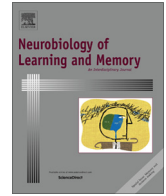




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Dissociable contributions of the prefrontal cortex to hippocampus- and caudate nucleus-dependent virtual navigation strategies



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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.

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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 sub-functions 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, Marigetto, & 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 \pm 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 (Marigetto 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 ($\geq 87.5\%$) 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

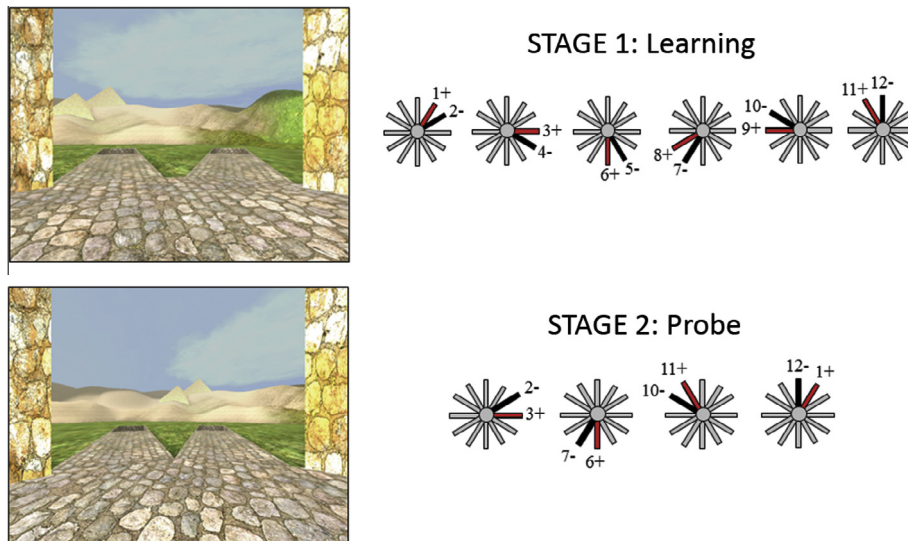


Fig. 1. The two stages of the virtual radial maze (left) with a schematic representation of the behavioural paradigm (right). The Concurrent Spatial Discrimination Learning Task (CSDLT) is a 12-arm maze surrounded by a landscape and landmarks. The arms are divided into six pairs. In each of these pairs, one arm contains an object and the other is empty. Participants must learn to locate the object within each pair of arms. The CSDLT is comprised of two stages: a learning stage and a probe stage. Participants are given learning trials until they can correctly find the object in 11 out of 12 presentations of arms. Once they reach the learning criterion, they are taken to the probe stage, in which the pairs of arms are recombined into new pairs of adjacent arms. Top panel, left: Example of a pair presentation in the learning stage. Arms #3 and #4 are presented together. A spatial strategy user learns the exact spatial relationship between a landmark and the object, e.g. “the object is a little to the right of the pyramid”. A response strategy user learns a response associated with a landmark, e.g. “when I see the pyramid, I have to go on the left pathway”. Top panel, right: Diagram of the 12-arm maze, showing all pairs of arms presented in the learning stage. Bottom panel, left: Example of a pair presentation in the probe stage. Arms #2 and #3 are presented together. A spatial strategy user performs well here because they learned the precise relationship between the landmark and the object, which allows them to choose the correct pathway, in this case the left pathway. A response strategy user performs poorly because the learned response will take them to the wrong pathway. As they see the pyramid, they take the left pathway. Bottom panel, right: Diagram of the 12-arm maze, showing all pairs of arms presented in the probe stage. Only four pairs of adjacent arms can be presented to avoid pairs in which both pathways contain an object or both pathways are empty.

interleaved in between the experimental trials. The task was exactly the same as in the experiment trials, except that participants could not learn the object locations. The control trials involve the same radial maze but this time it is surrounded by a homogeneous background that does not contain any landmarks. There is an object in each pair of pathways presented, but the location of the object is randomized, and participants are asked to choose a pathway at random. Thus, it is impossible to learn the location of the objects. Participants are told before the task that there is nothing to learn and that the objects are placed randomly in one pathway or the other. Furthermore, in order to prevent participants from attempting to learn the object locations, or to prevent them from mentally rehearsing what they learned during the experimental trials, they were asked to perform a backwards counting task, whereby they had to count backwards by 3 from 1000. We asked participants to count backwards during the control trials but not during the experimental trials. The backwards counting task was found to be an instrumental component of the control condition (Etchamendy et al., 2012).

2.3. Magnetic resonance imaging

The scanning session was comprised of 10-min scans, in which participants were given experimental and control trials in an alternated fashion. Because participants differed in the number of trials needed to reach the learning criterion, the number of scans varied from person to person.

Moreover, we used in-house software to record scanner frame times as well as keystrokes made by the experimenter. This allowed us to mark the beginning and end of each trial. For the fMRI analysis, we selected the frame times that corresponded to experimental and visuo-motor control trials.

We scanned participants at the Montreal Neurological Institute (MNI), using a 1.5 T Siemens Sonata scanner. Participants' heads were immobilized with an air cushion. A mirror was placed above

the head coil to allow participants to see a screen on which the CSDLT was projected. The session started with a two-minute localizer scan, followed by a 15-min anatomical scan. We used a three-dimensional gradient echo acquisition to collect 160 contiguous 1 mm T1-weighted images in the sagittal plane. We then acquired whole brain blood oxygen level-dependent (BOLD) signal images with 32 contiguous 4 mm axial slices parallel to the hippocampus (TR = 3000 ms; TE = 50 ms; field of view = 256 mm²; matrix size = 64 × 64; 300 whole brain scans/run). The preprocessing steps involved motion correction, normalization, bias field correction, segmentation, and smoothing and were performed using software developed at the MNI (MINC tools: <http://www.bic.mni.mcgill.ca/ServicesSoftware/HomePage>). We normalized the scans into MNI space (MNI 305; Collins, Neelin, Peters, & Evans, 1994; Evans et al., 1993), therefore all coordinates will be presented in MNI space. The BOLD images were smoothed using a 6 mm Gaussian Kernel.

2.4. Analyses

2.4.1. Analysis of behavioural data

We conducted one *t*-test to determine whether spatial and response strategy users differed in terms of the number of trials taken to reach the learning criterion on the CSDLT.

2.4.2. Analysis of fMRI data

To analyze the fMRI data, we used the FMRISTAT software package (Worsley et al., 2002). We generated individual and group-averaged *t*-statistical maps by contrasting experimental and control trials. We used an uncorrected *p* value of 0.001 for voxels lying within our a priori regions of interest, namely the hippocampus, caudate nucleus, and specific prefrontal regions such as the VMPFC, which includes the orbitofrontal cortex and ventral anterior cingulate cortex, and the DMPFC, which includes the dorsal anterior cingulate cortex as well as more dorsal regions. The *t*

values required to meet these significance thresholds were calculated using the number of participants. Because one participant's run was lost, we had an unequal number of participants for the different trials, i.e. $N = 22$ for the analyses taking into consideration the first three trials of the CSDLT and $N = 23$ for all other analyses. The t values are thus: $t = 3.53$ for $N = 22$ and $t = 3.51$ for $N = 23$. We also performed analyses that centred on the strategy groups separately, looking at activity in experimental vs. control trials. The t values for these contrasts are $t = 3.73$ for the response strategy group ($n = 17$) and $t = 5.89$ for the spatial strategy group ($n = 6$).

In previous studies (Etchamendy et al., 2012; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003), we found hippocampal BOLD activity early in learning while caudate nucleus activity was found later in learning. This late caudate nucleus activity is in line with the slow learning curve observed in rodents who use response strategies (Packard & McGaugh, 1996). Thus, in the current study we examined the following: the first three experimental trials taken together, the last two trials of the learning phase, as well as all learning trials averaged together. We looked at the BOLD activity in those who used a spatial strategy and those who used a response strategy separately and also made direct contrasts between the two strategy groups. We also correlated whole brain BOLD activity with probe performance. Finally, to examine functional connectivity we correlated the peak BOLD activity in the hippocampus with the BOLD activity in the whole brain.

2.4.3. Voxel-based morphometry

We used VBM to investigate the grey matter density differences between spatial and response strategy users. After normalization, shading artefacts in the anatomical scans were corrected using the N3 software package (Sled, Zijdenbos, & Evans, 1998). Each voxel was automatically labelled as white matter, grey matter, cerebrospinal fluid, or background using Intensity Normalized Stereotaxic Environment for the Classification of Tissues (INSECT; Zijdenbos, Forghani, & Evans, 2002). The skull and dura were masked from the brain. Grey matter was smoothed using an 8 mm full-width at half-maximum (FWHM) Gaussian kernel. We used general linear modelling to regress performance on the CSDLT against grey matter density in our regions of interest (Worsley et al., 2002). We also regressed the peak BOLD activity in the hippocampus against grey matter density in the whole brain in order to determine whether certain cortical areas co-vary with activity in the hippocampus during the task. The statistical maps were overlaid on the average of participants' anatomical scans. The same p and t values were used as in the fMRI analysis section for $N = 23$.

3. Results

3.1. Behavioural

Six participants scored 7/8 or above on the probe stage of the CSDLT and were categorized into the spatial strategy group. The remaining 17 participants, who scored below the cut-off of 7/8, were categorized into the response strategy group. The two strategy groups did not significantly differ in the number of trials required to reach the learning criterion ($t(21) = 1.54$, $p > 0.05$). Thus, the two groups learned at the same rate, which indicates that the task can be learned just as efficiently whether one uses a spatial or a response strategy. Participants performed above chance from the second trial on (average score on second trial: 4/6), indicating that they were indeed learning the task and not choosing the paths at random.

3.2. fMRI

We took three separate approaches to investigate the regions of the frontal cortex involved in spatial learning in the current task.

We (a) looked at brain regions active in the spatial strategy group, as defined by those who scored 7/8 or above on the probe stage of the CSDLT, (b) correlated BOLD activity and grey matter density with probe scores, knowing that the higher the scores, the more spatial learning is taking place, and (c) made correlations with BOLD activity in the hippocampus, as it is established that hippocampal activity occurs during spatial learning. The opposite was done for response learning.

First, we analysed brain activity early in learning by averaging the fMRI data collected in the first three trials. We contrasted spatial against response strategy users (spatial (experimental – control) > response (experimental – control)). As expected, those who used a spatial strategy exhibited greater BOLD activity in the right hippocampus compared to those who used a response strategy ($x = 40.1$, $y = -20.0$, $z = -18.0$; $t = 3.76$, $p < 0.001$; Fig. 2A). Spatial strategy users also showed greater BOLD activity in the right orbitofrontal cortex compared to response strategy users ($x = 20.2$, $y = 42.0$, $z = -17.9$; $t = 3.83$, $p < 0.0005$; Fig. 2B).

When looking at strategy groups separately (experimental > control), response strategy users showed greater BOLD activity in the left DMPCF at the beginning of learning in the first three experimental trials compared to the control trials ($x = -1.9$, $y = 34.0$, $z = 44.1$; $t = 4.36$, $p < 0.0005$; Fig. 3). In the spatial group, there was greater BOLD activity in the right hippocampus ($x = 23.1$, $y = -8.0$, $z = -26.0$, $t = 3.52$) in the first trial compared to the control trials and greater BOLD activity in the right orbitofrontal cortex activity ($x = 20.2$, $y = 42.0$, $z = -18.1$, $t = 3.85$) in the first three trials compared to the control trials, however these peaks did not reach the threshold for significance.

In order to investigate whether the pattern of brain activity during early acquisition of the task has an impact on navigation

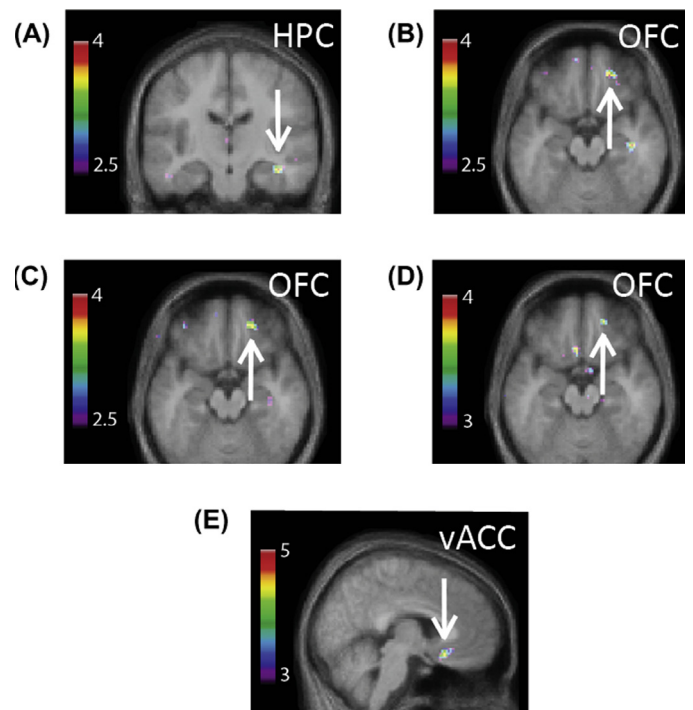


Fig. 2. Spatial learning is associated with activity in the hippocampus and orbitofrontal cortex. (A) Spatial > response contrast: spatial strategy users show more activity in the right hippocampus than response strategy users in the first three learning trials, as well as (B) more activity in the right orbitofrontal cortex (OFC). (C) There is a positive correlation between probe scores and right orbitofrontal cortex activity in the first three learning trials, indicating that spatial learning is associated with right orbitofrontal cortex activity. (D) There is a positive correlation between the peak in hippocampal activity and activity in the orbitofrontal cortex and in (E) the ventral anterior cingulate cortex (vACC).

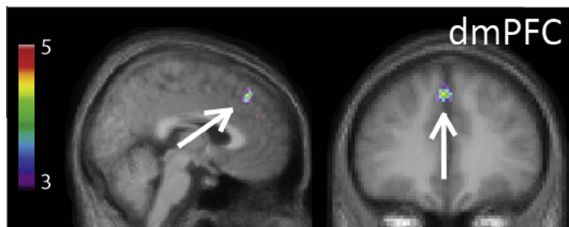


Fig. 3. Response learning is associated with activity in the dorsomedial prefrontal cortex. Experimental > control trials contrast in the response group: response strategy users show more activity in the dorsomedial prefrontal cortex (DMPFC) in the experimental vs. control conditions.

strategies, we correlated BOLD activity measured in the first three trials with probe stage scores. In other words, this analysis allows us to investigate whether the extent of spatial or response strategy use, as determined by probe performance, relates to certain patterns of activity during acquisition. We found a positive correlation between BOLD activity in the right orbitofrontal cortex and probe scores ($x = 20.2, y = 44.0, z = -18.1; t = 3.68, p < 0.001$; Fig. 2C). A higher probe score reflects greater spatial learning, thus spatial learning is associated with right orbitofrontal cortex BOLD activity early in learning. There were no significant negative correlations ($p > 0.001$). When we correlated whole-brain BOLD activity with the peak BOLD activity in the hippocampus, we found significant BOLD activity in the right orbitofrontal cortex ($x = 20.0, y = 44.0, z = -18.0; t = 3.76, p < 0.001$; Fig. 2D) and the left ventral anterior cingulate cortex ($x = -3.9, y = 20.0, z = -14.2; t = 4.34, p < 0.0005$; Fig. 2E) in the first experimental trial. In other words, increased BOLD activity in the hippocampus was associated with increased BOLD activity in the orbitofrontal cortex and the ventral anterior cingulate cortex early in learning.

Finally, we looked at brain activity late in learning, i.e. in the last two trials of the learning stage. We did not find any significant BOLD activity in our regions of interest when response strategy users were contrasted against spatial strategy users, nor did we find any significant correlations with probe scores or with whole brain BOLD activity. The fact that we did not observe caudate nucleus BOLD activity at the end of learning can be explained by the lack of overtraining (Iaria et al., 2003).

3.3. VBM

We regressed probe stage scores against whole brain grey matter density and found a negative correlation in the left DMPFC ($x = -2.2, y = 29.0, z = 38.1; t = -4.07, p < 0.0005$; Fig. 4A) and in the left dorsal anterior cingulate cortex ($x = 0, y = 43.0, z = 19.5; t = -3.72, p < 0.001$; Fig. 4B), which indicates that those who performed worse on the probe stage, i.e. response strategy users, had more grey matter density in the DMPFC, which includes the dorsal anterior cingulate area. There were no significant positive correlations between probe stage scores and whole brain grey matter density ($p > 0.001$). Interestingly, when we regressed the peak

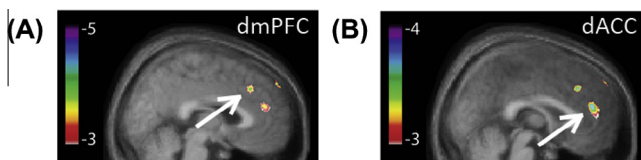


Fig. 4. Response learning is associated with increased grey matter in the dorsomedial prefrontal cortex and dorsal anterior cingulate cortex. There is a negative correlation between probe scores and grey matter in (A) the dorsomedial prefrontal cortex (DMPFC) and (B) the dorsal anterior cingulate cortex (dACC). These results suggest that grey matter in the DMPFC and dACC is associated with response learning, as low probe scores are indicative of response learning.

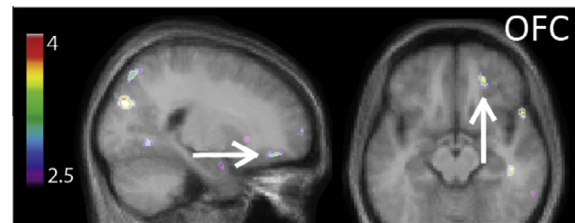


Fig. 5. Spatial learning is associated with increased grey matter in the orbitofrontal cortex. There is a positive correlation between the peak in hippocampal activity and grey matter in the orbitofrontal cortex (OFC). These results suggest that orbitofrontal cortex activity is associated with spatial learning, as spatial learning is characterized by hippocampal activity.

BOLD activity in the right hippocampus against whole brain grey matter density, we found a positive correlation in the right orbitofrontal cortex ($x = 22.1, y = 42.0, z = -14.9; t = 3.70, p < 0.001$; Fig. 5); this suggests that the more BOLD activity in the hippocampus, the more grey matter in the orbitofrontal cortex. The direct contrast between spatial and response strategy users did not yield any significant differences in the prefrontal cortex.

4. Discussion

The aim of the current study was to investigate the prefrontal neural correlates of navigation strategies. To this end, we used a virtual navigation task that could be solved using either a spatial or a response strategy. Young adults performed the CSDLT task while undergoing fMRI scanning. We then identified the prefrontal areas that were engaged during learning. Our results indicate that the VMPFC, which includes the orbitofrontal cortex, is associated with spatial learning, while the DMPFC is associated with response learning. Thus, there appears to be a double dissociation with regards to the involvement of the VMPFC and DMPFC in navigation strategies.

4.1. Spatial learning is associated with greater BOLD activity in the hippocampus and orbitofrontal cortex early in learning and greater orbitofrontal cortex grey matter density

Early in learning, spatial strategy users show significantly more BOLD activity in the hippocampus and orbitofrontal cortex than response strategy users. Performance on the probe, which assesses the extent of spatial strategy use, positively correlated with orbitofrontal cortex BOLD activity early in learning. These results suggest that orbitofrontal cortex activity is associated with spatial learning. Moreover, while spatial and response strategy users did not show any morphological differences in grey matter density when directly contrasted, individuals who had greater hippocampal BOLD activity early in learning also had greater orbitofrontal cortex grey matter density. This is in accordance with one of our previous findings that spatial strategy users have greater grey matter density in the orbitofrontal cortex than response strategy users (Bohbot, Lerch, Thorndyraft, Iaria, & Zijdenbos, 2007). Together, these results suggest that there is a functional coupling between the orbitofrontal cortex and the hippocampus early in spatial learning.

4.2. Response learning is associated with greater BOLD activity in the dorsomedial prefrontal cortex early in learning and greater dorsomedial prefrontal cortex grey matter density

Response strategy users show significantly more BOLD activity in the DMPFC during the learning trials than during the control trials. In terms of grey matter density, there was a negative correlation between probe scores and grey matter density in the DMPFC.

These findings indicate that the more response learning takes place, the more activity and grey matter density there is in the DMPFC. Thus, response learning engages the DMPFC.

4.3. Double dissociation of the ventromedial and dorsomedial prefrontal cortex in navigation strategies

Results from the rodent literature have shown that damage to the prefrontal cortex has an impact on spatial learning and memory (Kolb, Buhrmann, McDonald, & Sutherland, 1994; Kolb, Pittman, Sutherland, & Whishaw, 1982; Mogensen et al., 2004). Specifically, damaging or otherwise impairing the rodent VMPFC, which includes the prelimbic and infralimbic cortices as well as the medial orbitofrontal cortex, generally has a negative impact on spatial learning and memory (Delatour & Gisquet-Verrier, 2000; Fantie & Kolb, 1990; Floresco et al., 1997; Kesner & Ragozzino, 2003; Kolb, Sutherland, & Whishaw, 1983; Lee & Solivan, 2008; Seamans et al., 1995; Vafaei & Rashidy-Pour, 2004; Wang & Cai, 2008). To study spatial learning, a number of studies have used the spatial version of the Morris Water Maze, the delayed spatial win-shift task, or similar paradigms that require the hippocampus to solve the task. They found that VMPFC lesions (Delatour & Gisquet-Verrier, 2000; Fantie & Kolb, 1990) or reversible inactivation (Seamans et al., 1995; Vafaei & Rashidy-Pour, 2004; Wang & Cai, 2008) disrupted spatial learning and memory. Other studies disrupted the connection between the hippocampus and the VMPFC (Floresco et al., 1997; Wang & Cai, 2008) and found similar impairments. Delatour and Gisquet-Verrier (2000) showed that VMPFC lesions resulted in deficits that were selective to spatial learning, leaving response learning intact. They tested VMPFC-lesioned rats on a dry version of the Morris Water Maze. In one version of the task, the animal always started out from the same starting position, thus a response strategy could be used. In another version of the task, the animal started out at four different positions on the platform and therefore a spatial strategy was necessary to successfully find the reward. Results showed that VMPFC-lesioned rats were not impaired compared to controls in the task that had a single start position, a task which could be solved using a response strategy. Instead, they were impaired in the multiple start position task, which requires spatial learning in order to successfully solve the task. Using a response strategy would preserve performance on the single start position task because rodents are able to learn and use a specific sequence of motor responses from a single starting point to reach the target location. On the other hand, because the multiple start position task requires flexibility and could not be solved using a response strategy, the lesioned rats showed learning deficits. This particular study therefore shows a functional dissociation of the VMPFC in spatial and response learning. Another study (Kesner & Ragozzino, 2003) found VMPFC lesions to impair performance in an object-place learning task. In this task, an object (stimulus) is associated with a reward in one location, but in another location, the same object is not associated with a reward. DMPFC lesions did not lead to deficits on this task, indicating a functional dissociation of the VMPFC and DMPFC in object-place learning.

The involvement of the VMPFC in spatial learning is consistent with the functional and anatomical connections between the VMPFC and the hippocampus. Electrophysiological studies (Siapas, Lubenov, & Wilson, 2005; Young & Shapiro, 2011) show that neurons in the orbitofrontal cortex and hippocampus present coherent or phase-locked oscillations in the theta band, suggesting an exchange of information (Buzsáki & Chrobak, 1995; Buzsáki & Draguhn, 2004). Moreover, the orbitofrontal cortex is anatomically connected with the hippocampus (Barbas & Blatt, 1995; Cateño et al., 2005; Cavada, Company, Tejedor, Cruz-Rizzolo, & Reinosuarez, 2000; Roberts et al., 2007) and with other regions known

to play a role in navigation, such as the entorhinal, perirhinal, parahippocampal, and retrosplenial cortices (Barbas, 1993; Barbas & Blatt, 1995; Carmichael & Price, 1995a; Cavada et al., 2000; Kondo, Saleem, & Price, 2005; Morecraft, Geula, & Mesulam, 1992; Roberts et al., 2007). Overall, our results are in line with these findings, as we found that the orbitofrontal and ventral anterior cingulate cortices are associated with spatial learning and hippocampal BOLD activity. We hypothesize that patients with damage to these areas would show spatial learning impairments, as is seen in rodents.

The prefrontal cortex's role in response learning has received less attention (Mogensen, Moustgaard, Khan, Wortwein, & Nielsen, 2005; Packard & Knowlton, 2002). The few studies that have investigated it found that lesioning the DMPFC, which includes the dorsal anterior cingulate cortex and Frontal area 2, negatively impacts response learning (de Bruin et al., 1997, 2001). Using a response version of the Morris Water Maze, de Bruin et al. (1997) found that rats with damage predominantly to the DMPFC persisted in trying to solve the task using a spatial strategy. Once they switched to a response strategy, their learning was impaired (de Bruin et al., 1997, 2001). In their 2001 study, de Bruin and colleagues also tested rats with damage to the fimbria/fornix, which functionally disconnects the hippocampus as it removes its afferent and efferent connections. A double dissociation emerged: rats with fimbria/fornix lesions were impaired on the spatial version of the task and performed comparably to sham-operated rats in the response version of the task, while the opposite pattern of results was found for rats with DMPFC damage.

In humans, Woolley et al. (2013) found that engaging in a virtual spatial version of the Morris Water Maze produced BOLD activity in the caudate nucleus and DMPFC in early learning compared to a control condition. Although studies have shown that certain regions of the caudate nucleus seem to be congruent with the function of the hippocampus (Devan, McDonald, & White, 1999; Devan & White, 1999), the exact contribution of this region is not yet clear. However, Woolley et al. (2013) argue that the caudate nucleus and DMPFC BOLD activity probably reflected nonspatial processes (Woolley et al., 2013). For example, participants could have been circling the pool or using cardinal directions or other nonspatial cues at the beginning of learning. This is supported by de Bruin et al. (1997)'s earlier observation that rats, before adopting a spatial strategy in the Morris Water Maze, started off circling the pool or using a nonspecific strategy. Woolley et al. (2013) also had a resting state fMRI component to their study and they found that there is functional connectivity between the DMPFC and the caudate nucleus, which further supports the notion that the DMPFC is part of the response neural network together with the caudate nucleus. Our findings are in accordance with these previous studies, as we found greater DMPFC activity and grey matter to be associated with response learning.

The evidence above strongly suggests that there is a double dissociation of the VMPFC and DMPFC in spatial and response learning. While an impaired VMPFC consistently results in spatial learning deficits, response learning does not seem to be affected by similar damage. The DMPFC evidence presents the opposite pattern of results: damage or inactivation of this region causes response learning deficits, while spatial learning remains largely unimpaired.

4.4. The role of the ventromedial and dorsomedial prefrontal cortices in navigation

The specific contributions of the VMPFC and DMPFC to spatial and response learning remain to be elucidated. For instance, it is possible that the function of these areas is to initiate navigation strategies which are mediated by the hippocampus and caudate

nucleus. The current study design was aimed to dissociate navigation strategies after learning, a design that does not allow the investigation of temporal dynamics between the frontal cortex and the hippocampus and caudate nucleus. However, we may speculate as to the interactions between these brain areas. It may be that the orbitofrontal cortex activity preceded hippocampal activity, which would support the idea that this region initiates spatial learning. In the case of response learning, we found DMPFC BOLD activity at the beginning of learning. Therefore, our data suggest that activity in the frontal cortex may precede activity in the caudate nucleus, which is typically seen later in learning (Iaria et al., 2003). We know that in both rodents and humans, some individuals use a response strategy from the start while others start out with a spatial strategy and shift to a habit-based response strategy with practice (Iaria et al., 2003; McDonald & White, 1994; Packard & McGaugh, 1996). What, then, are the temporal dynamics between the prefrontal cortex regions associated with the two navigation strategies and the hippocampus and caudate nucleus? Insights can be gained from the motor learning literature. In Albouy's comprehensive review of the involvement of and interaction between the hippocampus, striatum, and prefrontal cortex in motor learning (Albouy, King, Maquet, & Doyon, 2013), it is proposed that the hippocampus and prefrontal cortex work together in early learning to promote hippocampus-dependent strategies. It is also proposed that the prefrontal cortex suppresses striatal activity and that striatal activity increases as prefrontal cortex activity decreases, as habitual learning takes place (Albouy, King et al., 2013; Albouy et al., 2013; Destrebecqz et al., 2005; Narayanan & Laubach, 2006). If the interaction between these memory systems and the prefrontal cortex is similar in navigation, then it is possible that the VMPFC and hippocampus are recruited early on in spatial learning and that striatal suppression is exercised through the functional connectivity between the DMPFC and caudate nucleus. Although we do not know whether the DMPFC's functional connectivity to the caudate nucleus is excitatory or inhibitory, we hypothesize that if it is indeed inhibitory, then activity in the response learning network would rise as activity in the spatial learning network and DMPFC decreases. This change in the pattern of activity would coincide with an increase in response learning. This hypothesis fits with Chang and Gold's (2003) findings on acetylcholine and memory systems. They found that acetylcholine levels rise in both the hippocampus and striatum in rats being trained on a cross maze. The increase occurs both earlier and more rapidly in the hippocampus, reaching a peak early on, in parallel with a slower and gradual increase in the striatum which reaches its peak much later in training. The early and sharp increase in hippocampal acetylcholine coincides with spatial strategy use, while the slow and gradual increase in striatal acetylcholine coincides with a shift towards response strategies (Chang & Gold, 2003). In summary, we hypothesize that the spatial learning network is active early on and suppresses activity in the response learning network. With practice, this spatial network activity would decrease and activity in the response learning network would concurrently increase as habitual response learning occurs. This hypothesis remains speculative, however future studies focusing on the functional connectivity of these areas with the hippocampus and caudate nucleus will shed light on this issue.

In the last decade, many lines of research have established that the prefrontal cortex has a role in reward-, or reinforcement-, guided decision-making. Thus, there is a possibility that the VMPFC and DMPFC differentially encode rewards in the context of navigation. In this case, finding a target while navigating in an environment would act as an intrinsic reinforcement or reward. Different groups have proposed that the VMPFC encodes stimulus-reward associations, while the DMPFC encodes action-reward associations (Camille, Tsuchida, & Fellows, 2011; Fellows, 2007;

Hadland, Rushworth, Gaffan, & Passingham, 2003; Holroyd & Coles, 2002; Izquierdo, Suda, & Murray, 2004; Kennerley, Dahmubed, Lara, & Wallis, 2009; Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; Matsumoto, Suzuki, & Tanaka, 2003; Ostlund & Balleine, 2007; Padoa-Schioppa & Assad, 2006; Procyk, Tanaka, & Joseph, 2000; Rolls, 2005, 2008; Rudebeck et al., 2008; Rushworth, Noonan, Boorman, Walton, & Behrens, 2011; Schoenbaum & Roesch, 2005; Shima & Tanji, 1998; Wallis, 2007; Walton, Devlin, & Rushworth, 2004; Zald & Andreotti, 2010). Thus, when one uses a spatial strategy, it is possible that the VMPFC and hippocampus encode different but complementary information: the VMPFC may encode stimulus-reward associations while the hippocampus encodes stimulus-stimulus associations. Similarly, when one uses a response strategy, it is possible that the DMPFC is encoding response-reward associations while the caudate nucleus encodes stimulus-response associations.

The VMPFC's proposed role in making stimulus-reward associations is supported by the fact that rodents and monkeys with damage in the VMPFC, more specifically in the orbitofrontal cortex, have trouble remapping reward to stimuli, as shown by their deficits in reversal learning (see Young & Shapiro, 2011 for a review). This proposed role is also consistent with the finding that there are place-selective neurons in the rodent VMPFC that fire when the rat is in specific locations and expects a reward (Pratt & Mizumori, 2001; Young & Shapiro, 2011), which would facilitate making associations between stimuli, rewards, and places. This differential reward encoding hypothesis is further supported by anatomy: the VMPFC receives connections from all sensory areas (Barbas, 2000; Carmichael & Price, 1995b; Cavada et al., 2000; Mackey & Petrides, 2010; Romanski, Bates, & Goldman-Rakic, 1999) and integrates multimodal information (Critchley & Rolls, 1996; Lipton, Alvarez, & Eichenbaum, 1999; Schoenbaum & Eichenbaum, 1995), while the DMPFC is predominantly connected to motor areas (Beckmann, Johansen-Berg, & Rushworth, 2009; Carmichael & Price, 1995a; Lu, Preston, & Strick, 1994). A diffusion tensor imaging study (Beckmann et al., 2009) additionally showed that the VMPFC is more likely to be connected to the hippocampus while the DMPFC is more likely to be connected to the caudate nucleus.

If the DMPFC does indeed support action-reward associations, then it would explain why we do not see caudate nucleus activity early in response learning, as in Iaria et al. (2003), Etchamendy et al. (2012), and in the current study. The DMPFC may be responsible for early response learning in making these associations, while these associations become independent of the DMPFC with practice, once a habit is formed and the caudate nucleus takes over.

5. Conclusion

To this day, it is unknown which factors determine behavioural outcome in a dual-solution task where either a spatial or response strategy can be used. The current paper is the first one that examines the involvement of the frontal cortex in a dual-solution navigation task in humans. We showed that spatial learning is associated with increased BOLD activity in the VMPFC, while response learning is associated with increased BOLD activity in the DMPFC. As such, we propose that, in humans, the VMPFC, and the orbitofrontal cortex in particular, is part of the spatial learning neural network that critically depends on the hippocampus, and that the DMPFC is part of the response learning neural network that critically relies on the caudate nucleus. Their exact contribution to human navigation, however, remains to be determined.

Interestingly, grey matter density in the orbitofrontal cortex increased with hippocampal engagement, and grey matter density in the DMPFC increased with response learning. Using hippocampus-based spatial strategies may lead to structural

changes in the orbitofrontal cortex, while using caudate nucleus-based response strategies may lead to structural changes in the DMPFC, resulting in greater grey matter density in these regions. On the other hand, the reverse is also possible, whereby increased grey matter density in the frontal cortex predisposes individuals to a specific navigation strategy. Supporting the former hypothesis, a study from our laboratory showed that spatial memory training leads to increased grey matter in the hippocampus and orbitofrontal cortex (Konishi et al., 2011). Alternatively, data in support of the second hypothesis show that certain genotypes predict hippocampal grey matter density more strongly than navigation strategies, suggesting that genotype has an influence on brain regions which in turn influence navigation strategies (Bhat et al., Submitted for publication). In sum, there is evidence supporting the hypothesis that navigation experience promotes grey matter in the frontal cortex as well as the alternative hypothesis whereby grey matter in the frontal cortex predicts navigation strategies.

Our results provide a basis for the study of the brain networks involved in human navigation. This approach further supports the broader view of functional integration. Indeed, most brain functions do not rely on single brain structures but rather on networks of areas that work together to produce behaviour and cognition.

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