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Dissociable contributions of the prefrontal cortex to hippocampus- and caudate nucleus-dependent virtual navigation strategies

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ABSTRACT

The hippocampus and the caudate nucleus are critical to spatial– and stimulus–response-based navigation strategies, respectively. The hippocampus and caudate nucleus are also known to be anatomically connected to various areas of the prefrontal cortex. However, little is known about the involvement of the prefrontal cortex in these processes. In the current study, we sought to identify the prefrontal areas involved in spatial and response learning. We used functional magnetic resonance imaging (fMRI) and voxel-based morphometry to compare the neural activity and grey matter density of spatial and response strategy users. Twenty-three healthy young adults were scanned in a 1.5 T MRI scanner while they engaged in the Concurrent Spatial Discrimination Learning Task, a virtual navigation task in which either a spatial or response strategy can be used. In addition to increased BOLD activity in the hippocampus, spatial strategy users showed increased BOLD activity and grey matter density in the ventral area of the medial prefrontal cortex, especially in the orbitofrontal cortex. On the other hand, response strategy users exhibited increased BOLD activity and grey matter density in the dorsal area of the medial prefrontal cortex. Given the prefrontal cortex's role in reward-guided decision-making, we discuss the possibility that the ventromedial prefrontal cortex, including the orbitofrontal cortex, supports spatial learning by encoding stimulus-reward associations, while the dorsomedial prefrontal cortex supports response learning by encoding action-reward associations.

1. Introduction

Learning to find our way in an environment is a process that involves perceptual, mnemonic, and executive components that are mediated by a large network of brain structures. Furthermore, different navigation strategies are also subserved by distinct neural networks, with the hippocampus and caudate nucleus as the main nodes in these networks. Although we are beginning to understand how these principal structures mediate the different strategies, we know little about the other brain areas that differentially support these processes.

Two navigation strategies can be used when learning to find one's way in an environment. The spatial strategy involves forming stimulus–stimulus associations between landmarks in an environment (O'Keefe and Nadel, 1978) or, in other words, learning the spatial relationships between landmarks. These are then organized into a cognitive map, which allows us to navigate more flexibly, for example when we have to find a shortcut. The other navigation strategy is the stimulus–response strategy. It involves learning a sequence of motor responses, such as left and right turns, from specific points that act as stimuli (e.g., gas station). In other words, stimulus–response associations are formed (White & McDonald, 2002). Learning a specific route by taking it repeatedly is a good example of how one uses a response strategy.

Various other structures have been investigated for their role in navigation. For example, structures such as the parahippocampal, entorhinal, and retrosplenial cortices are known to mediate subfunctions of navigation like scene processing, keeping track of one's location in space, or processing landmark information (Auger, Mullally, & Maguire, 2012; Bohbot et al., 1998; Brown, Wilson, & Riches, 1987; Hafting, Fyhn, Molden, Moser, & Moser, 2005). In the prefrontal cortex, rodent studies have identified distinct regions to be important for spatial and response learning, mostly in the medial prefrontal cortex (de Bruin, Moita, de Brabander, & Joosten, 2001; de Bruin, Swinkels, & de Brabander, 1997; Delatour & Gisquet-Verrier, 2000; Fantie & Kolb, 1990; Floresco, Seamans, & Phillips, 1997; Kesner & Ragozzino, 2003; Seamans, Floresco, & Phillips, 1995; Vafaei & Rashidy-Pour, 2004;

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Wang & Cai, 2008). When taken together, these studies suggest that the ventromedial part of the prefrontal cortex (VMPFC), which includes the orbitofrontal cortex as well as the prelimbic and infralimbic cortices, is important for spatial learning, while the dorsomedial part (DMPFC) is important for response learning. For example, Vafaei and Rashidy-Pour (2004) inactivated the orbitofrontal cortex of rats that were being trained on a spatial version of the Morris Water Maze. In this task, rats are placed in a pool and have to use distal cues in order to find a submerged platform that allows them to escape the pool. Rats with orbitofrontal cortex inactivation were impaired in learning to solve this task (Vafaei & Rashidy-Pour, 2004). The same was found when the prelimbic and infralimbic cortices were inactivated (Wang & Cai, 2008). de Bruin and colleagues (1997, 2001) investigated the impact of frontal cortex damage on the spatial and response versions of the Morris Water Maze. In the response version of the task, the start position varied from trial to trial in a random fashion but rats always had to perform the same sequence of movements from the start position in order to reach the hidden platform. The authors found that lesioning the DMPFC resulted in impairments that were selective to response learning but not spatial learning in the spatial and response versions of the Morris Water Maze (de Bruin et al., 1997, 2001). Importantly, there is little research on how the prefrontal cortex is involved in navigation strategies in humans.

Identifying the prefrontal areas that are associated with navigation strategies will allow us to better define the components of the neural networks that support spatial and response strategies. It will also begin to inform us about how the prefrontal cortex mediates the executive processes involved in these strategies.

Based on the literature, we hypothesize that spatial strategies will be associated with increased BOLD activity and grey matter density in the VMPFC. We also hypothesize that response strategies will be associated with increased BOLD activity and grey matter density in the DMPFC.

We analysed data from a previously conducted functional Magnetic Resonance Imaging (fMRI) study, in which we had scanned healthy young adults while they performed a virtual navigation task that dissociated between spatial and response strategies (Etchamendy, Konishi, Pike, Marighetto, & Bohbot, 2012). In the current paper, we identified the prefrontal areas where activity was specifically associated with spatial or response strategies. We also used voxel-based morphometry (VBM) to measure grey matter density correlates of these strategies.

In accordance with our hypotheses, we found that spatial strategies are associated with increased BOLD activity and grey matter density in the VMPFC, while response strategies are associated with increased BOLD activity and grey matter density in the DMPFC.

2. Methods

2.1. Participants

Twenty-three healthy young adults (14 women; 9 men) between the ages of 18 and 35 (mean age: 23.87 years old ± 3.80) participated in the study. All participants were right-handed and had no history of neurological or psychiatric disorders. They were scanned at the Montreal Neurological Institute. Informed consent was obtained from the participants in conformity with the local ethics committee.

2.2. Functional magnetic resonance imaging task

While being scanned, participants performed the Concurrent Spatial Discrimination Learning Task (CSDLT; Etchamendy et al., 2012). The CSDLT was developed using Unreal Tournament 2003 development kit (Epic Games, Raleigh, NC). This task was adapted for humans from a task traditionally used in rodents (Marighetto et al., 1999). The task consists of a 12-arm radial maze, surrounded by a landscape and landmarks, such as mountains, trees, and rocks (Fig. 1). At the end of each pathway, a staircase leads to a small pit where an object is found in some of the pathways. The task has two stages, the learning stage (Stage 1) and the probe stage (Stage 2). The task is also comprised of both experimental and control trials.

2.2.1. Experimental trials

Stage 1 (learning stage): The 12 pathways are divided into six pairs of adjacent paths. In this stage, participants are located on a platform at the centre of the maze and are presented with a single pair of pathways at a time, while the other pathways are hidden behind walls (Fig. 1). Within each pair of pathways, only one path contains an object; the other is empty. The goal is to learn in which pathway the object is located within each pair. Participants have to go down the pathway they believe contains an object. Once they reach the pit, they are automatically brought back to the central platform, where they are presented with the next pair of pathways. One trial is comprised of the presentation of all six pairs of pathways, done in a pseudo-random order. Performance is measured as the number of correct pathways visited by the participant in each trial. Participants are trained until they reach a performance criterion of 11/12 within two consecutive trials. A minimum of six trials is administered.

To learn the objects' locations, participants can use a spatial strategy, whereby they learn the precise spatial relationships between the landmarks and the target path, or a response strategy, whereby they choose the right or left pathway associated with a given landmark (see Fig. 1, top panel for an example).

Stage 2 (probe stage): Once participants reach the learning criterion, they are given two probe trials. In the probe trials, the pathways are recombined into new pairs of adjacent pathways. For example, pathway #3, previously presented with pathway #4 (Fig. 1, top left panel), is now presented with pathway #2 (Fig. 1, bottom left panel). The objects remain in the same pathways. In each of the two probe trials, only four recombined pairs of pathways are shown: this allows for the presentation of adjacent pathways with only one pathway containing an object. The pairs of pathways are thus shown in a slightly different perspective compared to the learning stage. However, the spatial relationships between the landmarks and the target pathways remain the same. Successfully finding the objects in Stage 2 demonstrates memory flexibility: participants are able to find the correct pathways even when the presentation of the pathways is different than in the learning phase; they are able to adapt their knowledge to the new pair presentations, which are seen from a different perspective. Performing well requires knowing the precise spatial relationships between the target paths and the landmarks (see Fig. 1, bottom panel) and flexibility, both hallmarks of the spatial strategy (Cohen & Eichenbaum, 1993; Eichenbaum, 2004). Hence, those who perform well on the probe are considered to have used a spatial strategy during learning (Etchamendy et al., 2012).

A performance of 7 out of 8 on the probe stage was used as the cut-off to distinguish those who used a spatial strategy ($\geqslant$87.5%) from those who used a response strategy (<87.5%). This cut-off was determined based on the fact that the probability of getting 7 correct choices out of 8, or an accuracy of 87.5% (when the two probe trials are taken together), by chance is less than 5%. Thus, a score of 7 out of 8 is required to obtain a binomial probability of $p < 0.05$ (Etchamendy et al., 2012).

2.2.2. Visuo-motor control trials

We included control trials to control for the visuo-motor demands of the experimental trials. The control trials were