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ORIGINAL ARTICLE

Hippocampal 5-HT_{1A} receptor binding is related to object–location memory in humans

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Abstract Animal studies suggest that serotonin, mediated by the 5-HT_{1A} receptor, plays a key role in spatial learning and memory. The role of serotonin in spatial memory in humans has, however, been less well studied. This study examined the relationship between serotonin receptor density in the human brain and spatial learning and memory using the 5-HT_{1A} receptor ligand ^{18}F-4-(2′-methoxyphenyl)-1-[2′-(*N*-2-pyridinyl)-*p*-fluorobenzamido]-ethylpiperazine ([^{18}F] MPPF) and positron emission tomography (PET). Ten neurologically healthy individuals underwent two [^{18}F] MPPF PET scans, one while performing a task which involves processing of high-level spatial information ('house scan'), and one while performing a task which involves processing of low-level spatial information ('tunnel scan'). Navigation, recall of arbitrary associations between objects and their spatial location, and ability to draw a plan of the environment were tested following the house scan. 5-HT_{1A} receptor binding did not differ significantly between processing high and low levels of spatial information. Hippocampal asymmetry in [^{18}F] MPPF binding, however, was associated with memory for object–location associations; lower right than left hippocampal binding potential (BP_{ND}) was related to better memory performance. We conclude that hippocampal serotonergic function plays a role in a fundamental component of human spatial memory, the ability to recall the location of encountered objects.

Keywords Serotonin 1A receptor · Positron emission tomography · [^{18}F] MPPF · Hippocampus · Spatial cognition · Navigation · Virtual environment

Introduction

Two fundamental parallels exist between the serotonergic system and spatial memory. Neuroanatomically, there is an overlap between serotoninergic pathways and regions involved in spatial cognition. In particular, the hippocampus proper is heavily implicated in this function (O'Keefe

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and Nadel 1978; Kesner and Hopkins 2006), and is enriched with the 5-HT_{1A} receptor (Lanfumey and Hamon 2000). Phylogenetically, both are ancient and exist in all mammalian species. Previous animal studies suggest that serotonergic effects, mediated by the 5-HT_{1A} receptor, play a role in spatial memory.

At the receptor level, modulation of serotonergic neurotransmission by agonists and antagonists alters spatial learning performance. For example, in Micheau and Van Marrewijk (1999), intraperitoneal or intraseptal administration of 8-OH-DPAT (a 5-HT_{1A} receptor agonist) improved acquisition of a spatial discrimination task in rats. Pharmacological manipulations of the neurotransmitter show that increased extracellular serotonin concentrations maintain or improve memory performance, and reductions in neurotransmitter level impair spatial memory. Compounds that damage serotonergic neurons in rats, such as 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'; Sprague et al. 2003), D-fenfluramine (Morford et al. 2002), methamphetamine (Vorhees et al. 2000), and parachlorophenylalanine (Mazer et al. 1997) also impair performance on spatial memory tasks. Single gene deletions in knockout mice provide further evidence for the role of serotonin in spatial memory (Sarnyai et al. 2000). Sarnyai's group assessed 5-HT_{1A} receptor-deficient mice on the hippocampus-related learning and memory tasks, the Morris Water Maze and the 'Y' shape Maze, and showed that a lack of 5-HT_{1A} receptors was specifically associated with impairments in performance of these tasks.

Animal research has been the principal contributor to our understanding of serotonergic neurotransmission during spatial memory. The literature on serotonin and spatial memory in humans is smaller and is characterized by conflicting findings. To date, human studies have examined the relationship between serotonin and spatial memory function by manipulating serotonin levels using acute tryptophan depletion in healthy participants or by assessing participants in which serotonin levels are reduced by the use of recreational drugs, such as MDMA or by treatment of depression with selective serotonin re-uptake inhibitors. Although tryptophan depletion studies have produced inconsistent findings (see for example, Cassano et al. 2002 versus Siepmann et al. 2003), an association between reduced levels of serotonin and spatial memory impairments is observed in recreational drug users (see Murphy et al. 2012 for a systematic review with meta-analyses). The contribution of confounding factors to impairments in spatial memory, such as polydrug use and chronic depression, however, has not been accounted for in these reports.

Given the methodological problems inherent in human depletion studies, we approached the issue by studying the relationship between serotonin receptor density and spatial learning and memory (object location, navigation, and floor plan drawing) in neurologically healthy participants using the PET ligand [^{18}F] MPPF which binds to the 5-HT_{1A} receptor. This methodology has recently been used in patients with temporal lobe epilepsy (TLE) using the 18FCWAY PET ligand. In their study, Theodore et al. (2012) showed that reduced left hippocampal 5-HT_{1A} receptor binding is related to delayed auditory verbal memory impairment, independent of the side of the epileptic focus. In the present study, [^{18}F] MPPF binding and performance on a spatial learning task were assessed contemporaneously to determine whether there is a relationship between receptor density and spatial memory ability. Because [^{18}F] MPPF binding is altered when large physiological changes occur such as during sleep (Derry et al. 2005), we requested participants to perform two virtual environment tasks with different amounts of spatial processing for the purpose of maintaining the fully awake state. This paradigm also allowed us to examine whether spatial processing per se affects 5-HT_{1A} receptor binding. We hypothesized that there is a constitutive relationship between serotonergic function and the biological trait of spatial memory ability.

One important aspect of human memory that cannot be studied well in animal models relates to lateralization of function. It is now thought that the domain of spatial memory is not lateralized as a unitary neurocognitive system, as originally envisaged by the strong form of the material-specificity hypothesis (Dobbins et al. 1998; Saling 2009). Rather, spatial memory is more likely to be underpinned by a dynamic interaction between right and left mesial temporal networks, depending on specific task demands (Burgess et al. 2002; Treyer et al. 2005). There is evidence, however, that specific elemental aspects of spatial memory (such as object–place association) are more likely to be right lateralized as determined by correlations with hippocampal volume (Abrahams et al. 1999, Crane and Milner 2005). To assess whether these structural correlations have a counterpart in serotonergic function, we examined the influence of lateralized differences in hippocampal serotonin receptor availability on spatial learning. We hypothesized that hippocampal [^{18}F] MPPF asymmetry would have a greater influence on performance of object–location memory tasks than on the performance of tasks involving navigation or floor plan drawing.

Materials and methods

The study was approved by the Human Research Ethics Committee of Austin Health, Melbourne, Australia, and participants were assessed on the basis of informed

consent, which was obtained according to the Declaration of Helsinki (British Medical Journal, July 18, 1964).

Participants

Ten male volunteers (mean age = 27.3 years; range = 18–40 years; nine right handed) were studied. Exclusion criteria were age less than 18 years, any previous or current significant medical (including neurological or psychiatric) illness, a history of head trauma, and current or prior use of substances with known action on the 5-HT system, such as illicit drugs. In view of the potential effects of mood and serum tryptophan on endogenous serotonin release, all participants completed the Beck Depression Inventory (BDI) (Beck and Steer 1987) and the Beck Anxiety Inventory (BAI) (Beck and Steer 1990) on the day of each PET scan. They were supplied with standardized meals for 24 h before each scan (no caffeinated drinks were permitted during this period), and serum tryptophan levels were measured 30 min prior to each scan.

Procedure

Each participant underwent two [^{18}F] MPPF PET scans (total mean injected dose = 4.5 mCi, SD = 0.5 mCi), one while performing a task which involves processing of high-level spatial information ('house scan'), and one while performing a task which involves processing low-level of spatial information ('tunnel scan'). The order of scans was randomized using random number generator in Matlab.

Radiochemistry

[^{18}F] MPPF was obtained by nucleophilic substitution of the aromatic nitro group using previously described methods (Le Bars et al. 1998). The purity of [^{18}F] MPPF was greater than 95 % in each synthesis, and specific activity ranged from 477 to 5,580 mCi/μmol.

PET scanning

PET scans were performed between 1 and 3 pm using a Philips-ADAC Allegro full-ring 3D PET Imaging System with GSO crystal detectors. Head movement was minimized using a molded head rest and head restraint. A transmission scan was acquired prior to the emission scan for the purpose of determining head position. Scans were acquired rostrally from and approximately parallel to the orbitomeatal line. The transmission data were also used for measured attenuation correction of the emission data in the image reconstruction stage. Emission scans were carried out using 256 trans-axial FOV list-mode acquisition protocol (FOV = 180 mm). The 60 min list-mode data were later sorted into 22 dynamic frames and reconstructed using the 3D RAMLA algorithm. Each frame of the reconstructed images contained 90 slices of 2 mm thickness. The resolution for the reconstructed images was about 6.6 mm in full width at half maximum in the axial direction and 7.1 mm in full width at half maximum in the trans-axial direction for a source located at 5 cm from the field of view (Fourin et al. 2002).

MRI scanning

To facilitate the registration of PET images and the anatomical interpretation of the PET data, each participant underwent a high-resolution three-dimensional T1-weighted MRI scan. The MRIs were acquired on a 1.5 T Signa Horizon Echospeed Superconducting Imaging System (General Electric Medical Systems, Milwaukee, WI). The three-dimensional spoiled gradient recalled echo acquisition (3DSPGR) comprised TR 10.4 ms, TE 2.2 ms, TI 350 ms, flip angle 20°, FOV 25 cm × 2 5 cm, matrix 256 × 256, voxel size = 1.3 mm × 0.97 mm × 0.97 mm.

Cognitive measures

A virtual house, previously described in Glikmann-Johnston et al. (2008), was used to induce high-level processing of spatial information. A newly designed virtual tunnel was used to elicit low-level processing of spatial information. Both tasks were constructed using 3D Studio MAX (Autodesk, Inc.) and Macromedia Director MX version 9.0 (Macromedia Inc.). They were displayed on a PC laptop (Toshiba Tecra S1) with a 15 inch screen. A joystick allowed participants to manoeuvre freely within the environments. Manipulation of the joystick provided the capacity to start and stop movement through the virtual environment at constant speed.

Virtual house task

The virtual house was a square structure comprising eight spaces of varying size (Glikmann-Johnston et al. 2008; see Figs. 1, 2). Each space contained objects located in conventional positions, such as a picture on the wall or a chair at a table. There were also objects positioned in arbitrary locations. These constituted the test objects within the object–location memory paradigm. Of a total of 11 test objects, three were geometric shapes (yellow sphere, pink cylinder, and blue rectangle), and eight were common objects (boat, tap, model car, shark, flower vase, balloon, piano, and fire extinguisher). The three shapes appeared a total of 15 times in various locations, and each of the eight common objects appeared in one room only. Window views to the exterior of the house differed according to the cardinal compass points towards which they were oriented.

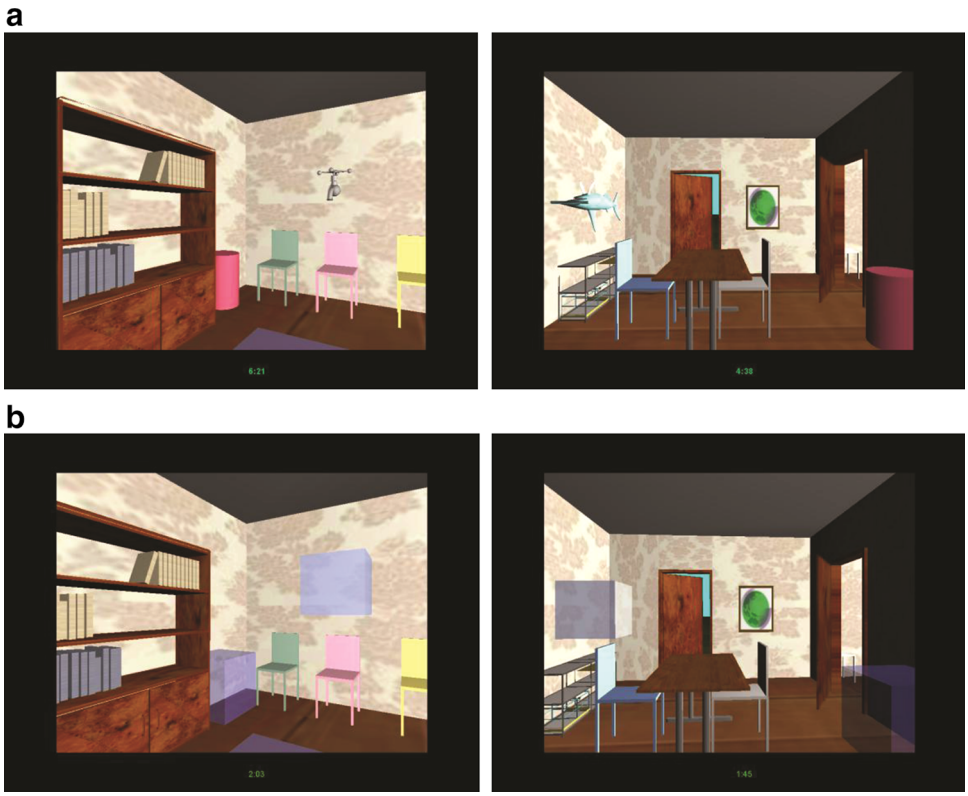

Fig. 1 The virtual house: a view from two different rooms when **a** test objects are present, and when **b** test objects are absent

Participants were instructed to explore the house for the duration of the PET scanning (60 min), and their recall of a route (navigation), memory for object location, and floor plan drawing were tested immediately after scanning.

Navigation At the start of the task, participants were told that there was a dog in the house, and that they were required to find it and remember *where* it was found. A sound of a barking dog was heard during the initial 30 min of exploration, followed by the appearance of the dog under a table in one of the rooms (5 in Fig. 2). Following free exploration, participants were asked to navigate from the entrance of the house to the room in which they found the dog by the *most direct route*. The number of spaces traversed to locate the dog was recorded. Time taken to reach the dog was measured.

Object location To assess memory for object location, participants re-entered the house, traversing a standard examiner prescribed route, but on this occasion the objects positioned in arbitrary locations (test objects) had been removed. A pale blue three-dimensional transparent box replaced the removed objects (see Fig. 1b). All conventionally placed objects (such as tables, chairs, and pictures) remained in the house. Prior to re-entry, however, a screen showing the objects appeared. The examiner named the objects on the screen, and then requested participants to recall the missing test objects that had occupied the position now marked by a blue box. One point was allocated for recalling each object in its correct location. The maximum score achievable on this task was 23 points.

Floor plan drawing Participants were required to draw a floor plan of the house illustrating its general outline, the spatial relations between the rooms, and their relative dimensions. Scoring was based on qualitative assessment of spatial distortions of the plan. See Fig. 2 for a schematic illustration of the house floor plan and scoring criteria.

Virtual tunnel task

A virtual tunnel provided the environment in which participants were tested for processing low-level spatial information. The tunnel was designed as a bare circular loop with minimal spatial or navigational features (see Fig. 3). Using the joystick, participants could freely manoeuvre within the tunnel, however, they were instructed to follow a continuous line on the floor of the tunnel for the duration of the PET scan. There were no additional tasks following scanning.

Data analysis

Kinetic analysis

A parametric image, obtained by estimating the binding potential (BP_{ND}) and K_1 ratio for each voxel, was

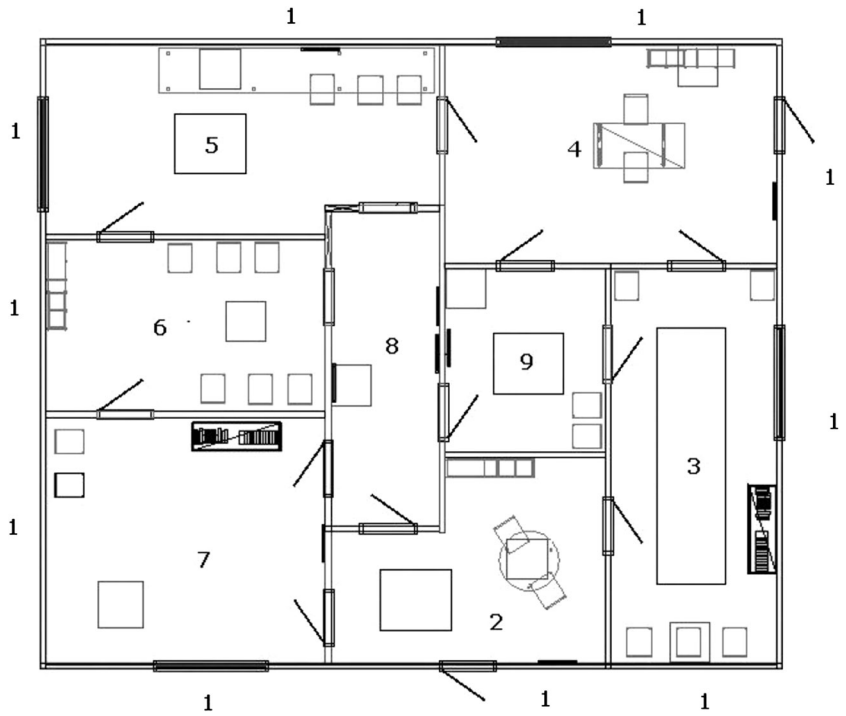

Fig. 2 Scoring scheme for house floor plan drawing: (*1*) large square outlining the overall shape of the house, and within: (*2*) L-shaped room with extension to the left surrounding right lower corner of 8; (*3*) large vertical rectangle to the left of, and the same length of 2 and 9; (*4*) horizontal rectangle above and the same length of 3 and 9; (*5*) horizontal rectangle to the left of 4, and above 6 and 8; (*6*) smaller rectangle between 5 and 7, with 8 to the right; (*7*) large square below 6, on the left of 2 and 8; (*8*) thin and long rectangle depicting a corridor between 2 and 5, along 6 and 7 to the left, and 9 to the right; (*9*) small square between 2 and 4, 8 to the left, and 3 to the right. For each unit scores were assigned according to the following criteria:

Correct shape of space	placed correctly	2 points
	placed incorrectly	1 point
Distorted or incomplete,	placed correctly	1 point
	placed incorrectly	½ point
Absent or not recognizable		0 points
Maximum		18 points

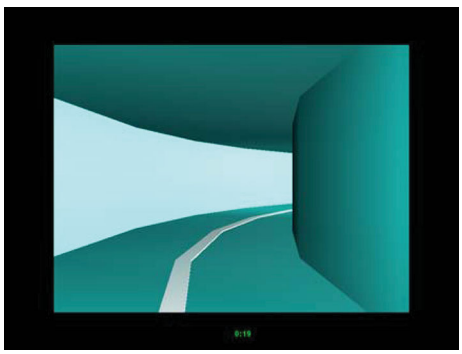

Fig. 3 The virtual tunnel: participants were instructed to follow the white line on the floor of the tunnel for the duration of the scan

generated for each PET dataset using a simplified reference tissue model (Lammertsma and Hume 1996) validated for [^{18}F] MPPF studies (Passchier et al. 2001). This model derives BP_{ND} from the ratio of the volumes of distribution of the ligand in the region of interest relative to the cerebellum, which has been shown to be devoid of 5-HT_{1A} specific binding (Burnet et al. 1995; Hall et al. 1997). No arterial sampling was performed, and K_1 was not directly measured. The cerebellum was manually segmented on MRI images using interactive mouse-driven software which enabled simultaneous display of coronal, sagittal, and axial images (display; http://www.bic.mni.mcgill.ca/software). Delineation of the cerebellum was performed by YGJ and included the vermian lobules, archicerebellum (nodules and flocculi), anterior, and posterior lobes. These MRI images were registered to an image comprising the sum of all frames from the dynamic PET acquisition. Each of the 22 frames from the raw PET dataset was initially blurred using Gaussian kernel with full width at half maximum of 9 mm. MRI to PET registration was performed using a six-parameter rigid body linear transformation (rotation and translation), and the software package AIR 3.08 (http://www.bishopw.loni.ucla.edu/AIR3/index.html) (Woods et al. 1992).

Regions of interest

Mean values for BP_{ND} and K_1 were calculated for the hippocampus. Manual segmentation of both hippocampi

was performed by YGJ on MRI images following rigid body registration to the MNI-152 template. The boundaries of the hippocampus were defined using previously described and validated anatomical landmarks established by Watson et al. (1992). At its anterior part, the alveus was used to distinguish the hippocampus from the amygdala. If the alveus was not visible, the inferior horn of the lateral ventricle was used as a marker to separate the hippocampal head from the amygdala. A horizontal line was drawn connecting the plane of the inferior horn of the lateral ventricle with the surface of the uncus. The inferior margin of the hippocampus was outlined to include the subicular complex and the uncal cleft with the border separating the subicular complex from the parahippocampal gyrus being defined as the angle formed by the most medial extent of those two structures. Measurements in the hippocampal body and tail included the subicular complex, hippocampus proper, dentate gyrus, alveus, and fimbria. In the hippocampal tail, the crus of the fornix, isthmus of the cingulate gyrus, and parahippocampal gyrus were excluded. The posterior border of the hippocampus was defined as the coronal slice in which the fornix clearly separated from the hippocampus and its fimbria. The total volume of each hippocampus was calculated using a voxel-counting algorithm. Mean values for BP_{ND} and K_1 ratio were calculated for the whole brain and for each hemisphere. The whole brain mask was obtained using the software FSL and manual editing. A mask for each hemisphere was obtained using the software SPM. Masks of the hippocampus, the two hemispheres, and whole brain were transformed into the coordinate space of the PET image using the above transformation matrix for the purpose of obtaining mean BP_{ND} and K_1 values.

Statistical analysis

Given the small sample size, the Wilcoxon's signed ranks test was used to compare mean [^{18}F] MPPF binding in the hippocampi, the two hemispheres, and in the whole brain in the house and the tunnel scans.

Analysis of covariance (ANCOVA) with repeated measures was used to compare asymmetry in hippocampal [^{18}F] MPPF binding (given by, right ROI BP_{ND} − left ROI BP_{ND}/whole brain BP_{ND}) during the house and tunnel scans, with spatial memory performance (navigation, object location, floor plan drawing) and hippocampal volume asymmetry (given by, right hippocampal volume − left hippocampal volume/whole brain volume) as covariates.

Separate stepwise multiple linear regressions for the house and tunnel scans were used to assess the relative contributions of the memory variables to asymmetry in hippocampal [^{18}F] MPPF binding. Hippocampal volume asymmetry was used as a covariate.

Results

Mean [^{18}F] MPPF BP_{ND} in hippocampi, hemispheres, and whole brain during house and tunnel scans are summarized in Table 1. Details of participants' performance on the spatial memory measures of the virtual house are outlined in Table 2. Overall, [^{18}F] MPPF binding did not change between processing high-level (house scan) and low-level (tunnel scan) spatial information. Further, the two spatial processing levels did not differ in their hippocampal and hemispheric asymmetry measures of [^{18}F] MPPF binding. Recall of object location was the only memory variable found to be associated with hippocampal [^{18}F] MPPF binding asymmetry in both spatial processing levels.

Change in [^{18}F] MPPF binding in processing high- versus low-level spatial information

There were no differences between house and tunnel scans in mean [^{18}F] MPPF binding in the hippocampi (right hippocampus $Z = -0.46$, $p = 0.6$; left hippocampus $Z = -0.76$, $p = 0.4$), hemispheres (right hemisphere $Z = -0.56$, $p = 0.6$; left hemisphere $Z = -0.76$, $p = 0.4$), or whole brain ($Z = -0.76$, $p = 0.4$).

Change in asymmetry [^{18}F] MPPF binding in processing high- versus low-level spatial information

Hippocampal asymmetry in [^{18}F] MPPF binding did not differ between house and tunnel scans, irrespective of whether spatial memory task performances and hippocampal volume asymmetry were controlled (see Table 3). The two spatial processing scans did not differ in their hemispheric asymmetry in [^{18}F] MPPF binding (see Table 3).

Relationship between asymmetry in [^{18}F] MPPF binding and spatial memory

Hippocampal asymmetry in [^{18}F] MPPF binding was significantly associated with performance on the object–location task in both house ($r = -0.78$, $p = 0.004$) and tunnel ($r = -0.87$, $p = 0.001$) scans. Performance on navigation and floor plan drawing, however, did not correlate with hippocampal [^{18}F] MPPF binding asymmetry in the house scan (navigation time $r = 0.4$, $p = 0.13$, navigation spaces $r = 0.4$, $p = 0.12$, floor plan drawing $r = -0.4$, $p = 0.13$) or tunnel scan (navigation time $r = 0.17$, $p = 0.32$, navigation spaces $r = 0.33$, $p = 0.18$, floor plan drawing: $r = -0.38$, $p = 0.14$). Hippocampal volumetric asymmetry did not correlate with any of the spatial memory measures (navigation time $r = 0.45$, $p = 0.19$; navigation

Table 1 Summary of mean [^{18}F] MPPF BP_{ND} in hippocampi, hemispheres, and whole brain during house and tunnel scans including percentage change in BP_{ND} between scans

Subj	House scan Mean [^{18}F]MPPF BP_{ND}					Tunnel scan Mean [^{18}F]MPPF BP_{ND}					Percentage change in BP_{ND} between tunnel and house scans[a]				
	Rhipp	Lhipp	Rhemi	Lhemi	Wbrain	Rhipp	Lhipp	Rhemi	Lhemi	Wbrain	Rhipp	Lhipp	Rhemi	Lhemi	Wbrain
1	0.34	0.45	0.13	0.14	0.13	0.31	0.41	0.13	0.13	0.13	9.6	9.7	N/C	7.7	N/C
2	0.84	0.84	0.27	0.25	0.26	0.75	0.77	0.24	0.23	0.24	12	9.1	12.5	8.7	8.3
3	0.88	0.93	0.22	0.25	0.23	0.90	0.91	0.20	0.23	0.21	−2.2	2.2	10	8.7	9.5
4	0.70	0.64	0.23	0.23	0.23	0.80	0.89	0.24	0.26	0.26	−12.5	−28.1	−4.2	−11.5	−11.5
5	0.90	0.95	0.28	0.30	0.29	0.69	0.73	0.22	0.22	0.22	30.4	30.1	27.3	36.4	31.8
6	1.11	1.04	0.32	0.35	0.35	1.05	0.95	0.31	0.33	0.33	5.7	9.5	3.2	6.1	6.1
7	0.82	0.89	0.32	0.33	0.32	0.96	1.10	0.39	0.42	0.40	−14.6	−19.1	−17.9	−21.4	−20
8	0.53	0.48	0.16	0.19	0.18	0.70	0.68	0.22	0.24	0.23	−24.3	−29.4	−27.3	−20.8	−21.7
9	0.48	0.63	0.15	0.17	0.16	0.66	0.79	0.22	0.20	0.21	−27.3	−20.2	−31.8	−15	−23.8
10	0.76	0.77	0.19	0.21	0.20	0.75	0.85	0.23	0.23	0.23	1.3	−9.4	−17.4	−8.7	−13
Mean	0.74	0.76	0.23	0.24	0.24	0.76	0.81	0.24	0.25	0.25	−2.6	−6.2	−4.2	−4	−4
SD	0.2	0.2	0.07	0.07	0.1	0.2	0.2	0.07	0.08	0.1	N/C	N/C	N/C	−12.5	N/C

Rhipp right hippocampus, *Lhipp* left hippocampus, *Rhemi* right hemisphere, *Lhemi* left hemisphere, *Wbrain* whole brain, *N/C* no change

[a] Percentage change in BP_{ND} between tunnel and house scans was calculated using the following formula: $((V2 - V1)/|V1|) \times 100$, where V1 = mean [^{18}F]MPPF BP_{ND} in tunnel scan and V2 = mean [^{18}F]MPPF BP_{ND} in house scan

Table 2 Details of participants' spatial memory performance

Participant	First task	Nav-time (s)	Nav-space (min = 3)	Obj-loc (max = 23)	Plan-draw (max = 18)
1	Tunnel	69	3	20	18
2	Tunnel	118	3	15	11.5
3	House	69	3	18	18
4	Tunnel	120	3	19	18
5	House	70	3	17	18
6	House	68	3	14	18
7	Tunnel	71	3	18	17
8	House	88	4	14	11
9	Tunnel	69	3	21	18
10	House	49	3	17	18
Mean		79.1	3.1	17.3	16.5
SD		22.97	0.3	2.4	2.8

Nav-time navigation time, *Nav-space* navigation spaces, *Obj-loc* object–location, *min* minimum, *max* maximum

spaces $r = 0.6$, $p = 0.06$; object location $r = 0.01$, $p = 0.97$, floor plan drawing $r = -0.58$, $p = 0.08$).

Performance on the object–location task was the only memory variable to enter the multiple regression model, producing an R^2 of 0.61 for the house scan [$F(1, 8) = 12.45$, $p = 0.008$], and an R^2 of 0.75 for the tunnel scan [$F(1, 8) = 24.47$, $p = 0.001$]. Object–location performance was negatively related to hippocampal [^{18}F] MPPF binding asymmetry in both scans [house scan $\beta = -0.78$, $t(8) = -3.53$, $p = 0.008$; tunnel scan $\beta = -0.87$, $t(8) = -4.95$, $p = 0.001$] (see Figs. 4, 5).

None of the memory measures met the criteria for inclusion when hemispheric [^{18}F] MPPF binding asymmetry was the dependent variable. The absence of a significant contribution is reflected in the first-order correlations. Hemispheric binding asymmetry did not correlate with object location ($r = 0.0001$, $p = 0.99$), navigation spaces ($r = -0.52$, $p = 0.12$), or floor plan drawing ($r = -0.16$, $p = 0.66$) in the house scan, although the contribution of navigation time approached significance ($r = 0.61$, $p = 0.06$). In the tunnel scan, object–location recall made no contribution ($r = 0.14$, $p = 0.7$) to hemispheric binding asymmetry, and neither did navigation time ($r = 0.04$, $p = 0.9$), navigation spaces ($r = -0.12$, $p = 0.75$), or floor plan drawing ($r = -0.24$, $p = 0.51$).

Discussion

This study examined the role of serotonin, mediated by the 5-HT_{1A} receptor subtype, in spatial learning and memory in ten healthy volunteers using [^{18}F] MPPF PET. There was an association between hippocampal asymmetry in [^{18}F] MPPF binding and performance on the object–location task. A lower BP_{ND} in the right versus the left hippocampus was related to better memory performance indicating that reduced right versus left hippocampal 5-HT_{1A} receptor availability enhances object–place associative memory. To the best of our knowledge, there are no previous human studies that show lateralized serotonergic modulation of object–location memory. This finding suggests that

Table 3 Results of ANCOVA comparing asymmetry in hippocampal and hemispheric [^{18}F] MPPF binding in the house and tunnel scans with consideration for participants' spatial memory performance and hippocampal volume asymmetry

Source	*df*	*F* test	*p* value
Hippocampal asymmetry	1	0.13	0.73
Hippocampal asymmetry × Nav-time	1	1.12	0.35
Hippocampal asymmetry × Nav-space	1	0.03	0.87
Hippocampal asymmetry × Obj-loc	1	1.62	0.28
Hippocampal asymmetry × Plan-draw	1	2.04	0.23
Hippocampal asymmetry × Hipp vol asymmetry	1	1.41	0.30
Hemispheric asymmetry	1	0.05	0.83
Hemispheric asymmetry × Nav-time	1	5.92	0.06
Hemispheric asymmetry × Nav-space	1	0.27	0.62
Hemispheric asymmetry × Obj-loc	1	2.67	0.16
Hemispheric asymmetry × Plan-draw	1	1.87	0.23

Nav-time navigation time, *Nav-space* navigation spaces, *Obj-loc* object–location, *Hipp vol asymmetry* hippocampal volume asymmetry, given by right hippocampal volume – left hippocampal volume/whole brain volume

individual variations in the asymmetry of endogenous serotonin release or receptor density contribute to object–location memory. Genetic differences between individuals might contribute to the relationship between task performance and constitutive changes in receptor availability. For example, polymorphisms in the serotonin-transporter-gene-linked polymorphic region (5-HTTLPR) affect 5-HT$_{1A}$ receptor availability (David et al. 2005). In humans (Roiser et al. 2006, 2007) and in primates (Jedema et al. 2010), specific polymorphisms are associated with superior performance on a variety of cognitive tasks, including hippocampal-dependent visual memory tasks.

The ability to learn the topographical configuration of an environment, to find objects successfully, recall previously encountered locations, and navigate through the environment are essential abilities for our day-to-day functioning in a topographical world (finding our way home, finding objects around the house such as keys, etc.). As such, there have been decades of research exploring how environments are represented internally, the key components of these representations, and the brain regions that support them. From the outset it became apparent that object locations, also known as landmarks, play a critical role in spatial learning and memory (Tolman 1948; Lynch 1960). In some theories, landmarks are regarded as the very building blocks of environmental representations (Lynch 1960; Siegel and White 1975). The use of [^{18}F] MPPF PET in the current study to explore this cognitive system in vivo provides preliminary understanding of its neurotransmitter basis. While the study was based on a homogenous group of healthy adult males and controlled procedures were used to eliminate confounding variables that may affect serotonin levels (for example, strict dietary regime, screening for signs of depression and anxiety, and measuring levels of serum tryptophan), our results, in particular the right-left asymmetry association, are hampered by small sample size, and therefore should be interpreted with caution. Further research with a larger group of participants, balanced according to sex is required to enhance generalization of results. The possible existence of task-specificity within the object–location paradigm found elsewhere (Treyer et al.

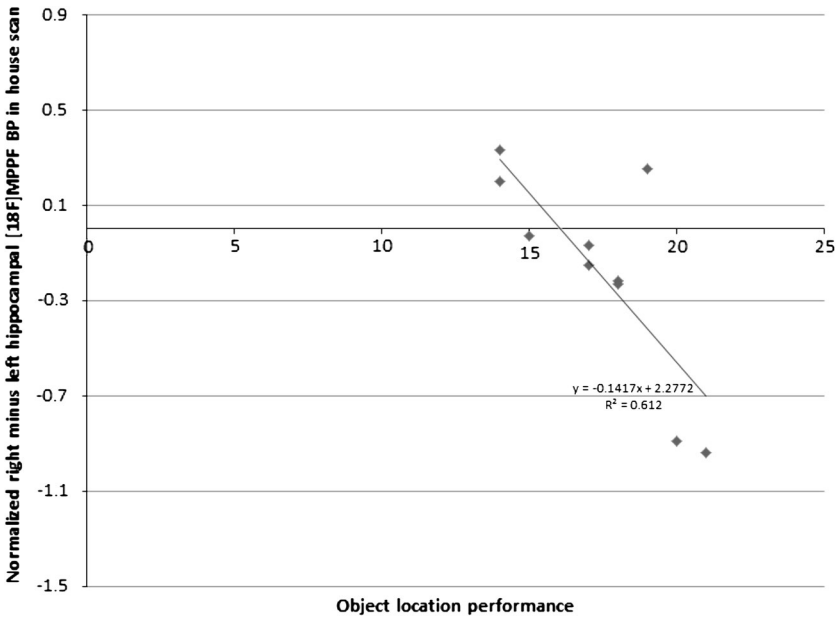

Fig. 4 Relationship between normalized right minus left hippocampal [^{18}F] MPPF binding in house scan and scores on the object–location task

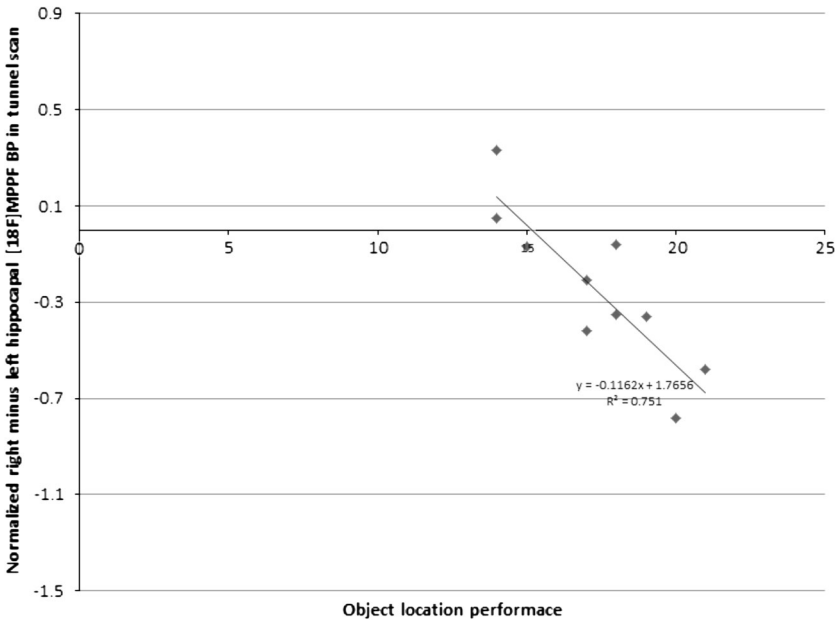

Fig. 5 Relationship between normalized right minus left hippocampal [^{18}F] MPPF binding in tunnel scan and scores on the object–location task

2005; Bellgowan et al. 2009; Saling 2009), calls for future research of this to characterize patterns of serotonergic lateralization at a mesial temporal level.

[^{18}F] MPPF is a selective antagonist at the pre- and post-synaptic 5-HT$_{1A}$-receptors (Thielen et al. 1996), with an affinity for the 5-HT$_{1A}$ receptor (Ki = 3.3 nMol/L) that is comparable to that of serotonin (Ki = 4.7 nMol/L) (Zhuang et al. 1994). A number of animal studies have shown that [^{18}F] MPPF binding is sensitive to endogenous serotonin release (Zimmer et al. 2002; Rbah et al. 2003). In humans, changes in [^{18}F] MPPF binding have been observed when large physiological alterations in serotonin release are expected, such as during sleep as opposed to wakefulness (Derry et al. 2005) or with supraphysiological, pharmacological challenge (for review see Paterson et al. 2010). Variations in [^{18}F] MPPF binding have been linked to several neurological (Truchot et al. 2007; Didelot et al. 2010) and psychiatric disorders (Praschak-Rieder et al. 2004) demonstrating altered serotonin receptor physiology when compared with healthy controls. In our study, 5-HT$_{1A}$ receptor binding did not differ significantly between high- and low-levels of spatial processing. These results are in keeping with the existing human [^{18}F] MPPF literature where large changes in extracellular endogenous serotonin are required to alter [^{18}F] MPPF binding in humans.

The association between right and left asymmetry in hippocampal [^{18}F] MPPF binding and memory for object location was not influenced by wider hemispheric [^{18}F] MPPF binding or by hippocampal volumes as evidence by the absence of significant correlations between right and left asymmetries in hemispheric ligand binding or hippocampal volumetry and the object–location variable. There was suggestion that measures of navigation (navigation time and navigation spaces) are associated with hemispheric binding asymmetry and hippocampal volume asymmetry (respectively), but the relevant correlations fell just short of significance.

The implications of our findings are twofold. First, they suggest that constitutive levels of 5-HT$_{1A}$ receptor availability modulate a fundamental associative component of spatial memory ability. Second, they suggest that this modulatory influence is lateralized. Although we are not able to distinguish between the contributions of changes in total receptor density (comprising unoccupied receptors and those occupied by serotonin) and of changes in fractional occupancy, it is of interest that a stronger memory-modulating effect (on a two-way avoidance shuttle box) was found after injection of 8-OH-DPAT or NAN190 (5-HT$_{1A}$ receptor agonist or antagonist, respectively) in the right CA1 region of the rat hippocampus when compared with the left (Belcheva et al. 1997, 2007).

Navigation and plan drawing were not associated with serotonin receptor density. Object–location memory is heavily dependent on medial temporal lobe structures, particularly the hippocampus (Stepankova et al. 2004; Crane and Milner 2005), and parahippocampal cortices (Owen et al. 1996; Maguire et al. 1998). Navigation, on the other hand, is more dependent on an extended network consisting of the hippocampus, parietal, occipitotemporal, cingulate, and parahippocampal cortices (Aguirre et al. 1996, 1998; Maguire 1997; Maguire et al. 1998; Jokeit et al. 2001). Few studies have involved plan drawing, but these also recruit a distributed network consisting of

parietofrontal (Mellet et al. 2000), as well as mesial temporal regions (Spiers et al. 2001; Glikmann-Johnston et al. 2008). Furthermore, studies examining right and left temporal lobe contributions to navigation (Maguire et al. 1996; Hartley et al. 2003) and plan drawing (Maguire et al. 2003) suggest that these measures are not lateralized. In all likelihood, "there is a dynamic interaction between left and right temporal lobes, depending on task demands" (Saling 2009). The rightward bias consistently seen in response to object–location paradigms (Smith and Milner 1981, 1989; Pigott and Milner 1993; Abrahams et al. 1997, 1999; Bohbot et al. 1998; Burgess et al. 2002; Sommer et al. 2005; Piekema et al. 2006; Doeller et al. 2008) fits well with present findings: in healthy participants, the right hippocampus is particularly involved in memory for object–location associations within an environment; in patients with right mesial temporal lobe epilepsy, performance on object–location tasks tends to be selectively impaired.

Spatial cognition (including spatial memory) is fundamental to survival across the phylogenetic spectrum, and has a much longer evolutionary history than verbal cognition (Ungerleider et al. 1998). Similarly, the serotonergic system is an ancient biochemical control system, profoundly influencing nearly every brain process through its different receptor subtypes (Allman 1999). Our findings suggest a role for serotonin in the lateralized modulation of a basic component of human spatial memory reflecting this long evolutionary trend.

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