



# Fimbria-Fornix Volume Is Associated With Spatial Memory and Olfactory Identification in Humans

Louisa Dahmani<sup>1</sup>, Blandine Courcot<sup>2</sup>, Jamie Near<sup>2</sup>, Raihaan Patel<sup>2</sup>, Robert S. C. Amaral<sup>2</sup>, M. Mallar Chakravarty<sup>2</sup> and Véronique D. Bohbot<sup>3\*</sup>

<sup>1</sup>Integrated Program in Neuroscience, McGill University, Montreal, QC, Canada, <sup>2</sup>Douglas Brain Imaging Center, Department of Psychiatry, McGill University, Montreal, QC, Canada, <sup>3</sup>Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, QC, Canada

White matter pathways that surround the hippocampus comprise its afferent and efferent connections, and are therefore crucial in mediating the function of the hippocampus. We recently demonstrated a role for the hippocampus in both spatial memory and olfactory identification in humans. In the current study, we focused our attention on the fimbria-fornix white matter bundle and investigated its relationship with spatial memory and olfactory identification. We administered a virtual navigation task and an olfactory identification task to 55 young healthy adults and measured the volume of the fimbria-fornix. We found that the volume of the right fimbria-fornix and its subdivisions is correlated with both navigational learning and olfactory identification in those who use hippocampus-based spatial memory strategies, and not in those who use caudate nucleus-based navigation strategies. These results are consistent with our recent finding that spatial memory and olfaction rely on similar neural networks and structures.

**Keywords:** spatial memory, navigation, hippocampus, fimbria-fornix, white matter, olfaction

## INTRODUCTION

Many people have experienced instances where a smell spontaneously brought back a vivid memory. Therefore, it would not come as a surprise that olfaction could be closely associated with hippocampal-dependent memory, characterized by its vividness and richness in detail (Moscovitch et al., 2005). Olfaction is a vital navigation tool for many species. Many animals use olfactory cues and gradients to locate prey or pups, identify territory, or to go back to previously visited places. Although not crucial for survival, humans are also capable of finding a target location using olfactory cues (Jacobs et al., 2015).

Over the years, numerous studies have investigated spatial memory and its neural correlates. Animal and human studies have found the hippocampus to play a critical role in both spatial memory (O'Keefe and Nadel, 1978; Packard et al., 1989; McDonald and White, 1993; Pigott and Milner, 1993; Maguire et al., 1998; Bohbot et al., 2002, 2004; Hartley et al., 2003; Iaria et al., 2003; Head and Isom, 2010) and olfaction (see Suzuki et al., 2001; Lundström et al., 2011 for reviews; Kjolvik et al., 2012; Wu et al., 2012).

Up until recently, the relationship between spatial memory and olfaction had not been directly investigated. In 2018, we demonstrated the existence of an intrinsic relationship between the two processes (Dahmani et al., 2018). However, this relationship is specific to certain types of navigation but not others. There are two distinct memory systems that can be used for navigation.

## OPEN ACCESS

### Edited by:

James Ainge,  
University of St Andrews,  
United Kingdom

### Reviewed by:

Benjamin J. Clark,  
University of New Mexico,  
United States  
Ehren Lee Newman,  
Indiana University Bloomington,  
United States

### \*Correspondence:

Véronique D. Bohbot  
veronique.bohbot@mcgill.ca

**Received:** 17 October 2019

**Accepted:** 23 December 2019

**Published:** 14 January 2020

### Citation:

Dahmani L, Courcot B, Near J, Patel R, Amaral RSC, Chakravarty MM and Bohbot VD (2020) Fimbria-Fornix Volume Is Associated With Spatial Memory and Olfactory Identification in Humans. *Front. Syst. Neurosci.* 13:87. doi: 10.3389/fnsys.2019.00087

One of these is the hippocampal memory system, which is critical for the spatial memory strategy. This strategy involves learning precise spatial relationships between landmarks in the environment, so as to form a cognitive map, or mental representation, of one's environment (O'Keefe and Nadel, 1978). The other memory system involves the caudate nucleus, which is critical for the stimulus-response strategy. This strategy involves learning a set of stimulus-response associations, e.g., a series of motor actions in response to a stimulus (Packard et al., 1989; McDonald and White, 1993). An example of this is route learning, where one must learn to turn left or right in response to various stimuli (e.g., turn left at the gas station). The stimulus-response strategy mainly relies on the caudate nucleus/dorsal striatum (Packard et al., 1989; McDonald and White, 1993; White and McDonald, 2002; Hartley et al., 2003; Iaria et al., 2003; Bohbot et al., 2007; Head and Isom, 2010; Konishi et al., 2013). Importantly, studies from our laboratory showed that gray matter in the hippocampus and caudate nucleus correlates with the respective use of spatial memory and stimulus-response strategies in dual-solution tasks (Iaria et al., 2003; Bohbot and Corkin, 2007; Etchamendy et al., 2012; Konishi and Bohbot, 2013; Konishi et al., 2013; Dahmani and Bohbot, 2015; Dahmani et al., 2018). Using these paradigms to identify individuals' spontaneous navigation strategies, we showed in a recent report that olfactory identification is associated with faster learning in participants who spontaneously used a spatial memory strategy (spatial learners), but not in those who used a stimulus-response strategy (response learners; Dahmani et al., 2018). This finding was consistent with our hypothesis that olfactory identification would be related to hippocampal-dependent navigation only. In the same study, we measured hippocampal gray matter volume and found it to be positively associated with both olfactory identification and spatial learning, but not with stimulus-response learning.

In the current article, we turn our attention to white matter. In rodents, many lesion studies have found the fimbria-fornix to be of crucial importance in spatial memory (Olton and Samuelson, 1976; Olton and Papas, 1979; Packard et al., 1989; McDonald and White, 1993, 1995; de Bruin et al., 2001), as it connects the hippocampus to most of its output regions. In contrast, fimbria-fornix lesions do not impair stimulus-response learning (Packard et al., 1989; McDonald and White, 1993; de Bruin et al., 2001). In humans, Iaria et al. (2008) found that hippocampal fractional anisotropy, which is thought to be a measure of structural white matter integrity, was positively associated with spatial learning and memory. However, whether the fimbria-fornix has a dissociable role in human spatial learning and stimulus-response learning is still unknown. Additionally, diffusion magnetic resonance imaging (MRI) measures, including fractional anisotropy, are still under debate, as their association with underlying white matter structure is not clear (Jones et al., 2013; Scholz et al., 2014). In the current study, we investigate the volume of the fimbria-fornix and use a dual-solution virtual navigation task to examine its association with spatial memory and stimulus-response learning. Similar to our previous study (Dahmani et al., 2018), we hypothesized that greater volume of the fimbria-fornix fiber system would be

positively associated with navigation and olfactory identification in spatial learners, but not response learners.

## MATERIALS AND METHODS

### Participants

We tested 60 healthy young adults between the ages of 18 and 35 (mean age =  $22.9 \pm 3.5$ ; 29 women, 31 men). This represents the same dataset as reported in Dahmani et al. (2018). Participants were excluded if they were not right-handed, if they had a history of neurological or psychiatric disorders, a history of alcohol or drug abuse, or if they suffered a head trauma followed by a loss of consciousness. Three participants did not complete the navigation task (4-on-8 Virtual Maze, described below) and two participants did not undergo MRI scanning. We, therefore, had 55 participants for the navigation and olfaction analyses. The protocol was approved by the local ethics committee of the Douglas Mental Health University Institute. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

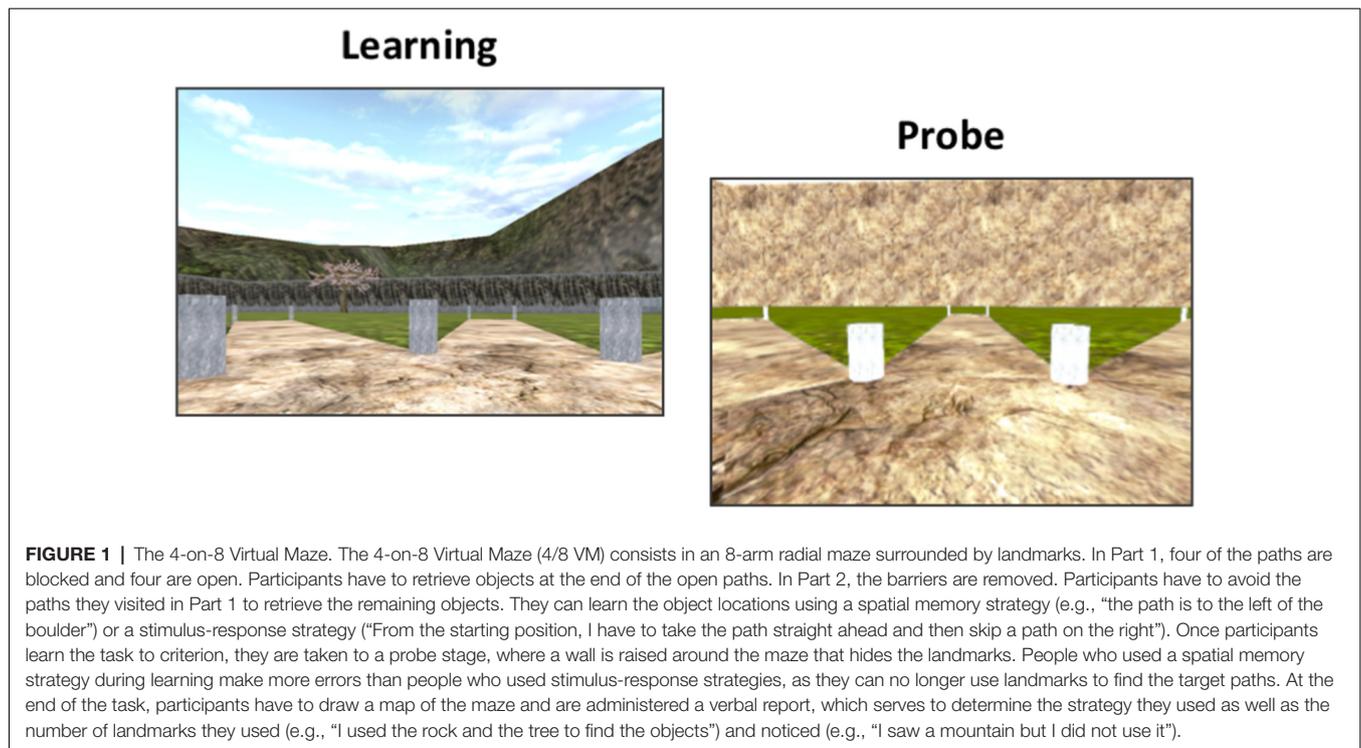
### Olfactory Identification

To assess olfactory identification, we administered the Monell Extended Sniffin' Sticks Identification Test (MONEX-40; Freiherr et al., 2012). This test consists of 40 felt-tip pens, each infused with an odor. The experimenter places each pen under the participant's nose for one to 2 s and the participant inhales the odor. For each pen, participants are asked to identify the odor from four written choices shown on a screen. The pens were developed to yield at least 35% accuracy across participants (Lundström, personal communication). Thus, in the current study, pens that yielded an overall accuracy that was lower than 35% were excluded from the analysis. Two pens were excluded (warm milk and honey) and the olfactory identification score was based on 38 items. Possible reasons for poor accuracy are degradation of the odor over time, unfamiliarity due to cultural differences, or variability in performance in specific cohorts.

### 4-on-8 Virtual Maze (4/8 VM)

The 4/8 VM (Figure 1) was developed using Unreal Tournament 2003 (Epic Games, Raleigh, NC, USA). The task was adapted from a maze task originally used in rodents (Olton and Samuelson, 1976; Packard et al., 1989) and consists in a radial maze surrounded by a rich landscape with proximal and distal landmarks. The maze is made of a central platform with eight paths branching out around it. There are two parts to each learning trial:

- Part 1: Out of the eight paths, four are blocked and four are accessible. Participants are instructed to visit the accessible paths, to retrieve objects at the end of the paths (which are not visible from the central platform), and to memorize their location. When ready, participants are taken to Part 2.
- Part 2: Here, we remove the barriers to make all the paths accessible. Participants are asked to avoid the paths they just visited in order to retrieve the remaining objects. Participants can use either a spatial memory strategy, by learning the spatial relationships between landmarks in the environment and the



target paths (e.g., “there is an object to the left of the tree and one to the right of the boulder”), or they can use a stimulus-response strategy, by learning a series of motor actions in response to a stimulus (e.g., “from the starting position, I have to go straight ahead and then skip the path on the right”).

A minimum of three and a maximum of eight learning trials are administered. The location of the objects does not change throughout the task except in the second trial. Participants are required to find the objects in Part 2 without making errors in at least one of the trials in order to reach the learning criterion. Once this is achieved, we administer a probe trial. Part 1 of the probe trial is the same as above. In Part 2, a wall is erected around the radial maze, blocking the landmarks from the participants’ view. Participants who used a spatial memory strategy (“spatial learners”) to memorize the object locations make more errors than participants who used a stimulus-response strategy (“response learners”), as they can no longer rely on the landmarks to find the paths containing the objects (Iaria et al., 2003). The probe trial is followed by a normal trial. Once the task is done, we conduct a verbal report, where we ask participants to describe how they solved the task. We used the verbal report to categorize participants into spatial or response learners. If participants mentioned learning the location of the pathways relative to several landmarks, they were categorized as spatial learners. If they mentioned using a counting strategy or a sequence starting from the start position of a single position demarked by one landmark, they were categorized as response learners. We previously showed that spontaneous strategies, i.e., strategies used in the very first trial, are associated with increased functional magnetic resonance imaging (fMRI)

blood oxygenation-level-dependent (BOLD) activity and gray matter in our regions of interest (Iaria et al., 2003; Bohbot et al., 2007). The verbal report is also used to determine how many landmarks participants noticed in the environment and how many landmarks they used on average throughout the learning trials.

The dependent variables are number of trials to criterion, the average number of errors on Part 2 of the learning trials (these provide two slightly different measures of navigational learning), spontaneous navigation strategy, number of landmarks noticed the average number of landmarks used during the learning phase of the task, and probe errors.

## Neuropsychological Assessment

To assess potential differences between spatial and response learners in neuropsychological status, we administered the following neuropsychological tests: the Rey Auditory Verbal Learning Task (Rey, 1941) to evaluate verbal memory, the Rey-Osterrieth Complex Figure (Meyers and Meyers, 1995) to assess visuospatial memory, and the Test of Non-verbal Intelligence-3 (Brown et al., 1997) to assess non-verbal intelligence. Spatial and response learners did not differ on these tests (all Bootstrap BCa 95% CI crossed 0).

## MRI Data Acquisition

We acquired anatomical MRI data at the Douglas Cerebral Imaging Centre, using a 3 Tesla Siemens Magnetom Trio scanner equipped with 12-channel array coil. We immobilized participants’ heads using support cushions. A localizer scan was first acquired, followed by a T1-weighted 3D MPRAGE anatomical scan with 192 contiguous 1 mm slices in the sagittal

plane (TR = 2,300 ms; TE = 2.98 ms; flip angle = 9; the field of view = 256 mm<sup>2</sup>), resulting in an acquisition time of 9:14 min.

## MRI Data Analysis

The Multiple Automatically Generated Templates (MAGeT) Brain tool was used to automatically segment extra-hippocampal white matter fiber bundles (Amaral et al., 2018; **Figure 2A**). This tool was developed to use a small set of high-quality atlases that were manually segmented as input. Participants' structural scans were processed with N4 intensity correction (Tustison et al., 2010). We then applied a head mask to ameliorate registration before running MAGeT-Brain. The Winterburn Atlas (Winterburn et al., 2013) was adapted to include the extra-hippocampal white matter bundles and is comprised of five manually-segmented brains (Amaral et al., 2018). In MAGeT-Brain, a library of 21 templates (Pipitone et al., 2014) is used to bootstrap each individual's segmentation. The templates were chosen by first segmenting all of the samples using the five manually segmented brains and then selecting the ones presenting the best registrations in order to increase registration quality for the full sample analysis. We used non-linear atlas-to-template registration to segment and label each template, which resulted in a unique delineation of the subfields for each individual template. The bootstrapping yields 105 candidate labels for each individual (5 atlases × 21 templates), which are subsequently fused through a voxel-wise majority vote to output one final segmentation (**Figure 2B**). We used the Automatic Normalization Tools (ANTS) registration technique for non-linear registration<sup>1</sup>. The extra-hippocampal white matter bundles that we inspected included the fimbria, fornix, and alveus of the hippocampus. Together, these form the fimbria-fornix white matter bundle. We visually inspected each output segmentation for quality control, which all segmentations passed.

## Analysis

We used SPSS Statistics 20 (IBM) for data analysis. We performed partial correlations between our olfaction and 4/8 VM variables and white matter volumes. Sex was used as a covariate because men have on average a larger brain than women. We used bootstrapped bias-corrected and accelerated 95% confidence intervals (Bootstrap BCa 95% CI; Field, 2009) to determine significance. Bootstrapping is a resampling method that uses a sample dataset and simulates 1,000 datasets from this set by resampling with replacement. This method is useful in that it inherently corrects for multiple comparisons (Westfall and Young, 1993; Field et al., 2012). Confidence intervals are an estimation of the population's true value, which makes them both more accurate and more robust than *p*-values (Rothman, 1978; Poole, 2001; Greenland et al., 2016), especially when bootstrapping methods are used (Westfall and Young, 1993). Resampling methods also offer the advantage of estimating Type I and Type II error rates more precisely than standard *p*-value adjustment methods (Field et al., 2012). It is, therefore, unnecessary to further correct for multiple

comparisons. Another advantage of bootstrapping methods is that they are non-parametric, and thus do not require to transform the data when it is not normally distributed (Haukoos and Lewis, 2005; Field et al., 2012). We used one-tailed confidence intervals when analyses were hypothesis-driven. We first investigated the overall right and left fimbria-fornix white matter volumes. These were determined by calculating the sum of the fimbria, fornix, and alveus of the hippocampus, for each hemisphere. If no significant correlation was found between overall fimbria-fornix volumes and our measures of interest, then we investigated the sub-regions (fimbria, fornix, and alveus of the hippocampus) separately to see if any effect existed at a smaller scale.

## RESULTS

Using participants' 4/8 VM verbal report, we categorized 23 participants as spatial learners and 32 participants as response learners. We performed two sets of analyses: we looked at the associations between: (1) navigation and white matter volumes; and (2) olfaction and white matter volumes. We hypothesized that, as with our previous behavioral and structural neuroimaging results (Dahmani et al., 2018), only spatial learners would show an association between fimbria-fornix volume, olfaction, and navigation. **Table 1** shows the correlation coefficients and bootstrap BCa 95% CI of the correlations between white matter volumes and navigation and olfaction variables for spatial and response learners, with sex as a covariate.

### Navigation

In spatial learners, we found that faster learning correlates with fimbria-fornix white matter volume: there was a significant negative correlation between right fimbria-fornix volume and average navigational learning errors [ $r = -0.40$ , Bootstrap BCa 95% CI (-0.66, -0.15; **Figure 3**, left)], and between right fimbria volume and number of trials to criterion [ $r = -0.35$ , Bootstrap BCa 95% CI (-0.57, -0.15)]. Additionally, there was a marginally significant negative correlation between left fimbria volume and average navigational learning errors [ $r = -0.31$ , Bootstrap BCa 95% CI (-0.60, 0.004)]. Average navigational learning errors did not significantly correlate with the left fimbria-fornix volume, although the correlation was in the hypothesized direction [ $r = -0.19$ , Bootstrap BCa 95% CI (-0.52, 0.10)]. Thus, faster learning in spatial learners is predominantly associated with the right fimbria-fornix.

Response learners showed no significant associations between fimbria-fornix volumes and navigational learning [all Bootstrap BCa 95% CIs crossed 0; e.g., average navigational learning errors and right fimbria-fornix volume,  $r = 0.10$ , Bootstrap BCa 95% CI (-0.26, 0.37; **Figure 3**, right)]. There were also no significant associations with sub-regions of the left or right fimbria-fornix (all Bootstrap BCa 95% CIs crossed 0).

Spatial and response learners did not show any correlations between fimbria-fornix volumes and either number of landmarks noticed/used or probe errors (all Bootstrap BCa 95% CIs crossed 0).

<sup>1</sup><https://github.com/vfonov/mincANTS>

**TABLE 1** | Partial correlations between variables of interest and white matter bundle volumes for spatial and response learners.

	Spatial learners <i>r</i> (CI)	Response learners <i>r</i> (CI)
<b>Average navigational learning errors</b>		
R fimbria-fornix	−0.40 (−0.66, −0.15)*	0.10 (−0.26, 0.37)
R fimbria	–	−0.09 (−0.42, 0.24)
R fornix	–	0.05 (−0.34, 0.41)
R alveus	–	0.23 (−0.16, 0.48)
L fimbria-fornix	−0.19 (−0.52, 0.10)	0.04 (−0.27, 0.29)
L fimbria	−0.31 (−0.60, 0.004)†	0.08 (−0.23, 0.32)
L fornix	−0.21 (−0.52, 0.08)	0.02 (−0.25, 0.25)
L alveus	0.003 (−0.40, 0.33)	0.04 (−0.32, 0.33)
<b>Number of trials to criterion</b>		
R fimbria-fornix	−0.09 (−0.42, 0.25)	0.08 (−0.19, 0.31)
R fimbria	−0.35 (−0.57, −0.15)*	−0.13 (−0.40, 0.14)
R fornix	−0.18 (−0.48, 0.14)	0.06 (−0.27, 0.31)
R alveus	0.17 (−0.15, 0.45)	0.20 (−0.16, 0.63)
L fimbria-fornix	0.05 (−0.26, 0.35)	0.01 (−0.28, 0.34)
L fimbria	−0.17 (−0.49, 0.13)	0.06 (−0.20, 0.39)
L fornix	0.06 (−0.25, 0.36)	−0.05 (−0.40, 0.31)
L alveus	0.09 (−0.16, 0.34)	0.09 (−0.19, 0.32)
<b>Olfactory identification</b>		
R fimbria-fornix	0.24 (−0.10, 0.55)	−0.12 (−0.37, 0.20)
R fimbria	0.41 (0.08, 0.68)*	0.18 (−0.13, 0.47)
R fornix	0.07 (−0.28, 0.41)	−0.24 (−0.50, 0.14)
R alveus	0.26 (−0.05, 0.69)	0.02 (−0.28, 0.31)
L fimbria-fornix	0.14 (−0.16, 0.43)	−0.03 (−0.35, 0.25)
L fimbria	0.01 (−0.37, 0.39)	0.03 (−0.28, 0.34)
L fornix	0.20 (−0.18, 0.52)	0.06 (−0.31, 0.35)
L alveus	0.01 (−0.33, 0.42)	−0.19 (−0.41, 0.05)

Correlation coefficients (*r*) are shown with bootstrap bias-corrected and accelerated 95% confidence intervals in brackets. All correlations were covaried with sex. R: Right; L: Left. \*Indicates correlations that are significant (bootstrap bias-corrected and accelerated 95% confidence intervals do not cross 0). †Denotes marginally significant correlations (confidence intervals barely cross 0).

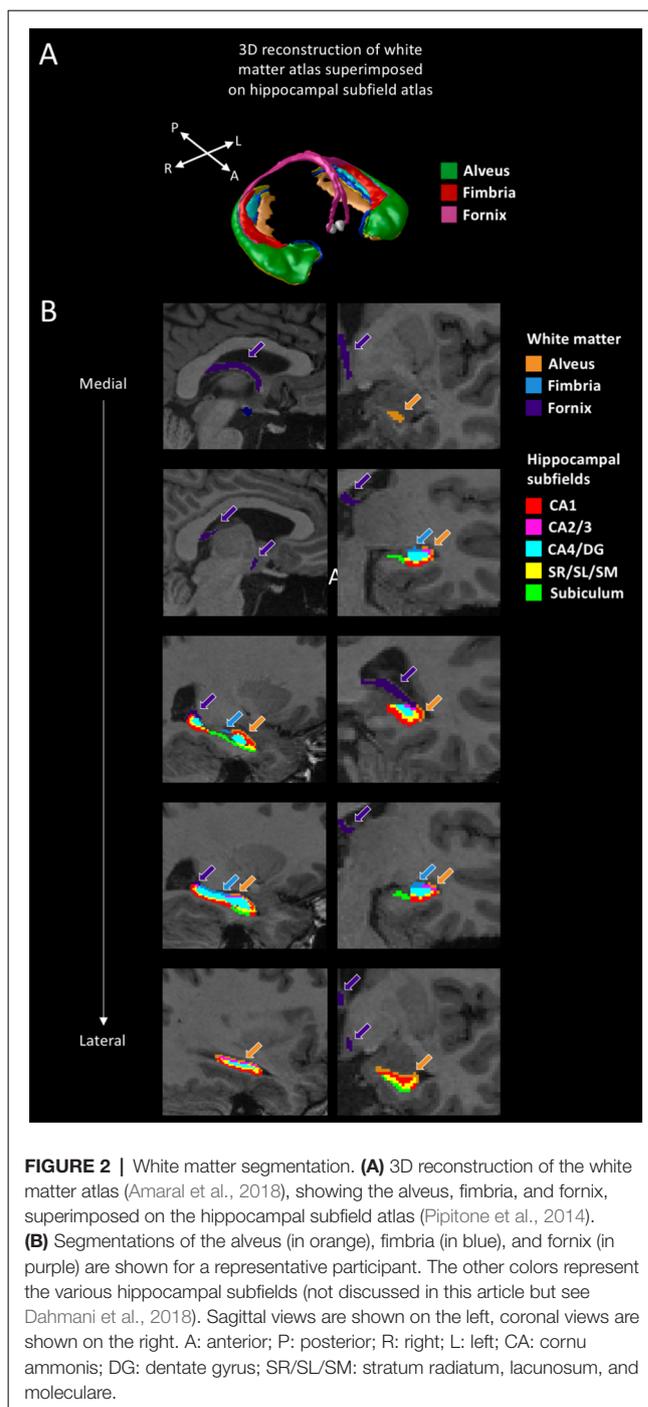
## Olfactory Identification

Spatial learners showed a significant positive correlation between olfactory identification and volume of the right fimbria [ $r = 0.41$ , Bootstrap BCa 95% CI (0.08, 0.68; **Figure 4**, left)]. They did not show a significant correlation between olfactory identification and right [ $r = 0.24$ , Bootstrap BCa 95% CI (−0.10, 0.55)] or left [ $r = 0.14$ , Bootstrap BCa 95% CI (−0.16, 0.43)] fimbria-fornix volumes, or with any sub-regions of the left fimbria-fornix (all Bootstrap BCa 95% CIs crossed 0).

In response learners, there were no associations between olfactory identification and right [ $r = −0.12$ , Bootstrap BCa 95% CI (−0.37, 0.20)] or left [ $r = −0.03$ , Bootstrap BCa 95% CI (−0.35, 0.25)] fimbria-fornix volumes. There were also no correlations with any of the fimbria-fornix sub-region volumes (all Bootstrap BCa 95% CIs crossed 0; e.g., right fimbria: **Figure 4**, right).

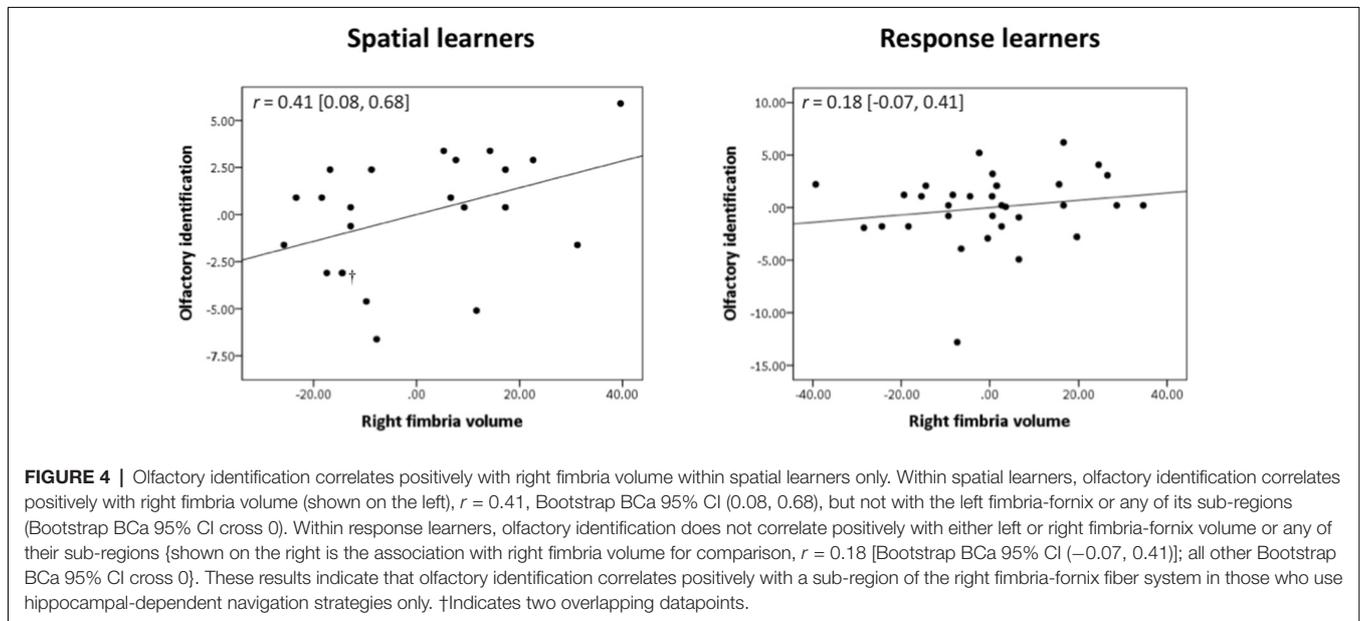
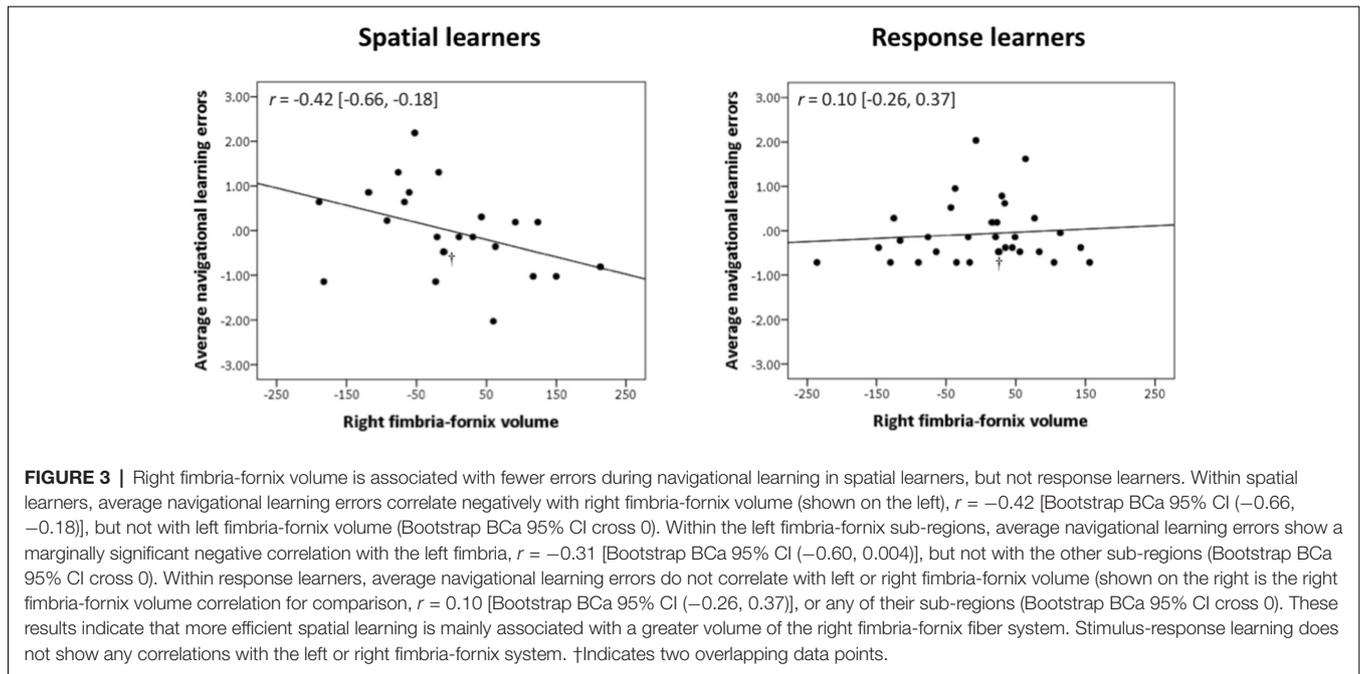
## DISCUSSION

In the current study, we examined whether the fimbria-fornix has a dissociable role in spatial learning and stimulus-response learning in humans. We found fimbria-fornix volume to be positively associated with spatial memory. As hypothesized, there is no association between fimbria-fornix volume and stimulus-



response learning, further strengthening the idea that these two forms of navigation rely on separate neural networks (O'Keefe and Nadel, 1978; Packard et al., 1989; McDonald and White, 1993). Similarly, within spatial learners, olfactory identification shows positive correlations with the fimbria-fornix, which is not the case within response learners.

These findings are consistent with our previous study (Dahmani et al., 2018), where we found both spatial learning and olfactory identification to be associated with hippocampal



gray matter volume, while there were no associations between stimulus-response learning and hippocampal volume.

In terms of lateralization, in our previous report we found an association between spatial memory, olfactory identification, and right hippocampal volume (Dahmani et al., 2018). Our white matter findings are concordant, as the effects we found predominantly involved the right fimbria-fornix fiber system. This is also consistent with a right-sided hippocampal lateralization for spatial memory and olfactory identification often reported in the literature (Habib and Sirigu, 1987; Zatorre and Jones-Gotman, 1990; Zatorre et al., 1992; Jones-Gotman and

Zatorre, 1993; Barrash, 1998; Bohbot et al., 1998; Savic et al., 2000; Burgess, 2002; Frasnelli et al., 2010; Kjellvik et al., 2012; Smitka et al., 2012).

The positive association between olfactory identification and the right fimbria-fornix bundle was observed in spatial learners, but not response learners, a pattern of results that reflects that of our previous study (Dahmani et al., 2018). These findings indicate that the fimbria-fornix is involved in olfactory identification in individuals who spontaneously use the hippocampal memory system. The hippocampus itself is reported to be involved in olfactory identification in

approximately half of the studies in the literature, while the other half does not report such involvement (Suzuki et al., 2001; Kjelvik et al., 2012, 2014; Seubert et al., 2013; Smitka et al., 2012; Segura et al., 2013). This inconsistency may be a product of inter-individual variability in hippocampal involvement. The fact that we found a correlation between olfactory identification and fimbria-fornix white matter among spatial learners but not response learners indicates that it may be useful to identify individuals' spontaneous navigation strategies in order to capture this inter-individual variability. We speculated in Dahmani et al. (2018) that response learners may more heavily rely on other nodes of the olfactory network, or that they may use a different neural network for olfactory processing. There is a lot of evidence that olfaction is influenced by top-down processing (Zatorre et al., 2000; Finkel et al., 2001; Gottfried and Dolan, 2003; de Araujo et al., 2005; Grabenhorst and Rolls, 2010; Ferdenzi et al., 2017) and cognitive strategies may influence the neural networks underlying it (Karunanayaka et al., 2014). Future studies should seek to elucidate the neural networks involved in olfactory identification using functional connectivity methods and to determine whether spatial and response learners differ in the way they process olfactory information.

Our findings may have implications for aging research. Both olfaction and spatial memory are impaired early on in cognitive aging and Alzheimer's disease (Henderson et al., 1989; Pai and Jacobs, 2004; Tu and Pai, 2006; Wilson et al., 2007, 2009; Devanand et al., 2008, 2015; Head and Isom, 2010; Stanciu et al., 2014; Allison et al., 2016; Lafaille-Magnan et al., 2017). Atrophy of the olfactory bulb, olfactory tract, entorhinal cortex, and hippocampus is also observed early in the disease (Pearson et al., 1985; Ferreyra-Moyano and Barragan, 1989; Talamo et al., 1989; Fox et al., 1996; Kaye et al., 1997; den Heijer et al., 2006). Our results suggest that dissociating individuals based on navigation strategies (spatial vs. response) combined with measuring errors during navigational learning and olfactory identification may be more sensitive to variations in hippocampal volume and hippocampal network white matter integrity, compared to looking at navigational learning errors or olfactory identification alone. It would be of interest to pursue this question in a future line of research.

In summary, our finding that fimbria-fornix volume is associated with spatial learning and olfactory identification is in line with our previous results (Dahmani et al., 2018). Not only are these two processes behaviorally linked, but they also share

## REFERENCES

- Allison, S. L., Fagan, A. M., Morris, J. C., and Head, D. (2016). Spatial navigation in preclinical Alzheimer's disease. *J. Alzheimers Dis.* 52, 77–90. doi: 10.3233/JAD-150855
- Amaral, R. S., Park, M. T. M., Devenyi, G. A., Lynn, V., Pipitone, J., Winterburn, J., et al. (2018). Manual segmentation of the fornix, fimbria, and alveus on high-resolution 3T MRI: application via fully-automated mapping of the human memory circuit white and grey matter in healthy and pathological aging. *Neuroimage* 170, 132–150. doi: 10.1016/j.neuroimage.2016.10.027
- Barrash, J. (1998). A historical review of topographical disorientation and its neuroanatomical correlates. *J. Clin. Exp. Neuropsychol.* 20, 807–827. doi: 10.1076/jcen.20.6.807.1114

many neuroanatomical substrates (Dahmani et al., 2018). In a comprehensive review, Jacobs et al. (2015) describes that the size of the olfactory bulb, a primary olfactory area, covaries with hippocampal size in many mammals (Reep et al., 2007) and with navigational demand, according to factors such as home range size (Gittleman, 1991) and predatory strategy (Reep et al., 2007). Taken together, these pieces of evidence are consistent with our findings that spatial memory and olfaction are closely linked.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of the Douglas Mental Health University Institute. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

LD and VB designed the study. JN, LD, and VB devised the MRI scanning protocol. LD performed the study, analyzed the data, and wrote the manuscript. BC, JN, and RP assisted with neuroimaging data preprocessing. RP, RA, and MC assisted with the MAGeT-Brain pipeline. VB supervised the study. All authors edited the manuscript.

## FUNDING

This research was supported by Natural Sciences and Engineering Research Council of Canada (NSERC) grant no. 239896-2013 and a Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best Doctoral Training Award.

## ACKNOWLEDGMENTS

We would like to thank Erica Chan, Meagan Bristowe, and Melissa Berman for their help with data collection.

- Bohbot, V. D., and Corkin, S. (2007). Posterior parahippocampal place learning in HM. *Hippocampus* 17, 863–872. doi: 10.1002/hipo.20313
- Bohbot, V. D., Iaria, G., and Petrides, M. (2004). Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resections. *Neuropsychology* 18, 418–425. doi: 10.1037/0894-4105.18.3.418
- Bohbot, V. D., Jech, R., Ruzicka, E., Nadel, L., Kalina, M., Stepánková, K., et al. (2002). Rat spatial memory tasks adapted for humans: characterization in subjects with intact brain and subjects with selective medial temporal lobe thermal lesions. *Physiol. Res.* 51, S49–S65.
- Bohbot, V. D., Kalina, M., Stepankova, K., Spackova, N., Petrides, M., and Nadel, L. (1998). Spatial memory deficits in patients with lesions to the right

- hippocampus and to the right parahippocampal cortex. *Neuropsychologia* 36, 1217–1238. doi: 10.1016/s0028-3932(97)00161-9
- Bohbot, V. D., Lerch, J., Thorndyraft, B., Iaria, G., and Zijdenbos, A. P. (2007). Gray matter differences correlate with spontaneous strategies in a human virtual navigation task. *J. Neurosci.* 27, 10078–10083. doi: 10.1523/JNEUROSCI.1763-07.2007
- Brown, L., Sherbenou, R. J., and Johnsen, S. K. (1997). *Test of Nonverbal Intelligence*. 3rd Edn. Austin, TX: Pro-Ed.
- Burgess, N. (2002). The hippocampus, space, and viewpoints in episodic memory. *Q. J. Exp. Psychol. A* 55, 1057–1080. doi: 10.1080/02724980244000224
- Dahmani, L., and Bohbot, V. D. (2015). Dissociable contributions of the prefrontal cortex to hippocampus-and caudate nucleus-dependent virtual navigation strategies. *Neurobiol. Learn. Mem.* 117, 42–50. doi: 10.1016/j.nlm.2014.07.002
- Dahmani, L., Patel, R. M., Yang, Y., Chakravarty, M. M., Fellows, L. K., and Bohbot, V. D. (2018). An intrinsic association between olfactory identification and spatial memory in humans. *Nat. Commun.* 9:4162. doi: 10.1038/s41467-018-06569-4
- de Araujo, I. E., Rolls, E. T., Velazco, M. I., Margot, C., and Cayeux, I. (2005). Cognitive modulation of olfactory processing. *Neuron* 46, 671–679. doi: 10.1016/j.neuron.2005.04.021
- de Bruin, J. P. C., Moita, M. P., de Brabander, H. M., and Joosten, R. N. (2001). Place and response learning of rats in a Morris water maze: differential effects of fimbria fornix and medial prefrontal cortex lesions. *Neurobiol. Learn. Mem.* 75, 164–178. doi: 10.1006/nlme.2000.3962
- den Heijer, T., Geerlings, M. I., Hoebeek, F. E., Hofman, A., Koudstaal, P. J., and Breteker, M. M. (2006). Use of hippocampal and amygdalar volumes on magnetic resonance imaging to predict dementia in cognitively intact elderly people. *Arch. Gen. Psychiatry* 63, 57–62. doi: 10.1001/archpsyc.63.1.57
- Devanand, D. P., Lee, S., Manly, J., Andrews, H., Schupf, N., Doty, R. L., et al. (2015). Olfactory deficits predict cognitive decline and Alzheimer dementia in an urban community. *Neurology* 84, 182–189. doi: 10.1212/wnl.0000000000001132
- Devanand, D. P., Liu, X., Tabert, M. H., Pradhaban, G., Cuasay, K., Bell, K., et al. (2008). Combining early markers strongly predicts conversion from mild cognitive impairment to Alzheimer's disease. *Biol. Psychiatry* 64, 871–879. doi: 10.1016/j.biopsych.2008.06.020
- Etchamendy, N., Konishi, K., Pike, G. B., Marighetto, A., and Bohbot, V. D. (2012). Evidence for a virtual human analog of a rodent relational memory task: a study of aging and fMRI in young adults. *Hippocampus* 22, 869–880. doi: 10.1002/hipo.20948
- Ferdenzi, C., Jousain, P., Digard, B., Luneau, L., Djordjevic, J., and Bensafi, M. (2017). Individual differences in verbal and non-verbal affective responses to smells: influence of odor label across cultures. *Chem. Senses* 42, 37–46. doi: 10.1093/chemse/bjw098
- Ferreira-Moyano, H., and Barragan, E. (1989). The olfactory system and Alzheimer's disease. *Int. J. Neurosci.* 49, 157–197. doi: 10.3109/00207458909084824
- Field, A. (2009). *Discovering Statistics Using SPSS*. London: Sage Publications.
- Field, A., Miles, J., and Field, Z. (2012). *Discovering Statistics Using R*. Thousand Oaks: Sage Publications.
- Finkel, D., Pedersen, N. L., and Larsson, M. (2001). Olfactory functioning and cognitive abilities: a twin study. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 56, P226–P233. doi: 10.1093/geronb/56.4.p226
- Fox, N., Warrington, E., Freeborough, P., Hartikainen, P., Kennedy, A., Stevens, J., et al. (1996). Presymptomatic hippocampal atrophy in Alzheimer's disease: a longitudinal MRI study. *Brain* 119, 2001–2007. doi: 10.1093/brain/119.6.2001
- Frasnelli, J., Lundstrom, J. N., Boyle, J. A., Djordjevic, J., Zatorre, R. J., and Jones-Gotman, M. (2010). Neuroanatomical correlates of olfactory performance. *Exp. Brain Res.* 201, 1–11. doi: 10.1007/s00221-009-1999-7
- Freiherr, J., Gordon, A. R., Alden, E. C., Ponting, A. L., Hernandez, M. F., Boesveldt, S., et al. (2012). The 40-item monell extended sniffin' sticks identification test (MONEX-40). *J. Neurosci. Methods* 205, 10–16. doi: 10.1016/j.jneumeth.2011.12.004
- Gittleman, J. L. (1991). Carnivore olfactory bulb size: allometry, phylogeny and ecology. *J. Zool.* 225, 253–272. doi: 10.1111/j.1469-7998.1991.tb03815.x
- Gottfried, J. A., and Dolan, R. J. (2003). The nose smells what the eye sees: crossmodal visual facilitation of human olfactory perception. *Neuron* 39, 375–386. doi: 10.1016/s0896-6273(03)00392-1
- Grabenhorst, F., and Rolls, E. T. (2010). Attentional modulation of affective versus sensory processing: functional connectivity and a top-down biased activation theory of selective attention. *J. Neurophysiol.* 104, 1649–1660. doi: 10.1152/jn.00352.2010
- Greenland, S., Senn, S. J., Rothman, K. J., Carlin, J. B., Poole, C., Goodman, S. N., et al. (2016). Statistical tests, P values, confidence intervals and power: a guide to misinterpretations. *Eur. J. Epidemiol.* 31, 337–350. doi: 10.1007/s10654-016-0149-3
- Habib, M., and Sirigu, A. (1987). Pure topographical disorientation: a definition and anatomical basis. *Cortex* 23, 73–85. doi: 10.1016/s0010-9452(87)80020-5
- Hartley, T., Maguire, E. A., Spiers, H. J., and Burgess, N. (2003). The well-worn route and the path less traveled: distinct neural bases of route following and wayfinding in humans. *Neuron* 37, 877–888. doi: 10.1016/s0896-6273(03)00095-3
- Haukoos, J. S., and Lewis, R. J. (2005). Advanced statistics: bootstrapping confidence intervals for statistics with “difficult” distributions. *Acad. Emerg. Med.* 12, 360–365. doi: 10.1197/j.aem.2004.11.018
- Head, D., and Isom, M. (2010). Age effects on wayfinding and route learning skills. *Behav. Brain Res.* 209, 49–58. doi: 10.1016/j.bbr.2010.01.012
- Henderson, V. W., Mack, W., and Williams, B. W. (1989). Spatial disorientation in Alzheimer's disease. *Arch. Neurol.* 46, 391–394. doi: 10.1001/archneur.1989.00520400045018
- Iaria, G., Lanyon, L. J., Fox, C. J., Giaschi, D., and Barton, J. J. (2008). Navigational skills correlate with hippocampal fractional anisotropy in humans. *Hippocampus* 18, 335–339. doi: 10.1002/hipo.20400
- Iaria, G., Petrides, M., Dagher, A., Pike, B., and Bohbot, V. D. (2003). Cognitive strategies dependent on the hippocampus and caudate nucleus in human navigation: variability and change with practice. *J. Neurosci.* 23, 5945–5952. doi: 10.1523/JNEUROSCI.23-13-05945.2003
- Jacobs, L. F., Arter, J., Cook, A., and Sulloway, F. J. (2015). Olfactory orientation and navigation in humans. *PLoS One* 10:e0129387. doi: 10.1371/journal.pone.0129387
- Jones, D. K., Knösche, T. R., and Turner, R. (2013). White matter integrity, fiber count, and other fallacies: the do's and don'ts of diffusion MRI. *Neuroimage* 73, 239–254. doi: 10.1016/j.neuroimage.2012.06.081
- Jones-Gotman, M., and Zatorre, R. J. (1993). Odor recognition memory in humans: role of right temporal and orbitofrontal regions. *Brain Cogn.* 22, 182–198. doi: 10.1006/brcg.1993.1033
- Karunanayaka, P., Eslinger, P. J., Wang, J. L., Weitekamp, C. W., Molitoris, S., Gates, K. M., et al. (2014). Networks involved in olfaction and their dynamics using independent component analysis and unified structural equation modeling. *Hum. Brain Mapp.* 35, 2055–2072. doi: 10.1002/hbm.22312
- Kaye, J. A., Swihart, T., Howieson, D., Dame, A., Moore, M., Karnos, T., et al. (1997). Volume loss of the hippocampus and temporal lobe in healthy elderly persons destined to develop dementia. *Neurology* 48, 1297–1304. doi: 10.1212/wnl.48.5.1297
- Kjelvik, G., Evensmoen, H. R., Brezova, V., and Häberg, A. K. (2012). The human brain representation of odor identification. *J. Neurophysiol.* 108, 645–657. doi: 10.1152/jn.01036.2010
- Kjelvik, G., Saltvedt, I., White, L. R., Stenumgård, P., Sletvold, O., Engedal, K., et al. (2014). The brain structural and cognitive basis of odor identification deficits in mild cognitive impairment and Alzheimer's disease. *BMC Neurol.* 14:168. doi: 10.1186/s12883-014-0168-1
- Konishi, K., and Bohbot, V. D. (2013). Spatial navigational strategies correlate with gray matter in the hippocampus of healthy older adults tested in a virtual maze. *Front. Aging Neurosci.* 5:1. doi: 10.3389/fnagi.2013.00001
- Konishi, K., Etchamendy, N., Roy, S., Marighetto, A., Rajah, N., and Bohbot, V. D. (2013). Decreased fMRI activity in the hippocampus in favor of the caudate nucleus in older adults tested in a virtual navigation task. *Hippocampus* 23, 1005–1014. doi: 10.1002/hipo.22181
- Lafaille-Magnan, M.-E., Poirier, J., Etienne, P., Tremblay-Mercier, J., Frenette, J., Rosa-Neto, P., et al. (2017). Odor identification as a biomarker of preclinical AD in older adults at risk. *Neurology* 89, 327–335. doi: 10.1212/WNL.0000000000004159
- Lundström, J. N., Boesveldt, S., and Albrecht, J. (2011). Central processing of the chemical senses: an overview. *ACS Chem. Neurosci.* 2, 5–16. doi: 10.1021/cn1000843

- Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., and O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science* 280, 921–924. doi: 10.1126/science.280.5365.921
- McDonald, R. J., and White, N. M. (1993). A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. *Behav. Neurosci.* 107, 3–22. doi: 10.1037//0735-7044.107.1.3
- McDonald, R. J., and White, N. M. (1995). Hippocampal and nonhippocampal contributions to place learning in rats. *Behav. Neurosci.* 109, 579–593. doi: 10.1037/0735-7044.109.4.579
- Meyers, J. E., and Meyers, K. R. (1995). *Rey Complex Figure Test and Recognition Trial: Professional Manual*. Odessa, FL: Psychological Assessment Resources.
- Moscovitch, M., Rosenbaum, R. S., Gilboa, A., Addis, D. R., Westmacott, R., Grady, C., et al. (2005). Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. *J. Anat.* 207, 35–66. doi: 10.1111/j.1469-7580.2005.00421.x
- O'Keefe, J., and Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford: Clarendon.
- Olton, D. S., and Papas, B. C. (1979). Spatial memory and hippocampal function. *Neuropsychologia* 17, 669–682. doi: 10.1016/0028-3932(79)90042-3
- Olton, D. S., and Samuelson, R. J. (1976). Remembrance of places passed: spatial memory in rats. *J. Exp. Psychol. Anim. Behav. Process.* 2, 97–116. doi: 10.1037/0097-7403.2.2.97
- Packard, M. G., Hirsh, R., and White, N. M. (1989). Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. *J. Neurosci.* 9, 1465–1472. doi: 10.1523/jneurosci.09-05-01465.1989
- Pai, M. C., and Jacobs, W. J. (2004). Topographical disorientation in community-residing patients with Alzheimer's disease. *Int. J. Geriatr. Psychiatry* 19, 250–255. doi: 10.1002/gps.1081
- Pearson, R., Esiri, M., Hiorns, R., Wilcock, G., and Powell, T. (1985). Anatomical correlates of the distribution of the pathological changes in the neocortex in Alzheimer disease. *Proc. Natl. Acad. Sci. U S A* 82, 4531–4534. doi: 10.1073/pnas.82.13.4531
- Pigott, S., and Milner, B. (1993). Memory for different aspects of complex visual scenes after unilateral temporal-or frontal-lobe resection. *Neuropsychologia* 31, 1–15. doi: 10.1016/0028-3932(93)90076-c
- Pipitone, J., Park, M. T. M., Winterburn, J., Lett, T. A., Lerch, J. P., Pruessner, J. C., et al. (2014). Multi-atlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates. *Neuroimage* 101, 494–512. doi: 10.1016/j.neuroimage.2014.04.054
- Poole, C. (2001). Low P-values or narrow confidence intervals: which are more durable? *Epidemiology* 12, 291–294. doi: 10.1097/00001648-200105000-00005
- Reep, R., Finlay, B., and Darlington, R. (2007). The limbic system in mammalian brain evolution. *Brain Behav. Evol.* 70, 57–70. doi: 10.1159/000101491
- Rey, A. (1941). L'examen psychologique dans les cas d'encéphalopathie traumatique. *Arch. Psychol.* 28, 215–285.
- Rothman, K. J. (1978). A show of confidence. *N. Engl. J. Med.* 299, 1362–1363. doi: 10.1056/NEJM197812142992410
- Savic, I., Gulyas, B., Larsson, M., and Roland, P. (2000). Olfactory functions are mediated by parallel and hierarchical processing. *Neuron* 26, 735–745. doi: 10.1016/s0896-6273(00)81209-x
- Scholz, J., Tomassini, V., and Johansen-Berg, H. (2014). "Individual differences in white matter microstructure in the healthy brain," in *Diffusion MRI*, eds H. Johansen-Berg and T. E. J. Behrens (Cambridge, MA: Elsevier), 301–316.
- Segura, B., Baggio, H. C., Solana, E., Palacios, E. M., Vendrell, P., Bargalló, N., et al. (2013). Neuroanatomical correlates of olfactory loss in normal aged subjects. *Behav. Brain Res.* 246, 148–153. doi: 10.1016/j.bbr.2013.02.025
- Seubert, J., Freiherr, J., Frasnelli, J., Hummel, T., and Lundström, J. N. (2013). Orbitofrontal cortex and olfactory bulb volume predict distinct aspects of olfactory performance in healthy subjects. *Cereb. Cortex* 23, 2448–2456. doi: 10.1093/cercor/bhs230
- Smitka, M., Puschmann, S., Buschhueter, D., Gerber, J. C., Witt, M., Honeycutt, N., et al. (2012). Is there a correlation between hippocampus and amygdala volume and olfactory function in healthy subjects? *Neuroimage* 59, 1052–1057. doi: 10.1016/j.neuroimage.2011.09.024
- Stanciu, I., Larsson, M., Nordin, S., Adolfsson, R., Nilsson, L.-G., and Olofsson, J. K. (2014). Olfactory impairment and subjective olfactory complaints independently predict conversion to dementia: a longitudinal, population-based study. *J. Int. Neuropsychol. Soc.* 20, 209–217. doi: 10.1017/s1355617713001409
- Suzuki, Y., Critchley, H. D., Suckling, J., Fukuda, R., Williams, S. C., Andrew, C., et al. (2001). Functional magnetic resonance imaging of odor identification: the effect of aging. *J. Gerontol. A Biol. Sci. Med. Sci.* 56, M756–M760. doi: 10.1093/gerona/56.12.m756
- Talamo, B. R., Rudel, R., Kosik, K. S., Lee, V. M.-Y., Neff, S., Adelman, L., et al. (1989). Pathological changes in olfactory neurons in patients with Alzheimer's disease. *Nature* 337, 736–739. doi: 10.1038/337736a0
- Tu, M.-C., and Pai, M.-C. (2006). Getting lost for the first time in patients with Alzheimer's disease. *Int. Psychogeriatr.* 18, 567–570. doi: 10.1017/s1041610206224025
- Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., et al. (2010). N4ITK: improved N3 bias correction. *IEEE Trans. Med. Imaging* 29, 1310–1320. doi: 10.1109/TMI.2010.2046908
- Westfall, P. H., and Young, S. S. (1993). *Resampling-Based Multiple Testing: Examples and Methods for p-value adjustment*. New York, NY: John Wiley and Sons.
- White, N. M., and McDonald, R. J. (2002). Multiple parallel memory systems in the brain of the rat. *Neurobiol. Learn. Mem.* 77, 125–184. doi: 10.1006/nlme.2001.4008
- Wilson, R. S., Arnold, S. E., Schneider, J. A., Boyle, P. A., Buchman, A. S., and Bennett, D. A. (2009). Olfactory impairment in presymptomatic Alzheimer's disease. *Ann. N Y Acad. Sci.* 1170, 730–735. doi: 10.1111/j.1749-6632.2009.04013.x
- Wilson, R. S., Arnold, S. E., Schneider, J. A., Tang, Y., and Bennett, D. A. (2007). The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. *J. Neurol. Neurosurg. Psychiatry* 78, 30–35. doi: 10.1136/jnnp.2006.099721
- Winterburn, J. L., Pruessner, J. C., Chavez, S., Schira, M. M., Lobaugh, N. J., Voineskos, A. N., et al. (2013). A novel *in vivo* atlas of human hippocampal subfields using high-resolution 3T magnetic resonance imaging. *Neuroimage* 74, 254–265. doi: 10.1016/j.neuroimage.2013.02.003
- Wu, K. N., Tan, B. K., Howard, J. D., Conley, D. B., and Gottfried, J. A. (2012). Olfactory input is critical for sustaining odor quality codes in human orbitofrontal cortex. *Nat. Neurosci.* 15, 1313–1319. doi: 10.1038/nn.3186
- Zatorre, R. J., and Jones-Gotman, M. (1990). Right-nostril advantage for discrimination of odors. *Percept. Psychophys.* 47, 526–531. doi: 10.3758/bf03203105
- Zatorre, R. J., Jones-Gotman, M., Evans, A. C., and Meyer, E. (1992). Functional localization and lateralization of human olfactory cortex. *Nature* 360, 339–340. doi: 10.1038/360339a0
- Zatorre, R. J., Jones-Gotman, M., and Rouby, C. (2000). Neural mechanisms involved in odor pleasantness and intensity judgments. *Neuroreport* 11, 2711–2716. doi: 10.1097/00001756-200008210-00021

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2020 Dahmani, Courcot, Near, Patel, Amaral, Chakravarty and Bohbot. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.