Brain and Cognition 92 (2014) 101–111

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Two distinct neural networks functionally connected to the human hippocampus during pattern separation tasks ☆

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ARTICLE INFO

Article history:
Accepted 23 October 2014
Available online 10 November 2014

Keywords:
Hippocampus
Pattern separation
Episodic memory
Functional connectivity

ABSTRACT

Previous studies from the human, rodent, and computational research have identified the hippocampus as a core structure mediating pattern separation. However, these investigations have generally focused on the role of distinct subregions of the hippocampus. Less well-understood is how the human hippocampus interacts with other brain regions to support pattern separation. The purpose of this study was to identify the functional networks connected to the hippocampus during delayed matching-to-sample pattern separation tasks promoting either spatial or temporal interference. Results revealed that the hippocampus was functionally connected to two distinct networks. The first network was characterized by correlated activation with the hippocampus primarily in bilateral temporal regions. This network was differentially related to spatial and temporal conditions, suggesting hippocampal connectivity to this network is modulated by interference type. A secondary network was characterized by correlations between the left hippocampus and several other sparsely distributed brain regions, including bilateral cerebellum and frontal and temporal cortices. This network was not modulated by interference type, suggesting that it may be a domain-general pattern separation network. We suggest that the hippocampus may play a role in integrating information from these networks to support performance on pattern separation tasks.

1. Introduction

Critical to episodic memory is the ability to reduce interference by separating, or orthogonalizing, similar memories; this process is known as pattern separation. Pattern separation works counter to pattern completion, the latter of which allows for accurate generalization when presented with noise or partial sensory input. Patten completion harnesses similarities and overlap in these representations. Pattern separation helps prevent catastrophic interference that results from the overwriting of already-stored similar memories by storing similar representations as distinct. When attempting to distinguish between highly overlapping events (such as the location of one's keys in the apartment today as opposed to yesterday) pattern separation is particularly important. Pattern separation is less important or unnecessary when the events are dissimilar (such as remembering your last birthday party versus your morning meeting with your supervisor; Yassa & Stark, 2011). A number of computational models (Becker, 2005; Leutgeb, Leutgeb, Moser, & Moser, 2007; Treves & Rolls, 1994), as well as rodent (Gilbert, Kesner, & DeCoteau, 1998; Gilbert, Kesner, & Lee, 2001; Goodrich-Hunsaker, Hunsaker, & Kesner, 2008; for a review see Kesner & Hopkins, 2006) and human (Bakker, Kirwan, Miller, & Stark, 2008; Hunsaker & Kesner, 2013; Kirwan & Stark, 2007; Kirwan et al., 2012; Lacy, Yassa, Stark, Muftuler, & Stark, 2010; Motley & Kirwan, 2012) studies have focussed on the hippocampi as core brain regions underpinning pattern separation.

Pattern separation in the hippocampi is thought to be achieved through the provision of distinct codes from the dentate gyrus (DG) to the *cornu ammonis* 3 (CA3) cell field via the sparse, yet powerful, mossy fibre pathway (Treves & Rolls, 1994). That is, most input to the hippocampi is relayed via its DG cell fields, which orthogonalize input by removing redundant information and sending disambiguated firing patterns to CA3 cells (Rolls, 1996). Behavioural

☆ *Grant Sponsor:* NARSAD, Brain and Behavior Research Fund (Young Investigator Award to Dr. Todd A. Girard).

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http://dx.doi.org/10.1016/j.bandc.2014.10.009
0278-2626/

evidence for the importance of the hippocampi in mediating pattern separation comes from rodent lesion studies assessing the orthogonalization of overlapping spatial and/or temporal information (Gilbert et al., 2001; Kesner & Hopkins, 2006). Hippocampal involvement in pattern separation has further been supported by human brain imaging studies (Clark, Manns, & Squire, 2002; Ekstrom & Bookheimer, 2007; Hayes, Ryan, Schnyer, & Nadel, 2004; Kesner & Hopkins, 2006; Kirwan et al., 2012; Yassa & Stark, 2011) that typically employ object-based continuous recognition paradigms (Bakker et al., 2008; Kirwan & Stark, 2007; Kirwan et al., 2012; Lacy et al., 2010), requiring subjects to discriminate between a memory representation and a highly similar lure item.

Computational models (Becker, 2005; O'Reilly & McClelland, 1994), rodent studies (Jerman, Kesner, & Hunsaker, 2006) and human neuroimaging studies (e.g. Bakker et al., 2008; Kirwan & Stark, 2007) have often conceptualized pattern separation in the hippocampus as a process that occurs during encoding. However, hippocampal pattern separation may also be engaged during the retention and retrieval of information. DiMattia and Kesner (1988) trained rodents on locating a spatial location in a water maze. Rats then underwent a lesion to the hippocampus or a control lesion. During test, rodents had to locate the same location they went to during study from four different locations. When hippocampal lesioned rats were tested from one of four locations, they showed a deficit, likely due to an inability to retain spatial information resulting in spatial interference operating during retrieval. Therefore hippocampally-mediated pattern separation may also be operating at retrieval (Kirwan & Stark, 2007).

In addition to supporting pattern separation, the human hippocampi are known to more generally support both spatial and temporal memory retrieval. For example, larger anterior hippocampal volumes predict better performance on both spatial and temporal context memory retrieval tasks (Rajah, Kromas, Han, & Pruessner, 2010). Moreover, an fMRI study using a virtual reality navigational task revealed that, despite unique activation of brain regions supporting spatial memory versus temporal memory, the hippocampi were integral for both at retrieval (Ekstrom & Bookheimer, 2007). Taken together, one means by which the hippocampi may support episodic memory retrieval (i.e., identifying the unique places/times associated with our experiences) might be by engaging in pattern separation when there is spatial and temporal interference.

Rodent studies of spatial and temporal pattern separation typically involve delayed match-to-sample paradigms using spatial or temporal interference. Gilbert et al. (2001) showed that spatial and temporal pattern separation may be dependent on different hippocampal subfields (see Kesner & Hopkins, 2006 for a review). For spatial pattern separation, a delayed-match-to-sample for spatial location task was used. Rats were trained to displace an object covering a food-well that was baited. At test, they were to choose between two identical objects, one of which covered the same well as the sample object (correct) or a second that covered a different unbaited well (incorrect). Demand on pattern separation was manipulated by increasing or decreasing the distance between the two objects. The closer together the two objects were, the greater the demand on pattern separation. For the spatial temporal order pattern separation task, a radial arm maze was used. A sequence of eight arms was presented to the animal by sequentially opening each door one at a time to allow access to the food reward at the end of the arm. On the choice phase, doors for two of the arms were opened and the rat had to enter the arm that had occurred earlier in the sequence to get a reward. Similar to the spatial task, as the temporal distance in the sequence between the two choice arms decreased, the difficulty increased. The results showed that DG lesions in rats resulted in a deficit on the spatial task but not the spatial temporal task, whereas CA1 lesions resulted in a deficit on the spatial temporal task but not spatial task.

We know of only one study that has directly examined spatial and temporal pattern separation in humans. Azab, Stark, and Stark (2014) recently explored pattern separation in the medial temporal cortices with spatial and temporal interference using similar lures in an incidental-encoding task with healthy young adults. During scanning, a sequence of four objects was shown in one of eight possible locations. Previously presented objects were repeated in different locations (spatial lure) and/or in different sequences (temporal lure). This study found that dentate gyrus/CA3 activity did not show specialization for spatial nor sequential (temporal) information, contrary to rodent evidence suggesting a subregional dissociation in dentate gyrus versus CA1 for spatial and temporal pattern separation respectively (Gilbert et al., 2001; Kesner & Hopkins, 2006). Rather, Azab et al. (2014) suggest that, since the dentate gyrus shows a strong pattern separation signal for both spatial and temporal conditions, it may act as a domain-general, universal pattern separator in humans. However, all subregions in the medial temporal lobes (MTL) tested, including the CA1 and subicular regions of the hippocampi, and the parahippocampal, entorhinal, and perirhinal cortices failed to show any sensitivity to both spatial and temporal interference. Yassa and Stark (2011) further suggest that hippocampal involvement in pattern separation may be domain-agnostic. Differential networks functionally connected to the domain-agnostic hippocampus may be engaged by a pattern separation task involving different information types. Specifically, it is possible spatial and temporal interference may be differentially mediated by extra-hippocampal, or extra-medial temporal lobe networks that are functionally connected to the hippocampi during pattern separation.

In this regard, the hippocampi do not function in isolation. They are unique recipients of highly processed multimodal input from a wide variety of associational and sensory cortices, as well as key subcortical forebrain, diencephalic, and brainstem nuclei (Amaral & Lavenex, 2007) and (Duvernoy, 2005). In turn, the hippocampi also project to diverse brain regions directly and via thalamic relay nuclei. For instance, the hippocampi directly project to inferior temporal association cortex, the temporal pole, and the prefrontal cortex (Duvernoy, 2005).

One means by which the hippocampi may support episodic memory retrieval (i.e., identifying the unique places/times associated with our experiences) might be by engaging in pattern separation when there is spatial and temporal interference. Examining whole-brain, extra-hippocampal networks will provide further insight into the neural substrates of pattern separation of spatial and temporal information during retrieval in the human brain beyond hippocampal subfields. We predict that while the hippocampi play a critical role in pattern separation, extended network connectivity would be modulated by the type of interference (spatial and temporal). In this exploratory study using a human analog to the paradigm used by Gilbert et al. (2001) above, our primary aim is to examine the whole-brain networks that correlate with hippocampal involvement during performance of pattern separation tasks and how they may be differentially influenced by the type of interference (spatial and temporal).

2. Methods

2.1. Participants

Fourteen healthy adults from the community with no history of neurological or psychiatric impairment participated in this study (9 female; M_{age} = 27.4 years, SD = 9.22, Range 18–55 years; M years of education = 16.46 years, SD = 2.33). All participants gave written