NeuroImage: Clinical 11 (2016) 73–80

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Hurt but still alive: Residual activity in the parahippocampal cortex conditions the recognition of familiar places in a patient with topographic agnosia☆

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ARTICLE INFO

Article history:
Received 27 July 2015
Received in revised form 16 December 2015
Accepted 2 January 2016
Available online 8 January 2016

Keywords:
Landmark agnosia
Human navigation
fMRI
Case
Stroke
Hemispheric laterality

ABSTRACT

The parahippocampal cortex (PHC) participates in both perception and memory. However, the way perceptual and memory processes cooperate when we navigate in our everyday life environment remains poorly understood. We studied a stroke patient presenting a brain lesion in the right PHC, which resulted in a mild and quantifiable topographic agnosia, and allowed us to investigate the role of this structure in overt place recognition. Photographs of personally familiar and unfamiliar places were displayed during functional magnetic resonance imaging (fMRI). Familiar places were either recognized or unrecognized by the patient and 6 age- and education-matched controls in a visual post-scan recognition test. In fMRI, recognized places were associated with a network comprising the fusiform gyrus in the intact side, but also the right anterior PHC, which included the lesion site. Moreover, this right PHC showed increased connectivity with the left homologous PHC in the intact hemisphere. By contrasting recognized with unrecognized familiar places, we replicate the finding of the joint involvement of the retrosplenial cortex, occipito-temporal areas, and posterior parietal cortex in place recognition. This study shows that the ability for left and right anterior PHC to communicate despite the neurological damage conditioned place recognition success in this patient. It further highlights a hemispheric asymmetry in this process, by showing the fundamental role of the right PHC in topographic agnosia.

1. Introduction

Neuroimaging studies in healthy participants have pointed out the specificity of the region of the posterior parahippocampal cortex (PHC), since the discovery of its high sensitivity to places and buildings as opposed to other stimulus categories (Aguirre et al., 1998; Epstein and Kanwisher, 1998). This place-sensitive area supports the coding of the spatial layout of scenes, a necessary step before their encoding and later recognition (review in Epstein, 2008), and a challenging task given the number of places that we cross every day. A related function is the coding of objects-place associations, particularly on the right hemisphere (Owen et al., 1996). However, the contribution of PHC to the visual recognition process itself remains unclear (Sewards, 2011; Spiers and Maguire, 2007), since previous neuroimaging studies yielded mixed findings in neurologically healthy participants (Epstein, 2008; Epstein et al., 2007), see also (Epstein and Higgins, 2007) and supported a clearer role of the retrosplenial complex (RSC) in this function (Epstein, 2008; Spiers and Maguire, 2007; Sugiura et al., 2005). Thus, it is uncertain to which extent the PHC is implicated during place recognition, beyond its role in perceptual processing.

More insights may be gained with the study of brain-lesioned patients, by determining whether a target area is necessarily required for place analysis, or whether this function can be shouldered by a any other brain region. Topographic agnosia or disorientation is a neurological condition in which patients become unable to find their way in the environment following a focal brain damage (Aguirre and D'Esposito, 1999; De Renzi, 1982). In a specific form of this disorder called landmark agnosia (Aguirre and D'Esposito, 1999), a lesion around the right posterior PHC — the region of the right anterior lingual gyrus/PHC/medial fusiform gyrus — usually impairs spatial orientation in familiar environments, but spares the ability to describe them (e.g. Busigny et al., 2014; Habib and Sirigu, 1987; Landis et al., 1986; Takahashi and Kawamura, 2002). This condition arises as a failure to recognize typical landmarks known before the lesion occurrence (Incisa della Rocchetta et al., 1996; Landis et al., 1986; Pallis, 1955; Rainville et al., 2005; Whiteley

☆ Place recognition in topographic agnosia.

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http://dx.doi.org/10.1016/j.nicl.2016.01.001

and Warrington, 1978), disrupting the interaction between perceptual and memory processes (Brunsdon et al., 2007). However, the specific study of the relationships between landmark agnosia, place familiarity, and the location of the lesion in patients with peri-hippocampal lesions has yielded mixed findings, with patients either showing preserved (Habib and Sirigu, 1987; Takahashi and Kawamura, 2002) or altered recognition of known places (Habib and Sirigu, 1987; Hecaen et al., 1980; Incisa della Rocchetta et al., 1996; Pallis, 1955; McCarthy et al., 1996; Takahashi and Kawamura, 2002; Whiteley and Warrington, 1978). A common feature of patients with preserved topographic abilities in familiar environments is the sparing of visual areas located posterior to the PHC (review in Sewards, 2011). On the other hand, disconnection following a focal lesion of the PHC may play a role in this particular neurological disorder (Ffytche et al., 2010; see also Kleinschmidt and Vuilleumier, 2013). Indeed, successful navigation in familiar environments not only involves the PHC, but also a wide range of occipital, medial parietal, temporal and frontal areas (meta-analysis in Boccia et al., 2014). Thus, a disconnection between the right PHC and other areas of this network may also play a role in this disorder.

Our goal was to investigate place recognition mechanisms in a stroke patient with damage including mainly the right PHC/hippocampus and part of the medial fusiform cortex. The location and extent of the lesion caused a severe prosopagnosia and a partial landmark agnosia (see Hecaen et al., 1980; McCarthy et al., 1996; Pallis, 1955; for similar cases of combined prosopagnosia and topographic agnosia following analogous lesions), providing the unique opportunity to disentangle successful versus unsuccessful place recognition mechanisms in the same participant. Photographs of personally familiar and unfamiliar places were displayed during event-related fMRI of an incidental categorization task (van Assche et al., 2016). An additional post-scan visual recognition test allowed classifying recognized versus unrecognized familiar places. We first examined the functional integrity of the right and left PHC during basic visualization of places, checking that the left but not right PHC region remained functionally active after the lesion. Then, we assessed the involvement of the PHC during the analysis of recognized (familiar) scenes as compared with unrecognized (familiar or unfamiliar) scenes by means of direct comparison, to specifically probe for brain processes associated with overt place recognition. Moreover, task-based functional connectivity was performed to illuminate the role of functional interactions during overt place recognition. If the PHC plays a fundamental role in this process, then it should be more recruited for recognized places in the patient, either in the contralesional and/or ipsilesional side. If not, the patient should show compensatory activity elsewhere during the recognition process.

2. Material and methods

2.1. Case report

Patient PR is a right-handed male, 68 years of age at the time of the present evaluation. He graduated from a university-level business school and is a businessman in the finance domain. One year prior to the current study, he had been admitted to the Neurology Unit of the Geneva University Hospital following a first minor cardio-embolic ischemic stroke involving the right parietal cortex and the occipital cortex bilaterally. The neurological status did not reveal any particular visual field defect. On this occasion, he underwent a series of standard neuropsychological tests assessing language, praxis, executive, memory, attention and visual-perceptual abilities (see *Supplementary Table 1*). This first neuropsychological testing revealed signs of associative visual agnosia, difficulties in verbal and visual episodic memory, and a mild executive impairment. All other assessed cognitive functions were unimpaired. In a second evaluation one month later (*Supplementary Table 1*), only verbal working memory difficulties and a mild executive impairment (inhibition) were observed. Signs of associative visual agnosia and verbal episodic memory difficulties had disappeared. Concerning visual episodic memory, his performance improved and was within the normal range, however from a clinical standpoint, immediate recall was estimated to be insufficient given his high educational level. At this time, PR continued working full-time as a business expert.

Ten months later, the patient was admitted again in the same unit due to unprecedented and acute visual complaints consisting in an inability to recognize close family members as well as slight difficulties in orientating himself in his neighborhood. The neurological status was normal, except a left superior quadranopsia which did not affect the following testing. During a third neuropsychological examination (*Supplementary Table 1*), PR was alert and fully cooperative. His expression was fluent, and his verbal comprehension intact. No visuo-constructive apraxia, neglect, or any other generalized visuo-spatial impairment was observed. Verbal episodic memory was intact. With reference to executive and attentional functions, PR showed mild difficulties in cognitive flexibility and selective attention (Bells' test). With regard to visuo-perceptive abilities, signs of associative agnosia were observed (Visual Object and Space Perception Battery; Birmingham Object Recognition Battery). For the evaluation of prosopagnosia, we used a standard battery from the Geneva University Hospital in addition to standard neuropsychological testing (Benton Face Recognition Test). The patient performed significantly worse than a control group (t-test Crawford & Garthwaite, 2007) at the recognition of famous faces (patient = 54% correct; control group = 77 ± 12% correct; $p < 0.01$), famous faces occupation sorting (matching semantic and visual inputs; patient: 56% correct; control group: 90 ± 9% correct; $p < 0.01$), gender identification (patient = 66%; control group = 92 ± 5% correct; $p < 0.01$), and at a short version of the Jane task (patient: 50% correct; control group = 80 ± 15% correct; $p < 0.01$; Mondloch et al., 2002; *Supplementary Table 2*).

Concerning the topographical domain (Table 1), the patient presented some difficulties in the identification of famous buildings (hesitation, latency, utilization of verbal strategies to facilitate the identification), and a significantly impaired ability to recognize places that are highly familiar for him (26/40 recognized familiar places; see post-scan procedure and results section). In contrast, tests assessing spatial representations were intact as judged by his normal performance on tests evaluating specific spatial abilities (i.e. landscape perspective test, cognitive map recall test, map drawing). Moreover, his capacity to navigate in the hospital was adequate (using both verbal and spatial strategies). In sum, PR presented a mild landmark agnosia, a severe prosopagnosia, signs of associative agnosia and very mild executive and attentional difficulties.

Table 1
Neuropsychological assessment of the patient's topographical abilities (impaired performance in bold).

Landmark identification	
Identification of famous buildings	**19/23, hesitations, latencies**
Egocentric space	
Landscape Perspective Test[1]	
Rotational movement	6/7
Translational movement	4/6
Road-Map Money test[2]	32/32
Allocentric space	
Localization of landmarks on a map	Ok
Spatial cognition about familiar environments	
Identification of personally familiar places (see results section)	**26/40**
Familiar egocentric space: Route description	Ok
Familiar allocentric space:	
Cognitive Map Recall test[1]	17/24
Map and route drawing	Ok
Spatial cognition about unfamiliar environments	
Navigational abilities in the hospital	Ok

[1] Descloux et al. (2015).
[2] Money et al. (1965).

Structural MRI revealed an acute occipito-temporal stroke involving the right PHC along the posterior–anterior axis, the posterior part of the hippocampus and the medial portion of the adjacent fusiform gyrus, sparing the most lateral part of the right fusiform gyrus (Fig. 1). The damage was compatible with a lesion of the right parahippocampal place-sensitive area and an impaired ability to recognize personally familiar places in our experiment.

2.2. Participants

Recognition performance and brain activity in the patient was compared with a group of 6 elderly controls (3 males; 5 right-handed; mean age = 68.8 ± 2.1 years old; mean education years = 16.8 ± 2.9), without previous or current neurological or psychiatric disease. This protocol was approved by the Ethic Central Commission of the University Hospital of Geneva. Informed consent was obtained from the participants following the ethical principles of the Declaration of Helsinki.

In this study, we followed strictly the same procedure as described previously (van Assche et al., 2016).

2.3. Pre-scan selection of personally familiar and unfamiliar place stimuli

A few weeks before the fMRI session, the patient was asked to enumerate places he knew well in and around Geneva, as well as to describe some typical routes in the city which he used to take several times a week. His descriptions followed a route-based strategy describing how to go from one place/street to the next to reach a particular destination, and included street names. We selected these personally relevant locations with Google Street view and used them as stimuli for the familiar places condition in the fMRI experiment. The same procedure was applied for the control group.

2.4. Post-scan recognition test

After scanning, the patient was submitted to a self-paced surprise place recognition test. All photographs of familiar places were presented again. The patient had to indicate the name and/or the location of the place shown. A place was considered as *Familiar Recognized* whenever its name was correctly retrieved, or at least when it was correctly localized. In all other cases, the familiar place was classified as *Familiar Unrecognized*. The same procedure was conducted in the control group.

2.5. MRI procedure

2.5.1. Activation task

We used an incidental categorization task, which required no explicit recognition abilities (van Assche et al., 2016). Photographs of familiar and unfamiliar places were displayed during fMRI scanning. The participant had to indicate whether the places shown in the photographs were “lively” (e.g. imagining noise or traffic jam) or “calm” compared with a place of reference. Familiar places in the city were named as the reference. Photographs were presented in series of four, shown each in turn during 2 s at the centre of the screen (Fig. 2). Each picture of a given series was a particular viewpoint of the same place. In addition to personal familiarity with places, the succession of the viewpoints within each series was manipulated. In the *Sequential Order* of presentation, the sequence of four pictures could mimic a point of view similar to one turning gradually his head from left to right or the reverse.

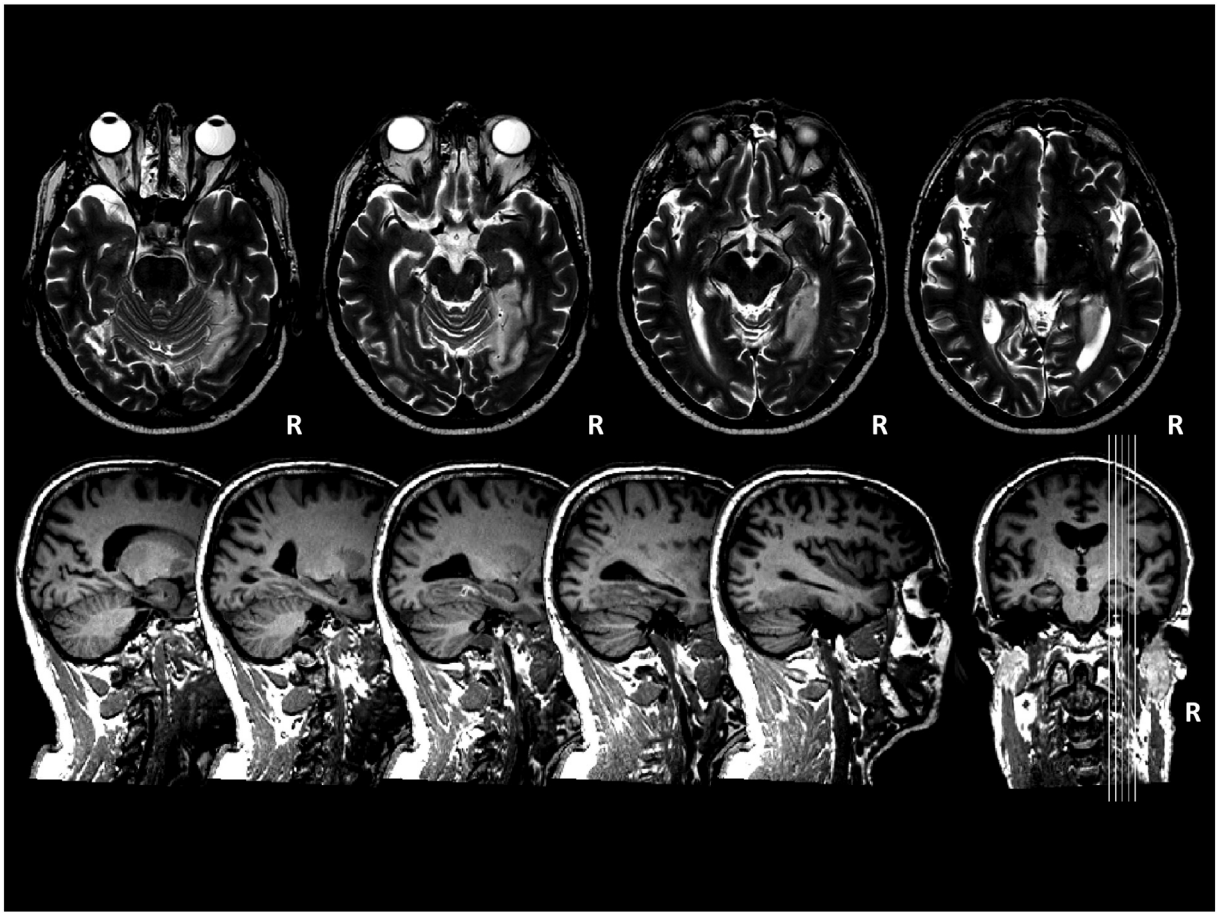

Fig. 1. T2-weighted MRI (*top row*) and T1-weighted MRI (*bottom row*) of the stroke patient (neurological convention). The right occipito-temporal stroke damaged the right parahippocampal cortex along the posterior–anterior axis, posterior part of the hippocampus and medial part of the fusiform gyrus, sparing the most lateral part of the fusiform gyrus and the anterior medial temporal lobe (including the hippocampus and perirhinal cortex). R = Right side.

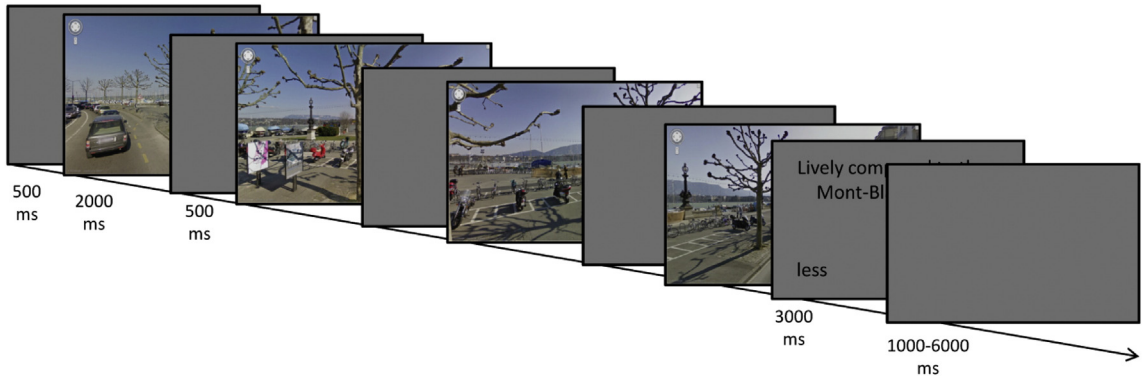

Fig. 2. Categorization task. At each trial, viewpoints of familiar or unfamiliar places were presented in series of four, shown each in turn during 2 s at the center of the screen. Each picture of a given series was a different viewpoint of the same place.

Alternatively, in the *Scramble Order* of presentation, pictures were presented in a non-progressive order. There were also two unfamiliar control conditions, one in which the same picture was repeated four times within a series (*repeated* condition), the other in which all pictures of a series were taken from different places (*different* condition). The participant indicated his categorical judgment after each series of four pictures, by pressing one of two buttons of a response box at the end of each series. There were 20 trials per condition.

2.5.2. Equipment

Data were acquired on a 3T MRI system (Trio TIM, Siemens, Germany) with a 12 channel head coil. Visual stimuli were back projected on a screen (E-prime 1.0, Psychology Software Tools Inc., Pittsburgh). Head movements were prevented using an ergonomic air head cushion.

2.5.3. Scanning protocol

Whole brain functional images were collected using a susceptibility weighted EPI sequence (TR/TE = 1810/30 ms; flip angle = 90 degrees; PAT factor = 2; FOV = 255 mm; matrix size = 64 × 64 pixels). 32 transversal slices were acquired in an interleaved descending manner (slice thickness = 4 mm, interslice gap = 1 mm, voxel size = 4 mm isotropic). High-resolution anatomical images were acquired using a T1-weighted, 3D sequence (MPRAGE; TR/TI/TE = 1900/900/2.32 ms; flip angle = 9 degrees; voxel size = 0.9 mm isotropic; 256 × 256 × 192 voxels).

2.6. Imaging data analysis

Anatomical volumes of the patient were normalized to a T1 template of elderly individuals (Rorden et al., 2012) using a lesion cost function masking (Brett, Leff, Rorden, & Ashburner, 2001). The lesion was manually delineated to create a mask that excluded the lesion from the non-linear transformation during the normalization step.

Functional images were pre-processed and analyzed using a standard procedure implemented in Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for NeuroImaging London). All volumes were first temporally realigned and resampled to the acquisition time of the middle slice. The data were then spatially realigned to the first slice. The anatomical volumes were spatially coregistered to the mean functional image resulting from the spatial realignment. Functional images were then normalized to the MNI EPI template, resampled to 3 mm isotropic voxels and smoothed with a Gaussian kernel (8 mm full-width at half-maximum).

In the patient, data were modeled according to the General Linear Model (GLM) which modeled all conditions across recognition states and head movements. In controls, the GLM modeled all task conditions, plus occasionally unrecognized places (as described in van Assche et al., 2016), as well as head-movements. Each regressor was convolved to a canonical hemodynamic function. A high-pass filter (cut off = 128 s) and a first-order autoregressive function were applied to account for temporal autocorrelation. Statistical parametric maps (t-maps) were obtained by comparing each condition with baseline activity. Functional connectivity analyses were performed using the generalized PPI approach (McLaren et al., 2012). Whole-brain analyses were performed on a voxel-wise basis, at a threshold $p < 0.001$ uncorrected (minimal cluster size = 5) for within-subject comparisons and $p < 0.005$ (minimal cluster size = 10) for between-subject comparisons, unless specified differently.

For the sake of clarity and simplicity, only data related to the manipulation of familiarity are presented in this paper.

2.7. Scene localizer scan

The response of the right scene-sensitive area around the PHC was investigated in the patient, in order to check how brain responses to pictures of unfamiliar places were impacted by the lesion. Four blocks of scenes, buildings or scrambled stimuli were presented in alternation. In each block, 18 stimuli of the same category were displayed for 750 ms with an interval of 500 ms. The patient performed a one-back task in which he had to press a right button at each stimulus repetition. The scanning parameters were identical as in the main experiment. For the analyses, the GLM modeled all conditions plus head-movements. The region of the posterior PHC was functionally localized using the Scenes > Scrambled Scenes t-contrast at the whole-brain level at a liberal threshold ($p < 0.05$ uncorrected, $k > 5$), in order to maximize the possibility to observe activity around the lesion site.

3. Results

3.1. Behavioral data

First, recognition performance in the patient confirmed a partial agnosia for personally familiar places despite the extended lesion. He was able to visually recognize 26 out of 40 familiar places (65% correct). His recognition abilities still contrasted with the performance achieved by the Control group (97.92% correct recognitions; SD = 1.88), and this difference was statistically significant (one-tailed $p < 0.001$; effect size = 17.491; 95% CI = 7.095–28.038; Crawford and Garthwaite, 2007).

3.2. Scene localizer

Consistent with the lesion site in the right hemisphere, the patient showed activation of the left but not right scene-sensitive area, around the posterior PHC/fusiform gyrus (MNI coordinates: peak 1: -21, −40, −2, t = 2.37; peak 2: -24, −55, −14; t = 2.29; cluster size: 100 voxels; Fig. 3). In the right temporal lobe, brain activity was instead observed laterally to the lesion site, much more laterally than in the left

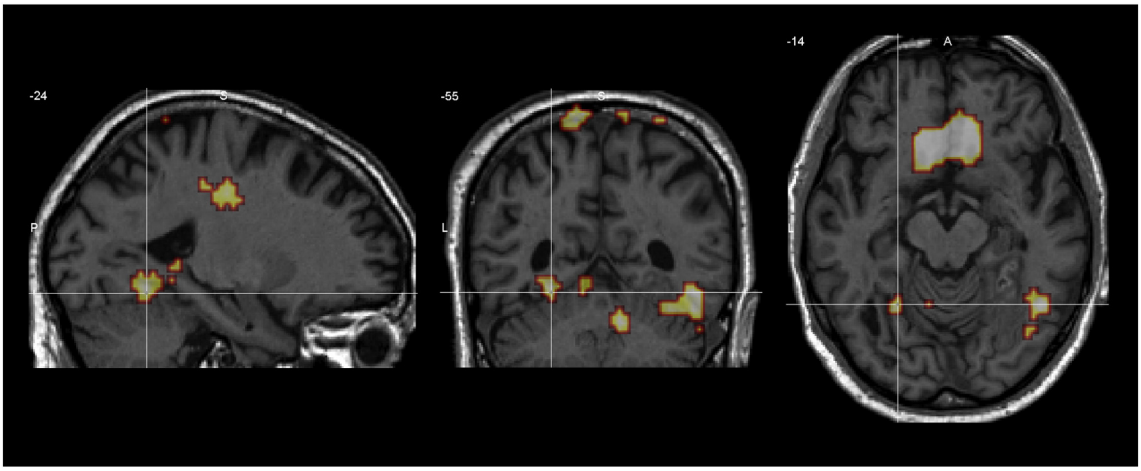

Fig. 3. The Scenes > Scrambled Scenes contrast shows that only the left posterior parahippocampal cortex remains functionally active and sensitive to pictures of places after the right occipito-temporal stroke ($p < 0.05$ uncorrected). Instead, activity in the right side is observed laterally to the lesion. Brain activity is superimposed on the anatomical T1 of the patient.

hemisphere (MNI coordinates: peak 1: 45, −55, −14; t = 2.44; peak 2: 45, −55, −23, t = 2.22; cluster size: 111 voxels). This confirms that the lesion site has become functionally irresponsive to randomly presented places. However, the lateral activity in the right side might indicate a form of functional reorganization related to place processing or the mobilization of other processes to perform this function.

3.3. Imaging data

We first compared brain activity in patient and controls, to check the functionality of the lesion area and more globally, to highlight areas of hypo- and/or hyper-activity in the patient during the visualization of personally familiar and unfamiliar places.

3.3.1. Patient – Control comparison

3.3.1.1. Familiar places. For Familiar places, the Controls > Patient contrast notably revealed differential activity in the right PHC, including around the lesion site (including in the anterior and posterior portions of the lesioned tissue), as well as in the right posterior fusiform gyrus region ($p < 0.005$; Table 2, *upper panel*). The reverse contrast (Patient > Controls) revealed enhanced activity in the anterior insula bilaterally in the patient, as well as right temporo-parietal junction, left precentral and middle cingulate gyrus.

3.3.1.2. Unfamiliar places. The Controls > Patient comparison again revealed decreased activity in the right posterior fusiform region in the patient (including in the posterior portion of the lesioned tissue). The reverse contrast, Patient > Controls, showed the same brain areas as for familiar recognized, with the additional recruitment of the right opercular IFG and left orbital IFG ($p < 0.005$; Table 2, *lower panel*).

The comparison of brain activity between the patient and the control group thus confirms that the lesion area was systematically hypo-activated in the patient, for both familiar and unfamiliar places.

3.3.2. Familiar place processing according to recognition in the patient

A first analysis compared brain activity for Recognized places against Unrecognized and Unfamiliar places jointly, to characterize the key areas involved in place recognition irrespective of place familiarity. This comparison (Recognized > (Unrecognized + Unfamiliar)) not only revealed an implication of the fusiform gyrus, inferior temporal gyrus and lingual gyrus in the intact side, but also an involvement of the PHC in the anterior portion of the lesion ($p < 0.001$; Fig. 4, *top*; Table 3, *upper panel*). This cluster of activity encompassed both lesioned and perilesional (spared) tissue. The bilateral orbital inferior frontal gyrus (IFG), cerebellum, and left middle orbito-frontal cortex (midOFC) were additionally recruited.

To better understand the association between right PHC and successful recognition, we investigated its functional connectivity by defining it as a seed region (sphere, 10 mm radius) in the following PPI analysis. In the Recognized > Unrecognized comparison, functional coupling increased between the right anterior PHC in the lesion side, and the left anterior PHC in the intact side ($p < 0.001$, Table 3, *middle panel*). Interestingly, this region was located in the homologous region of the lesion site, adjacent to the one observed in the scene localizer (Fig. 4, *bottom*). Importantly, increased functional coupling was also observed with the infero-temporal cortex bilaterally, and right dorsolateral PFC. In marked contrast with the previous comparison, the Recognized > Unfamiliar contrast (PPI analysis) revealed enhanced coupling between the right anterior PHC and the left cerebellum only, without any coupling with the left PHC. Altogether, the findings indicate a

Table 2
Activation peaks (MNI peak coordinates) for the comparison between Controls and the Patient for Familiar Recognized places (*upper panel*) and Unfamiliar places (*lower panel*); $p < 0.005$ uncorrected, minimal cluster size = 10. L = Left, R = Right, PHC = parahippocampal cortex, IFG = inferior frontal gyrus.

		MNI coordinates			T value	Cluster size
		x	y	z		
Familiar Recognized: Patient vs. Controls						
Controls > Patient						
R	Cerebellum	24	−37	−26	8.515	20
	PHC	24	−40	−14	6.562	
R	Inferior occipital/posterior Fusiform gyrus	42	−64	−14	7.236	31
Patient > Controls						
R	Temporo-parietal junction	45	−22	7	7.534	24
R	Anterior Insula/Putamen	33	11	−11	13.866	48
L	Anterior Insula	−30	11	7	7.733	49
L	Precentral Gyrus	−45	−7	40	6.959	17
L	Middle cingulate gyrus	−9	20	34	5.742	10
Unfamiliar: Patient vs. Control						
Controls > Patient						
R	Posterior fusiform gyrus	27	−70	−8	5.784	28
Patient > Controls						
R	Putamen/Anterior insula	21	14	−5	15.771	100
L	Anterior insula/Putamen	−27	14	7	7.793	23
L	Posterior insula	−36	−22	−8	5.892	11
R	opercular IFG	30	8	34	9.067	16
L	orbital IFG	−39	20	−14	6.303	16
L	Postcentral gyrus	−48	−7	40	6.425	10
L	Middle cingulate gyrus	−18	−19	40	12.583	15

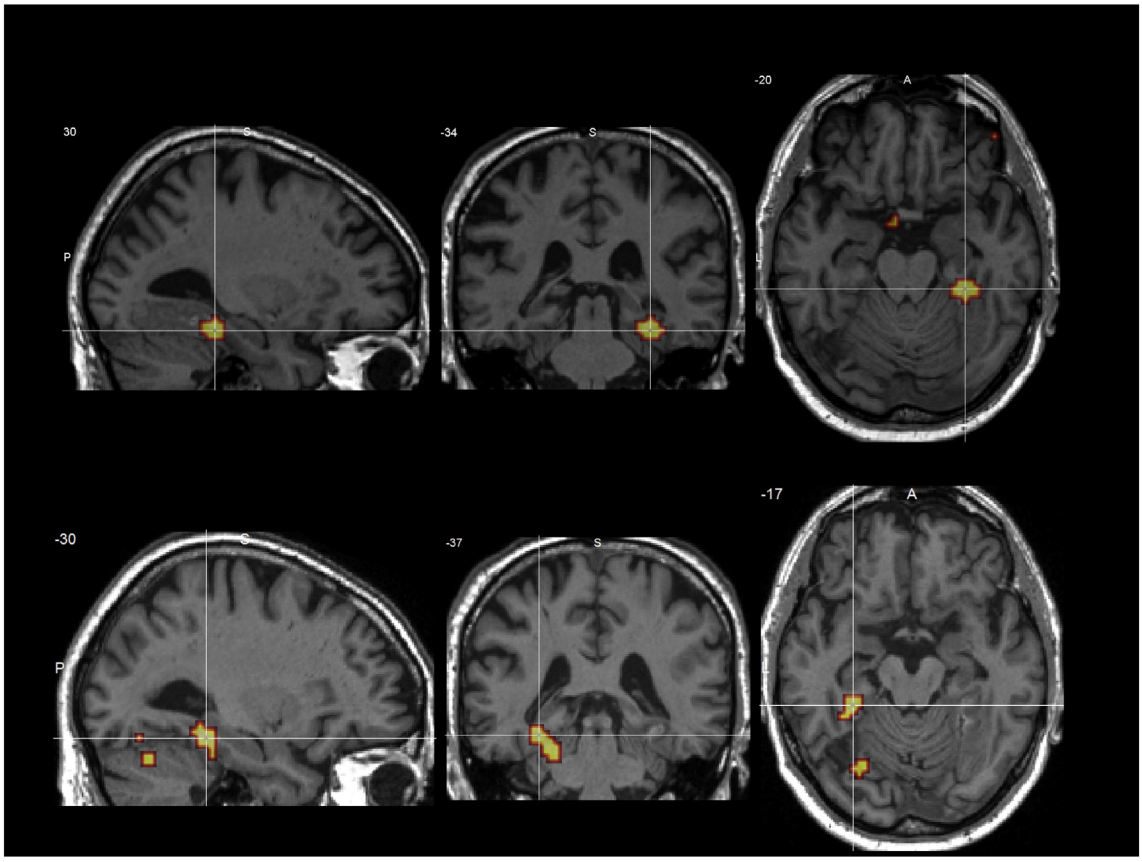

Fig. 4. *Top*. The region of the right parahippocampal cortex (PHC) located in the anterior portion lesion site activates for recognized familiar places ($p < 0.001$). MNI peak coordinates: 30, −34, −20. Brain activity is overlaid on the normalized anatomical T1 of the patient. *Bottom*. Functional connectivity analysis showing enhanced functional coupling between the right PHC in the lesion side (seed region) and left PHC in the intact side for the comparison between recognized and unrecognized familiar places ($p < 0.001$; MNI peak coordinates: 30, −37, −17).

crucial contribution of the anterior PHC in both hemispheres in the recognition of familiar places.

We next compared activity between recognized and unrecognized familiar places with standard contrasts in the patient, to isolate the brain areas enabling visual recognition in the case of personally familiar places. The Recognized > Unrecognized places comparison globally revealed more left-sided activity, with activations in bilateral middle occipital gyri, left cuneus, RSC, inferior parietal lobule (IPL), and right lingual gyrus ($p < 0.001$; Table 3, *lower panel*). Finally, for the reverse contrast (Unrecognized > Recognized), increased activity was observed in the left fusiform gyrus and bilateral orbital gyrus ($p < 0.005$).

To summarize, the right anterior PHC was clearly activated when personally familiar places were recognized, indicating a crucial implication in the analysis of personally familiar places. This region showed increased functional connectivity with the anterior PHC in the contralesional side for recognized compared with unrecognized familiar places. Moreover, joint recruitment of visual areas, left occipito-parietal, left retrosplenial and anterior PFC differentiated between successfully and unsuccessfully recognized places in the patient during the display of familiar information.

3.3.3. Familiar vs. unfamiliar places in controls

The Familiar > Unfamiliar places contrast revealed a widespread network of activity, including postero-medial areas bilaterally, left PHC, bilateral lateral temporal areas and VMPFC (see *Supplementary Table 3* and *Supplementary Fig.* 1; $p < 5 \times 10^{-4}$). These findings are in line with our previous data obtained in a group of young participants (van Assche et al., 2016).

4. Discussion

We studied a patient with an extended lesion in the right HC/PHC/medial fusiform gyrus, to investigate the functional role of the PHC in the context of a quantifiable landmark agnosia. This represented a unique opportunity to characterize the brain areas that are necessarily involved in overt place recognition. First, a comparison of brain activity with controls indicated ubiquitous hypo-activation of the right PHC for both familiar and unfamiliar places, confirming that the right PHC was dysfunctional. Secondly, the possibility to access place identity explicitly was associated with increased activity in the right ipsilesional PHC, in a region overlapping with the anterior portion of the lesion site, as well as left fusiform and lingual gyrus in the intact side. Crucially, for personally familiar places, functional connectivity was increased between the PHC in the lesion (right) side, and the PHC in the contralesional side. This last region was located in the homologous region of the lesion in the healthy side, anterior to a scene-sensitive parahippocampal region observed in an independent localizer. Moreover, neural correlates of place recognition were observed in a set of areas comprising bilateral visual areas, the RSC and inferior parietal lobule in the intact hemisphere, and the right IFG.

A key result was the finding of residual activity in the PHC on the lesion side, together with the recruitment of the fusiform gyrus in the intact side, when familiar places were recognized and despite the lesion. This suggests that the right PHC is mandatory in the processing stream leading to visual place recognition. This finding is in accordance with previous lesion studies highlighting the fundamental role of the right PHC in spatial memory (Aguirre and D'Esposito, 1999; Bohbot et al., 1998; Ploner et al., 2000), as well as clinical descriptions of much

Table 3
Upper panel: Activation peaks (MNI peak coordinates) for Recognized places in patient PR, characterizing brain activity associated with successful recognition irrespective of place familiarity ($p < 0.001$ uncorrected). *Middle panel*: Activation peaks of the PPI analysis with right anterior PHC as seed region (sphere, 10 mm radius; $p < 0.001$ uncorrected, minimum cluster size = 20 voxels). *Lower panel*: Activation peaks for recognized compared with unrecognized places in the patient, highlighting the brain areas supporting the recognition of familiar places ($p < 0.001$ uncorrected).L = Left, R = Right, PHC = parahippocampal cortex, IFG = inferior frontal gyrus, RSC = retrosplenial complex.

		MNI coordinates			T value	cluster size
		x	y	z		
Familiar Recognized > (Unrecognized + Unfamiliar)						
R	PHC	30	−34	−20	4.19	36
L	posterior Fusiform gyrus	−36	−58	−11	4.73	24
L	anterior Fusiform gyrus	−33	−19	−32	3.59	6
L	Lingual gyrus	−12	−43	−5	3.53	8
L	Inferior temporal gyrus	−48	−43	−26	4.46	6
R	Cerebellum	15	−49	−38	4.38	86
L	Superior orbital gyrus	−9	59	−14	3.88	6
L	orbital IFG	−42	44	17	4.33	14
R	orbital IFG	48	47	−17	4.78	24
Functional connectivity: right PHC as seed						
Recognized > Unrecognized						
L	Posterior PHC	−30	−37	−17	3.91	151
L	Inferior temporal gyrus	−39	−22	−26	3.66	
L	Cerebellum	−24	−46	−35	3.65	
R	Inferior temporal gyrus	57	−13	−23	4.15	21
R	Cerebellum	12	−85	−41	4.01	20
R	Frontal pole	15	65	22	3.72	37
Recognized > Unfamiliar						
L	Cerebellum	−9	−85	−41	3.93	48
R	Middle frontal gyrus	48	32	28	3.85	43
R	triangular IFG	57	23	34	3.42	
Familiar Recognized > Unrecognized						
L	Cuneus	18	−103	13	3.46	9
L	Middle Occipital Gyrus	−36	−82	13	3.93	30
R	Middle Occipital Gyrus	39	−76	10	3.61	27
R	Lingual Gyrus	9	−82	−5	3.88	54
L	Middle Occipital Gyrus/IPL	−33	−91	31	3.62	9
L	RSC	−15	−55	10	3.67	26
L	Lateral midOFC	−30	53	−8	3.58	8
Familiar Unrecognized > Recognized						
L	Fusiform gyrus	−42	−67	−14	2.948	5
L	Superior orbital gyrus	−15	59	−14	3.231	11
R	Mid-orbital gyrus	12	53	−8	2.960	24

more severe landmark agnosia following brain damage in this area (e.g. Aguirre and D'Esposito, 1999; Busigny et al., 2014; Habib and Sirigu, 1987; Landis et al., 1986; Takahashi and Kawamura, 2002). Nonetheless, our results go beyond, by specifying a neural mechanism for this type of agnostic disorder. Indeed, a related and important result was the increased functional connectivity between the PHC in the lesioned tissue and the PHC in the intact side associated with the recognition of personally familiar information (Recognized > Unrecognized contrast). This was not the case when looking at the effect of familiarity (Recognized > Unfamiliar contrast). This left anterior PHC region was located close to a functionally preserved place-sensitive area shown to be functionally preserved in a functional localizer, and homotopic to the lesion site.

Together with adjacent occipito-temporal structures, the posterior aspect of the right PHC is known to form a functional complex dedicated to the analysis of the spatial layouts of scenes (Epstein, 2008). Moreover, it has been suggested that the visuo-spatial function of posterior PHC contrasts with a memory-related function in more anterior sites within this region (Aminoff et al., 2013; Epstein, 2008), in line with recent fMRI data highlighting an anterior–posterior functional segregation expressed by greater functional connectivity with occipital and retrosplenial areas respectively (Baldassano et al., 2013; Nasr et al., 2013). Our findings are in accordance with this proposal. Interestingly, the PHC is involved in the reinstatement of specific episodic memories triggered by single stimuli previously paired with scenes (Hayes et al., 2007; Staresina et al., 2012). Such anterior/posterior PHC interactions may perhaps not be necessary in case of verbal instead of visual stimulation (Willment and Golby, 2013); but see (Kennepohl et al., 2007), as this rather depends on the hippocampal complex in the left side (Burgess, 2002) and/or top-down influences by prefrontal cortex (Preston and Eichenbaum, 2013). Thus, it may be hypothesized that the ability to access place identity in the context of landmark agnosia is conditioned by the capacity for scenes, after their visual processing in the posterior PHC, to activate reinstatement of personal and/or semantic memories in a more anterior memory-related region of PHC.

The study of a patient with unilateral brain lesion also allowed investigating whether the right and left PHC are equally involved in place recognition. Because the implication of the right PHC was predictive of recognition success in this patient, the data suggest a preponderant role of the right PHC in this process. Further studies are however required to understand whether this specific region is specialized in the retrieval of scene context (e.g. Aminoff et al., 2013), the recognition of objects in scenes (Hayes et al., 2007; Martin et al., 2013), or both (Harel et al., 2013). In addition, a gradient from abstract to concrete object response has been described in the PHC (Baldassano et al., 2013). Here, the patient notably failed to recognize familiar places when they lacked salient or unique landmarks, as described in Mendez and Cherrier (2003), that is, when the he was unable to analyze spatial configurations properly. Moreover, the right PHC showed increased functional coupling with the inferior temporal gyrus bilaterally, known for its role in visual object recognition at the terminal portion of the ventral pathway (Mishkin et al., 1983). Thus and despite pathological scores at object recognition as measured by conventional neuropsychological tests, the experimental data suggest that object recognition problems do not fully account for the topographic agnosia here.

Finally, another finding was that successful place recognition in the patient was associated with the recruitment of a distributed network beyond PHC, implicating visual occipito-temporal areas bilaterally, the left RSC, and lateral midOFC. The RSC is particularly known to be strongly sensitive to place familiarity (Epstein, 2008; Sugiura et al., 2005; van Assche et al., 2016) and involved during mental navigation in a familiar environment (Ino et al., 2002; Rosenbaum et al., 2004). Also, previous work strongly implicates visual areas in patients with deficits of topographical memory (Aguirre and D'Esposito, 1999; Busigny et al., 2014; Takahashi and Kawamura, 2002). A similar network of occipito-temporal and parieto-medial areas was recently reported to be strongly mobilized during the visualization of familiar environments in healthy participants (Boccia et al., 2014; Nemmi et al., 2015). Our data corroborate these findings, by showing similar key areas at work in a patient with dysfunctional right posterior hippocampal complex.

4.1. Limitations of the study

The data may be limited by the possibility to generalize the current patient's functioning to similar patients with occipito-temporal lesions. Many factors may modify brain functioning after a lesion, such as the time between the infarct and the study, age of the patient or extent of the lesion. Nonetheless, the data are in line with previous reports of landmark agnosia. Moreover, because prosopagnosia and landmark agnosia were not equally affected in this patient, it was not possible to reliably assess whether compensatory processes that accompany the recognition of familiar places also extend to other stimulus categories such as faces. More studies are necessary to better understand the role the intact hemisphere can play in preserved processes.

5. Conclusions

In summary, the study of a patient with a mild landmark agnosia due to right occipito-temporal lesion has revealed the fundamental role of

the right PHC in the analysis of familiar places that leads to recognition. Importantly, successful recognition was associated with increased functional connectivity between both anterior PHC in each hemisphere. These interactions between homologous regions of PHC may provide a fundamental mechanism enabling perceptual inputs to activate corresponding representations held in long-term memory. Finally, successful recognition was accompanied by the recruitment of a network implicating occipito-temporal, retrosplenial and posterior parietal areas, similarly as in neurologically intact subjects.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.01.001.

Conflict of interest

No conflict of interest.

Acknowledgments

This work was funded by the Swiss National Science Foundation under grant n°320030_138163 (FA); and the Société académique de Genève (NAC 08-025 to FA). We are grateful to Bruno Bonet and Lore Legrand for assistance during data collection and Benoit Musel for helpful discussions. We also thank the anonymous reviewers for their useful suggestions.

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