 Results from global network analysis during mental simulation.

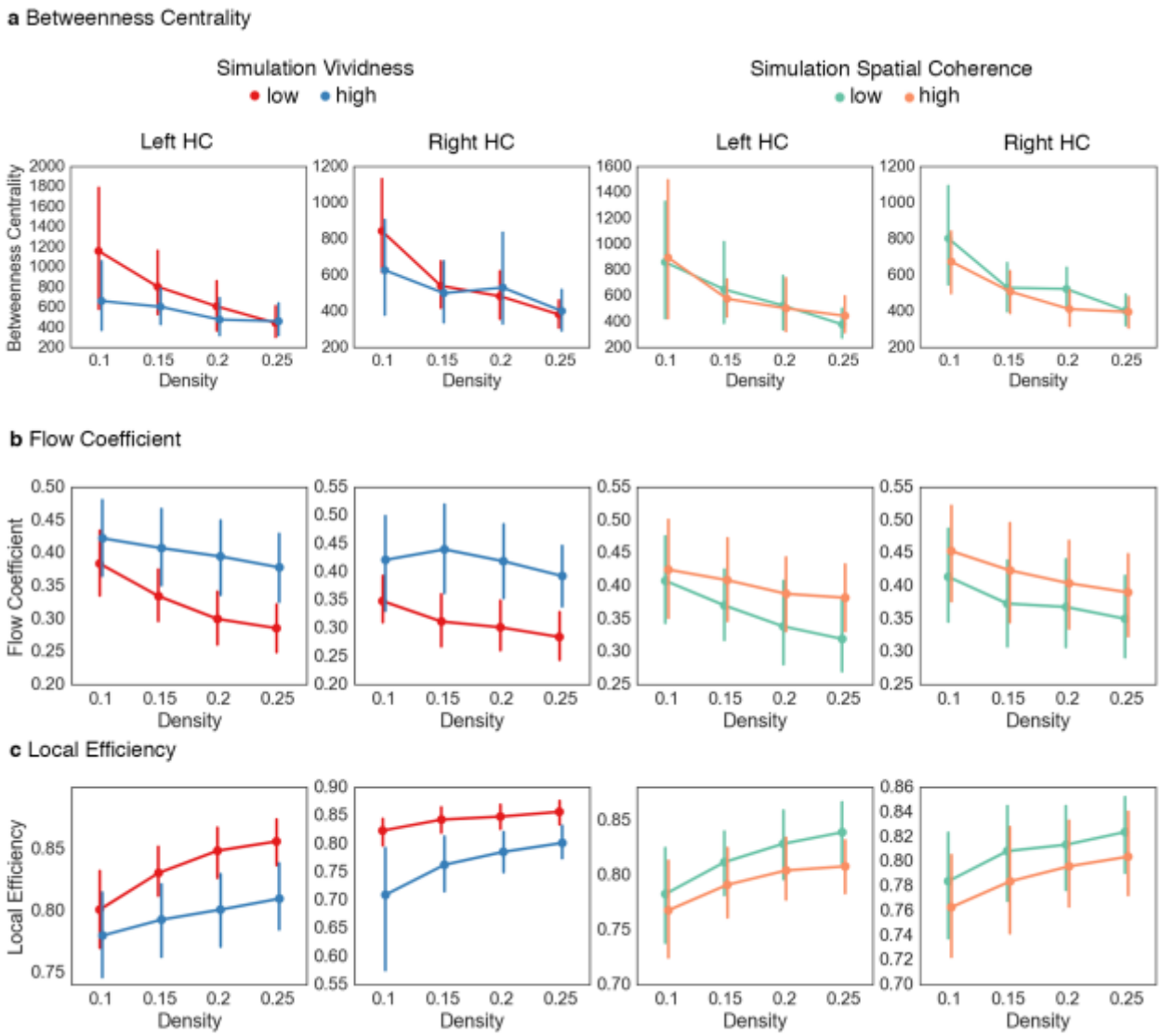
(a) No statistical differences were found between the simulation and navigation blocks in the modularity index *Q* across a range of density thresholds. (b) Similarly, no statistical differences

were found except at $k = 0.25$. However, comparison of the mean values for each block type revealed minor differences. Error bars represent 95% confidence intervals.



7.6 Results from general psychophysiological interaction analyses on mental simulations. (a) Simulations with high visual vividness were found to have increased functional connectivity between the right hippocampus (HC) and a cluster located in the superior division of the left lateral occipital cortex. Graph on right shows Fisher transformed z-scores for the low vividness and high vividness simulation periods. (b) Similarly, increased functional connectivity was observed between the left HC and a cluster within both left angular gyrus and the superior division of the lateral occipital cortex. Fisher transformed *r*-values for high and low spatial coherence simulations are on the right. Table 6.2 lists regions and number of voxels per region

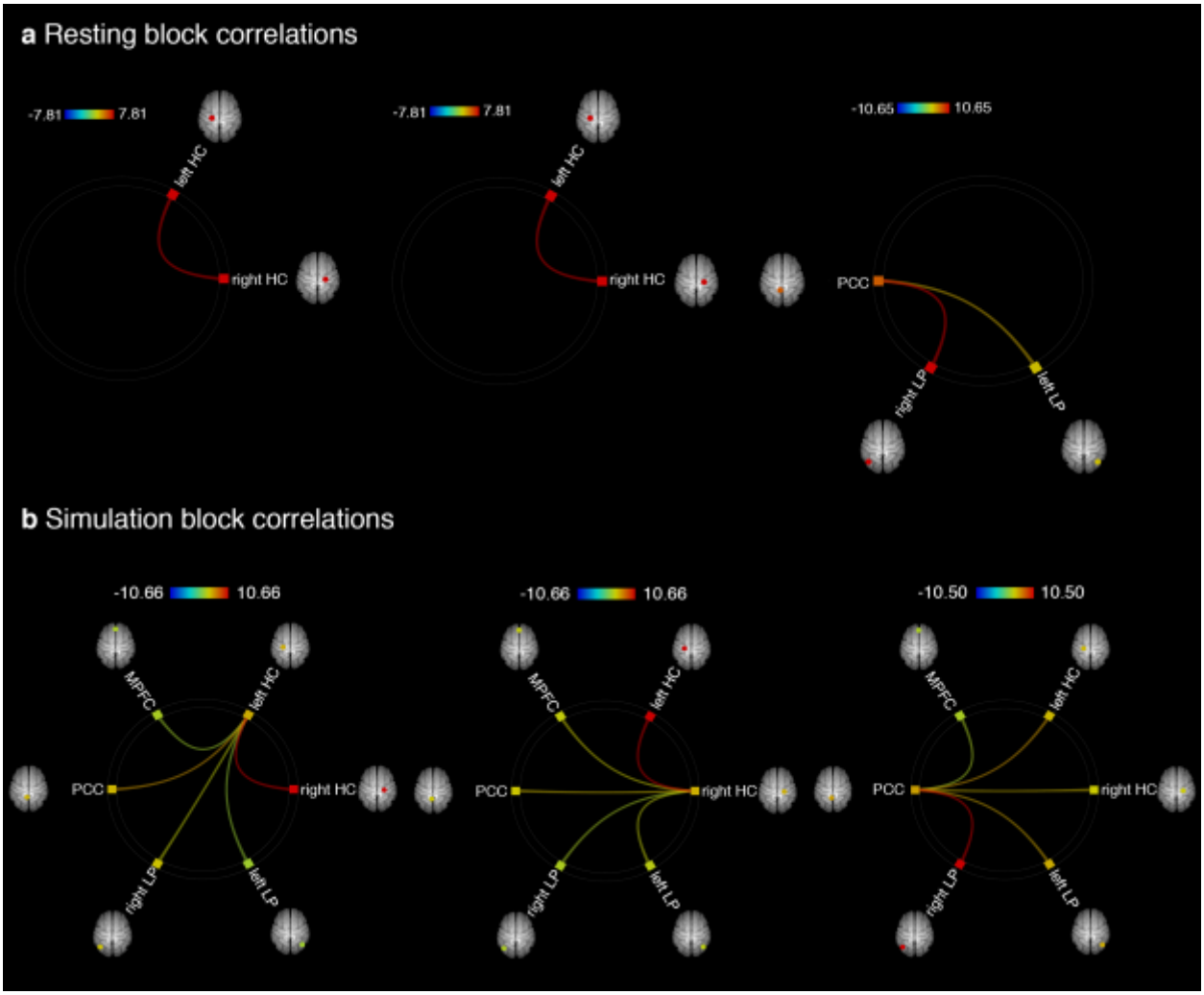
for each cluster. Statistically significant clusters were identified using a voxel height threshold of $p < 0.001$ and a cluster threshold of $p_{FWE} < 0.05$. Error bars represent standard error of the mean.



7.7 Results from hippocampal network analyses on mental simulations.

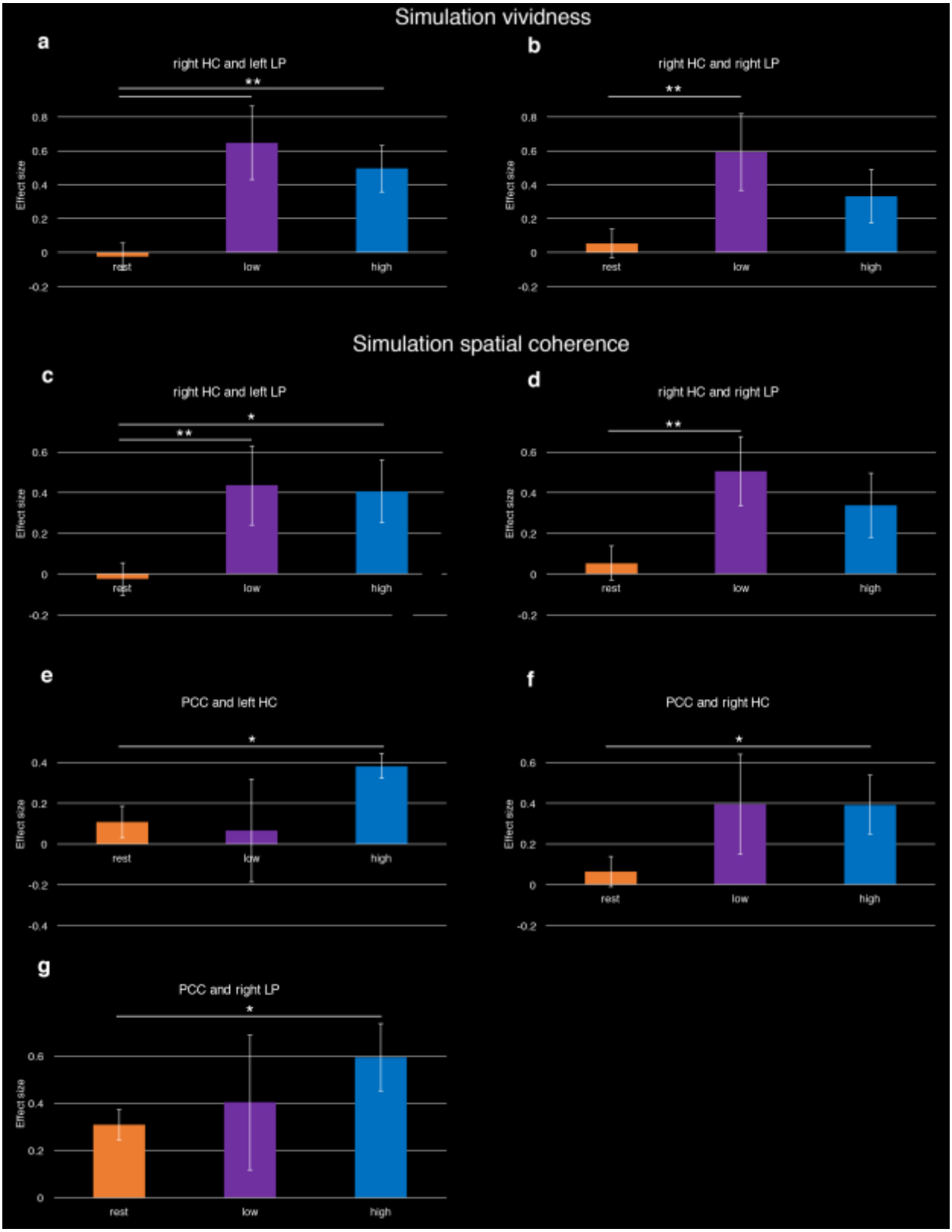
(a) No statistically significant differences were found in the betweenness centrality of the left or right hippocampus (HC) comparing either low and high vivid or spatially coherent mental simulations. (b) Increased flow coefficient values were found during highly vivid simulations in the right and left HC across higher density thresholds. (c) Decreased local efficiency values were found during highly vivid mental simulations in the right and across the higher density thresholds in the left HC. No statistical differences were observed between high and low spatial coherence

mental simulations. Density thresholds represent the percentage of strongest connections in each network. Error bars represent 95% confidence intervals.



7.8 Topological overlap of default mode network during mental simulations and resting blocks.

ROI-to-ROI functional connectivity rings for the left (left side) and right (middle) hippocampus (HC), and the posterior cingulate cortex (right side; PCC). (a) *t*-statistics showing statistically significant non-zero correlations between regions during rest blocks. (b) *t*-statistics showing statistically significant non-zero correlations between regions during mental simulation blocks. All visualized connections are based on Fisher transformed *r*-values and tested using a threshold of $p_{FDR} < 0.05$.


Simulation vividness
a
right HC and left LP
**
Effect size
0.8
0.6
0.4
0.2
0
-0.2
rest
low
high
b
right HC and right LP
**
Simulation spatial coherence
c
right HC and left LP
*
**
d
right HC and right LP
**
e
PCC and left HC
*
-0.4
f
PCC and right HC
*
g
PCC and right LP
*

7.9 Comparison of effect sizes for ROI-to-ROI functional connections based on mental simulation fidelity.

Top row displays increased effect sizes for correlations in low vividness and high vividness simulation blocks relative to rest between (a) the right hippocampus (HC) and the left lateral parietal (LP) cortex and (b) the right LP (b). For simulations with low and high spatial coherence ratings relative to rest, there were increased effect sizes between (c) the right HC and the left LP, as well as between (d) the right HC and right LP for low spatial coherence simulations. Additionally, for simulations with high spatial coherence relative to rest, there were increased effect sizes for correlations between the posterior cingulate cortex (PCC) and (e) the left HC, (f) the right HC, and (g) the right LP. * $p < 0.05$ and ** $p_{FDR} < 0.05$.

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