Parietal and hippocampal contribution to topokinetic and topographic memory

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SUMMARY

This paper reviews the involvement of the parietal cortex and the hippocampus in three kinds of spatial memory tasks which all require a memory of a previously experienced movement in space. The first task compared, by means of positron emission tomography (PET) scan techniques, the production, in darkness, of self-paced saccades (SAC) with the reproduction, in darkness, of a previously learned sequence of saccades to visual targets (SEQ). The results show that a bilateral increase of activity was seen in the depth of the intraparietal sulcus and the medial superior parietal cortex (superior parietal gyrus and precuneus) together with the frontal sulcus but only in the SEQ task, which involved memory of the previously seen targets and possibly also motor memory.

The second task is the vestibular memory contingent task, which requires that the subject makes, in darkness, a saccade to the remembered position of a visual target after a passively imposed whole-body rotation. Deficits in this task, which involves vestibular memory , were found predominantly in patients with focal vascular lesions in the parieto-insular (vestibular) cortex, the supplementary motor area–supplementary eye field area, and the prefrontal cortex.

The third task requires mental navigation from the memory of a previously learned route in a real environment (the city of Orsay in France). A PET scan study has revealed that when subjects were asked to remember visual landmarks there was a bilateral activation of the middle hippocampal regions, left inferior temporal gyrus, left hippocampal regions, precentral gyrus and posterior cingulate gyrus. If the subjects were asked to remember the route, and their movements along this route, bilateral activation of the dorsolateral cortex, posterior hippocampal areas, posterior cingulate gyrus, supplementary motor areas, right middle hippocampal areas, left precuneus, middle occipital gyrus, fusiform gyrus and lateral premotor area was found. Subtraction between the two conditions reduced the activated areas to the left hippocampus, precuneus and insula.

These data suggest that the hippocampus and parietal cortex are both involved in the dynamic aspects of spatial memory, for which the name 'topokinetic memory' is proposed. These dynamic aspects could both overlap and be different from those involved in the cartographic and static aspects of 'topographic' memory.

1. INTRODUCTION

The purpose of this paper is to address the question of a particular aspect of spatial memory: the memory of self produced movement in a spatial environment. The mathematician H. Poincaré wrote: 'To localise a point in space is to imagine the movement necessary to reach it' (Poincaré 1970, p. 67). By this statement he proposed a dynamic theory of spatial memory very different from the current theories, which suppose that, because there are 'place cells' in the hippocampus, or because spatial coordinates seem to be represented in the parietal cortex, the brain codes space on static 'topographical maps' (Andersen 1995; O'Keefe & Nadel 1978). Indeed, most studies concerning spatial memory have considered visual representational memory in static object recognition and recall processes (Mishkin *et al*. 1983; Smith & Milner 1981). In addition, most studies of the neural basis of spatial memory have been based on types of mental exploration of the environment that adopt a 'survey' type of strategy, although dissociations between route and topographical memory have been found (Incisa della Rocchetta *et al*. 1996). In the field of visual exploration, alternative hypotheses have been proposed (Droulez & Berthoz 1990, 1991; Colby *et al*. 1995) which promote the idea that the brain is using some dynamic processes to represent space and to control either executed or imagined movements. In addition, it is proposed that during whole-body motion and the so-called 'path integration' process, movement itself (rather than, or in addition to, distance) is stored in a way that is not yet known: it has recently been shown, by using a mobile robot on which subjects could be transported passively and

subsequently asked to reproduce their linear displacement, that displacement memory seems to involve dynamic storage of movement patterns based on multisensory cues (Berthoz *et al*. 1995), an idea that is in accordance with the general view that internally simulated action is a fundamental element of perception and spatial memory (Berthoz 1997).

This paper reviews some recent experimental results concerning the problem of which cortical areas are involved in the storage and retrieval of movement in memory, with a particular reference to the parietal cortex and hippocampus. The author is interested in self-generated movements, such as those produced during eye movements or a locomotor trajectory, which involve not only the memory of visual objects or space but also vestibular memory and the memory of idiothetic cues and motor actions.

First, some previous findings concerning memorized eye movements are recalled; these findings demonstrated that the parietal cortex is involved in memorized sequences of saccades, together with the frontal lobe, although it is not involved in spontaneous self-paced saccades in darkness or in imagined saccades.

Secondly, experiments are reviewed concerning the contribution of the vestibular system to spatial memory during whole-body rotation in 'vestibular contingent memory saccades', tasks that reflect the memory of a passively imposed whole-body motion (Bloomberg *et al*. 1988; Israël & Berthoz 1989). The present paper concentrates on passively induced whole-body rotation.

Thirdly, the problem of topographical memory is considered. Some recent results concerning the memory of previously learned spatial locomotor routes are also reviewed.

2. CONTRIBUTION OF THE PARIETAL CORTEX TO THE MEMORY OF SEQUENCES OF SACCADIC EYE MOVEMENTS TO VISUAL TARGETS

Eye saccades are an interesting model for studying the involvement of the parietal cortex in memory. The contribution of the parietal cortex to visually evoked saccades has been extensively reviewed (Thier & Karnath 1997; see also Andersen, this volume). In a series of experiments with the use of positron emission tomography (PET), regional cerebral blood flow (rCBF) was measured in human subjects during self-generated saccades in total darkness. Three distinct paradigms were used.

Subjects were first asked to perform self-paced horizontal saccades in total darkness (Petit *et al*. 1993). Three main cortical areas were found to be activated: the frontal eye field (FEF) which is located in the precentral gyrus, the supplementary eye field (SEF) and the median cingulate gyrus. No activation of the parietal cortex was seen in this case. The same three areas were activated when the subjects were asked to perform imaginary self-paced saccades in total darkness (Lang *et al*. 1994).

The subjects were then asked to perform, from memory and in total darkness, a sequence of five prelearned visually guided saccades (Israël *et al*. 1993*a*; Petit *et al*. 1996*a*). In the baseline condition subjects were asked to relax, eyes open in darkness (REST). In the first active condition subjects were asked to execute self-paced voluntary horizontal saccades as in the previous sets of experiments (SAC). In the third condition the subjects were shown a set of five successive positions of light-emitting diodes (LEDs) on a horizontal bar a few minutes before the scan and were asked to make saccades to these five visual targets (SEQ). The targets were placed at 0, 5, 10 and 15° on each side of the primary position but were chosen randomly for each session. The subject was shown these targets five times to allow learning of the sequence. As the subject had to return to the centre, the total number of saccades in a sequence was in fact six. Horizontal electro-oculography was measured to assess that subjects were performing the task. Standard SPM and HMSD analyses were performed on the blood-flow measurements.

Subtraction between the SEQ and SAC conditions revealed that the parietal cortex was activated during the recall of the sequence of memorized saccades. The repetition in total darkness of the prelearned sequence of horizontal saccades led to a bilateral increase in activation at the depth of the intraparietal sulcus, extending towards both the lateral and the medial superior parietal cortex, i.e. the superior parietal gyrus and precuneus, respectively (figure 1). Activation of the intraparietal sulcus has been previously shown in monkeys; the role of this structure in the planning of visually guided saccades has been suggested (Barash *et al*. 1991; Andersen, this volume) but this was the first evidence in humans for an involvement of this structure in internally generated saccades from memory (see also the review by Pierrot-Deseilligny *et al*. (1995)).

Activation of the superior parietal sulcus during this memory task has to be related to numerous recently found activations of this structure. This point will not be discussed here, as it has been extensively reviewed (Petit *et al*. 1996*b*). Activation of the precuneus could be related to the generally accepted role of this area in the recall of visual scenes (Fletcher *et al*. 1995).

These results suggest that the parietal cortex is indeed involved in the recall of visually guided saccades and in the organization of saccade sequences from memory. It should be noted that this function is probably performed in conjunction with the superior frontal sulcus, which was found to be activated in the SEQ task and not in the other tasks. A bilateral activation was found at the depth of the superior frontal sulcus; the activated area overlaps areas 6 and 8 and this overlap makes the designation of prefrontal or premotor difficult. However, this area was clearly distinct from the FEF. Several recent PET studies have found superior frontal activation during memorized spatial tasks requiring spatial memory. This area does therefore seem to belong to the dorsal stream involved in spatial processing and may be particularly important in the memory component of the task described here (Haxby *et al*. 1994; Courtney *et al*. 1996).

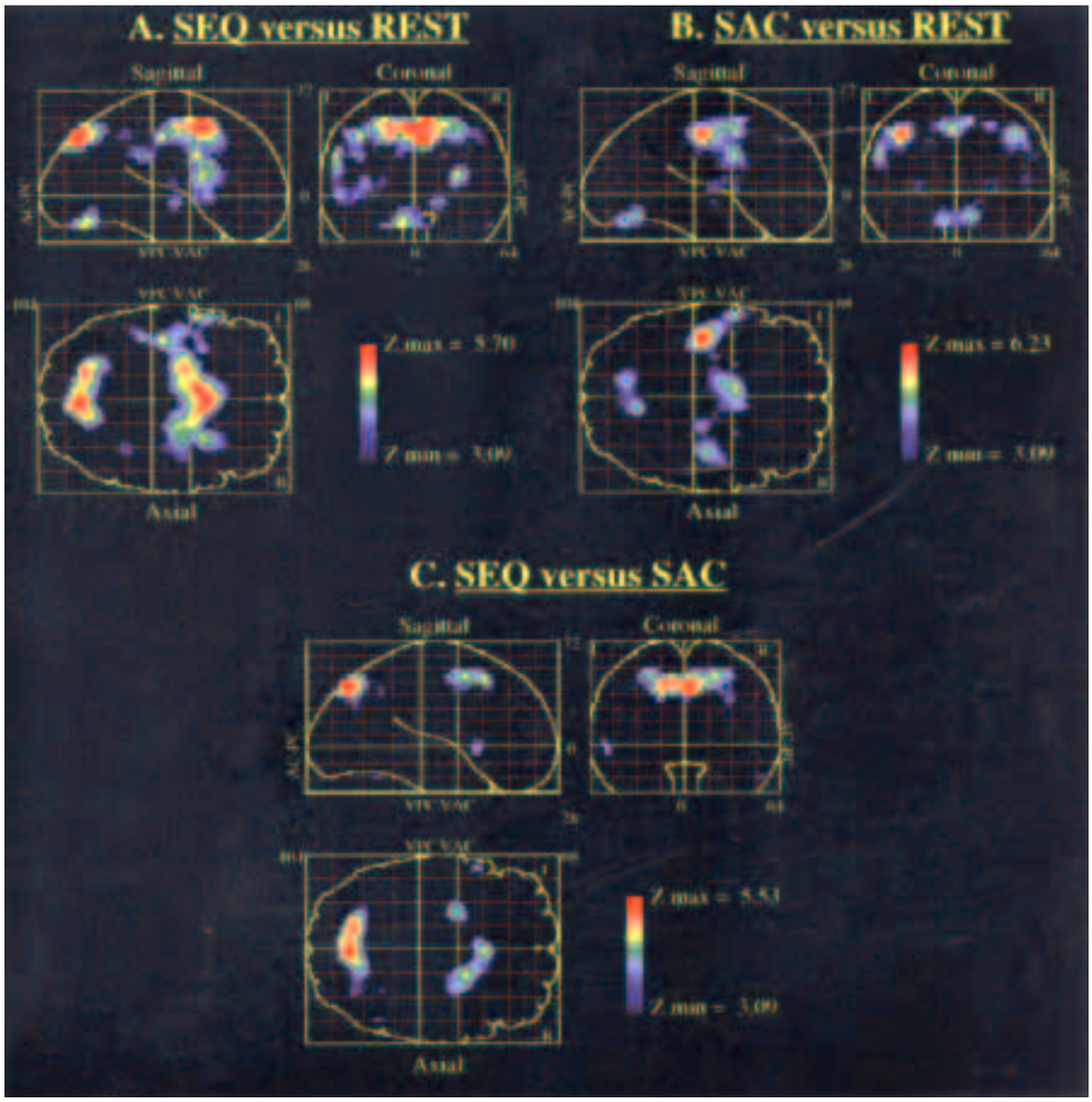

Figure 1. Brain areas activated during the reproduction of a previously learned sequence of saccades. PET scan recordings of the brain areas activated during the execution of saccades in total darkness (see text). Three conditions are compared: the execution of self-paced saccades without any memory task (SAC), the execution of previously learned sequences of saccades to remembered visual targets (SEQ), and rest (REST). Statistical parametric maps are shown for three comparisons: (*a*) SEQ versus REST; (*b*) SAC versus REST; (*c*) SEQ versus SAC. Voxels significant at the given threshold of $p < 0.001$ (Z score > 3.09), uncorrected for multiple comparisons, are displaced on single sagittal, coronal, and axial projections of the brain. The spatial location of each activated area can be established by comparing its position in the three views. AC–PC, anterior commissure–posterior commissure; R, right. (From Petit *et al*. 1996*a*.)

3. CONTRIBUTION OF THE PARIETAL CORTEX TO VESTIBULAR MEMORY

(*a*) *The problem of path integration: is distance coded and memorized separately from direction?*

Animals, including humans, have been shown to have a remarkable sense of direction and a propensity for navigation and 'path integration' which allow them to return to the initial location of their travels. The basic mechanisms underlying navigation and homing have long been questioned, for example with homing pigeons as a fruitful model and paradigm. It is, however, probable that navigation and path integration are subserved by a large variety of mechanisms according to the specific species and the particular type of travel (navigation across the planet by a bird is a totally different problem from homing behaviour or memory of a locomotor path). All these capacities, however, draw upon brain mechanisms for spatial cognition and spatial memory.

The contribution of the vestibular system to the orientation and localization of the body in space after a displacement, in animals and humans, has also long been suggested (Beritoff 1965; Potegal 1982). Beritoff was the first to report that animals (cats and dogs) can return blindfolded to their starting position after they

have been passively transported. Because accurate performance in this task was only achieved in animals with an intact vestibular system, he concluded that the vestibular organs are required for navigation in the dark. He also observed that deaf–mute children with lesioned labyrinths could not, when blindfolded, retrace the route along which they had been taken, whereas normal children were perfectly able to do so. This result was confirmed in rats by Miller *et al*. (1983), who observed a degradation of the performance after vestibular lesion. These results have been reviewed by Wiener & Berthoz (1993).

Quantitative experiments concerning the capacity to compute actual displacement during passive whole-body motion on the basis of vestibular signals in humans were later reported (Metcalfe & Gresty 1992; Young 1984; Mergner *et al*. 1983; Schweigart *et al*. 1993). In addition, psychophysical measurements of the relative contribution of proprioceptive and vestibular input for the detection of head and/or trunk rotation have recently been described. Finally, several studies in humans have shown that the brain can estimate and memorize the travelled path solely from vestibular information, not only from angular but also from linear motion (Berthoz *et al*. 1987, 1995; Israël & Berthoz 1989; Israël *et al*. 1993*b*).

During locomotion, it has been demonstrated that human subjects can reach a previously seen visual target on the floor several metres away with eyes closed (Thomson 1983). These results, confirmed by several groups, indicate that information about step length, derived from proprioceptive or outflow motor command signals as well as from vestibular signals, could contribute to the updating of the mental representation of the subject's location in space and allow for path integration (Mittelstaedt & Glasauer 1991; Glasauer *et al*. 1994). Patients with a vestibular deficit could perform without error the simple task of walking in a straight path to a previously seen target a few metres away (Glasaver *et al*. 1994) but accumulated errors when asked to perform a triangular or rectangular path composed of successive turns, and also if they were asked to locomote through a previously seen circular trajectory (Takei *et al*. 1997). It seemed that the main deficit in these two tasks was a directional error, as the total distance seemed to be unimpaired. This points to a definite contribution of the vestibular system to the detection of *direction*, whereas *distance* could be coded by the motor and proprioceptive system.

The hypothesis discussed in this paper is that vestibular patients have a specific deficit of the head-direction cell system. This deficit leads to a deficit in the ability to store direction; in the absence of vision or in the presence of conflicting visual cues, it also leads to a deficit in the evaluation of direction.

The term 'integration' could therefore correspond to several different processes: (i) spatial integration over the whole travelled trajectory, i.e. the computation of the travelled distance by cumulating successive positions along the path, a method that can be achieved, for example, by counting or measuring the steps during locomotion; (ii) time integration of the velocity or acceleration signals generated during self-motion, for instance the inertial vestibular signals; (iii) multisensory integration of all the messages delivered during self-motion, including its duration. These three interpretations are not mutually exclusive.

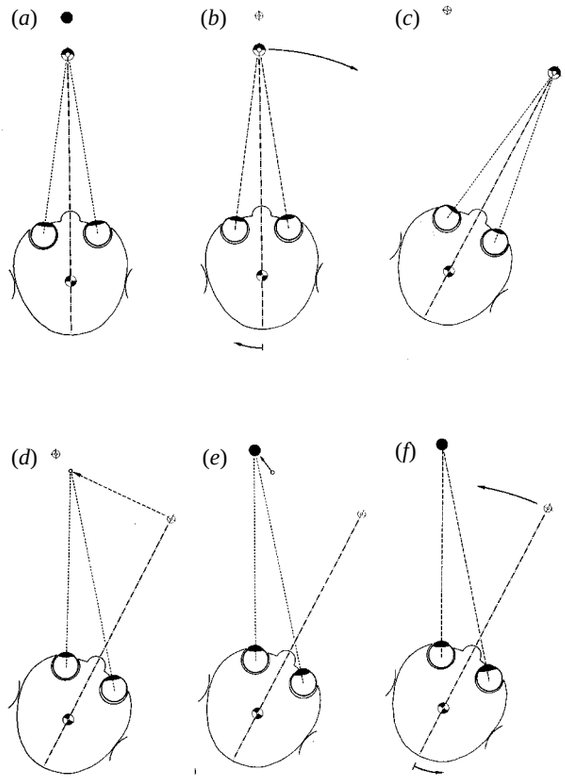

Figure 2. The memory contingent saccade task. (*a*) The subject, seated on a turntable, views two targets: a head-fixed and an earth-fixed target. (*b*) The subject is passively rotated in darkness, only viewing the head-fixed target, and is asked to remember the location of the earth-fixed target. The only information available to the subject about the rotation is derived from the horizontal semicircular canal. (*c*) The subject is still and views the head-fixed target for a few seconds to let the vestibular effects decrease. (*d*) The head-fixed target is turned off and the subject has to remember the location of the previously seen earth-fixed target in total darkness. (*e*) The subject makes a saccade to the remembered target in total darkness. Then the light is turned on and the subject makes a corrective saccade if the saccade in darkness was not of the appropriate amplitude. (*f*) The turntable is returned to the initial position for control.

To understand the respective contributions of these different sensory systems to path integration, the vestibular projections to the cerebral cortex and hippocampus are first decided below. The deficits in a vestibular memory task of patients with focal cortical lesions are then examined.

(*b*) *Vestibular projections to the parietal cortex and hippocampus*

Recent work by Grüsser and others in the monkey (Gulyás & Roland 1994; Grüsser *et al*. 1990*a*,*b*, 1991)

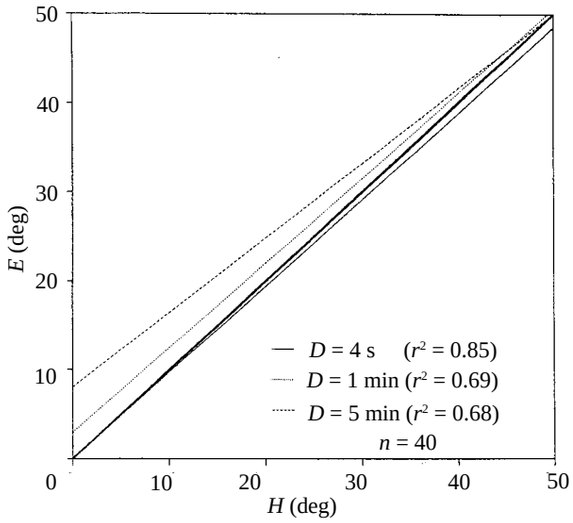

Figure 3. The memory contingent saccade can be executed with a delay. Three regression lines between the amplitude of the vestibular memory contingent eye saccade (*E*) and head rotation (*H*) when the subject was asked to wait with a delay of 4 s, 1 min and 5 min, respectively. In this form the task becomes a form of delay task well suited to test spatial memory of a passive whole-body rotation. (From Israël *et al*. 1991.)

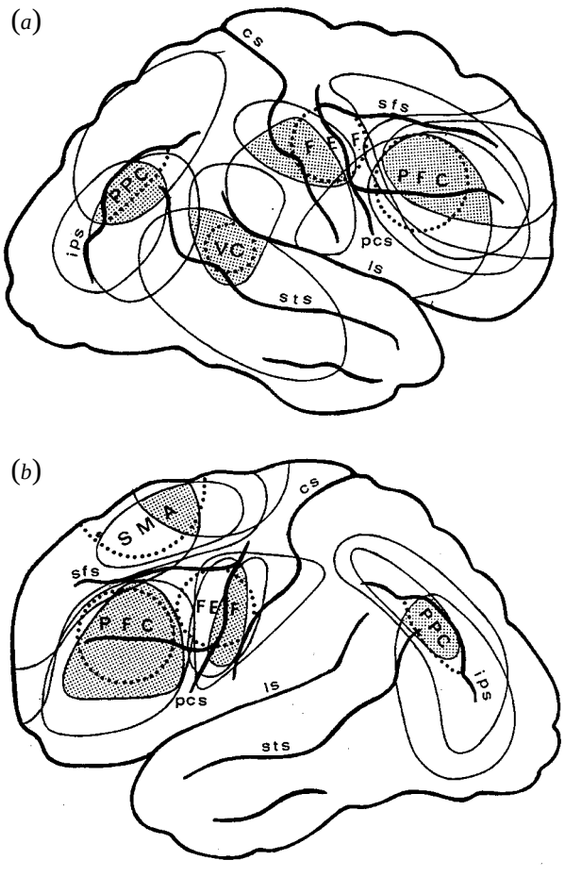

Figure 4. Location of the lesions of patients who were tested with the vestibular memory contingent saccade task. PPC, posterior parietal cortex; FEF, frontal eye field; SEF, supplementary eye field; PFC, prefrontal cortex; VC, vestibular cortex. Deficits in the task were mainly found in patients with lesions of the PFC, VC, or SEF. cs, ips, sfs, pcs, ls, sts indicate respectively the central, intraparietal, syfrian, precentral, lateral and superior temporal sulci. (From Israël *et al*. 1995.)

and from PET studies (Vallar *et al*. 1990; Bottini *et al*. 1994) in humans have confirmed the existence of an area in the parietoinsular cortex that is involved in the processing of multisensory, and particularly vestibular, cues about head motion in space. This parietoinsular vestibular cortex (PIVC) is probably the essential station in the transmission of ascending vestibular information from the vestibular nuclei, through the sensory thalamus, to the cortical areas involved in the elaboration of spatial cues, which are now identified as areas 6, 3a, 2v, T3 and 7a in the monkey. The same areas project to the vestibular nuclei in the monkey (Faugier-Grimaud & Ventre 1989; Ventre & Faugier-Grimaud 1988; Akbarian *et al*. 1993; Guldin *et al*. 1993).

Vestibular signals may also reach the cerebral cortex and the hippocampus through a second route. A head direction cell system has been discovered by Ranck (1984) and Taube *et al*. (1990). Further studies (Taube 1995; Sharp *et al*. 1995) have revealed that a second route (other than the PIVC route) from the vestibular nuclei through the anterior thalamus, the mamillary bodies and the subiculum could reach the hippocampus after receiving visual environmental information from the parietal cortex, and contribute to the reconstruction at this level of spatial localization and movement detection.

To gain insight into the contribution of the vestibular system to cortical functions a further study has been made of the vestibular activated areas by using both caloric and galvanic stimulation. Brain activity has been recorded by functional magnetic resonance imaging (fMRI) of the whole brain.

Caloric stimulation was applied to seven subjects by injection of cold water to the left ear and compared with a rest condition (Lobel *et al*. 1997). The activated areas were the left temporoparietal junction (probably the PIVC), the postcentral gyrus, the premotor cortex, the insular cortex, the posterior middle temporal gyrus, the inferior parietal lobule, the frontal cortex, the anterior cingulate gyrus and the hippocampal gyrus. On the right side these areas were also activated, but more rarely. This list does contain several of the areas already found in other PET studies; however, the activation of the hippocampus had not been reported previously.

To verify the activation of the hippocampus by vestibular stimulation, as had been predicted by previous results obtained in the monkey (O'Mara *et al*. 1997) and in the rat (Wiener *et al*. 1995; Gavrilov *et al*. 1995), this region was investigated specifically in a dedicated campaign (Vitte *et al*. 1996). Cold water was injected into the right ear during a visual fixation task and the results were compared with visual fixation alone. Ipsilateral activation of the hippocampal formation (including the subiculum) was found in eight subjects and in three of those subjects three times for each subject. This activation may result from an indirect activation of the hippocampus, either through

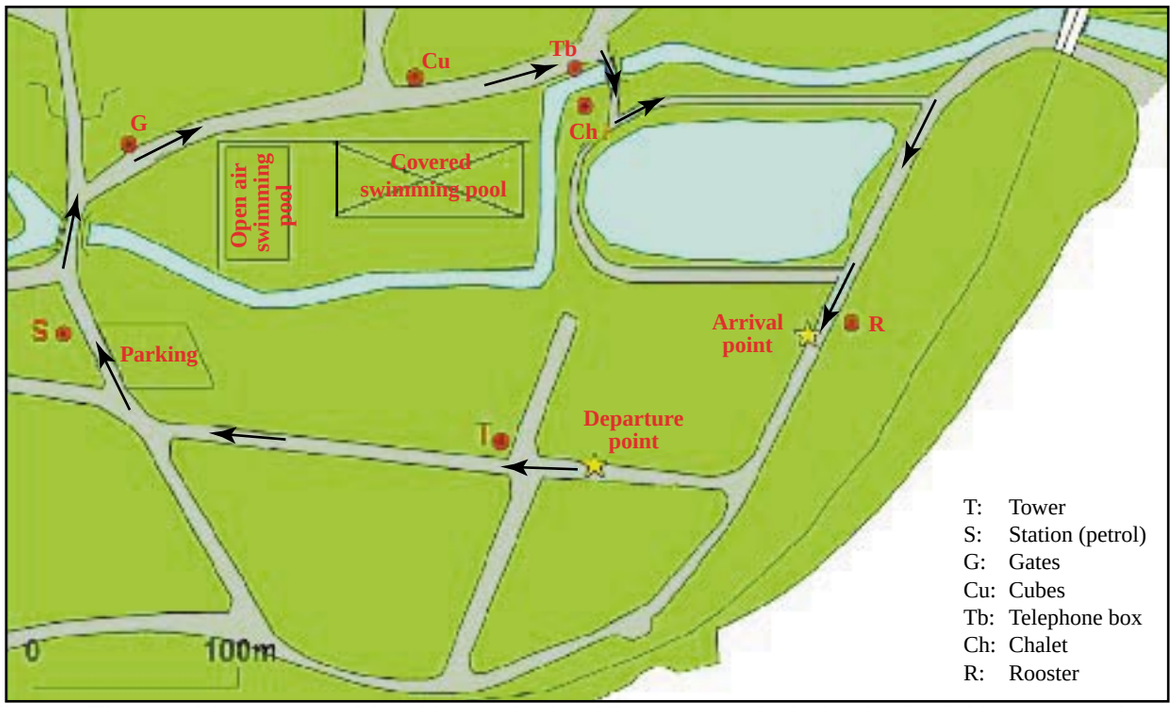

Figure 5. The map of the trajectory of the subjects in the city of Orsay (see text for further details). Subjects were conducted to the departure point and walked with eyes open along the path, which was divided into seven segments. Each of the segments was marked by a prominent landmark, which the subjects were asked to remember. When laying in the PET scan they had to remember their walk. This procedure was aimed at giving them a 'route' type of memory of the path.

the PIVC or through the head-direction cell system, which is thought to carry vestibular information about horizontal head rotation to the hippocampus via the thalamus and pre- or postsubiculum.

More recently, this experiment has been repeated with bipolar, binaural galvanic stimulation of the labyrinth in six subjects (Lobel *et al*. 1997). This stimulation consisted of a sinusoidal current of frequency 1 Hz and maximum intensity 2–3.5 mA applied for 30 s. The stimulation induced an illusion of pendular rotation of the body in the frontal plane (the subject lying in the MRI apparatus) and torsional eye movements, which were not measured. This is the first successful attempt to use galvanic stimulation in fMRI studies. Two sets of experiments were performed. Rest and stimulation were first compared. During stimulation no control task was given to the subjects. Galvanic stimulation was then superimposed on this simple motor task. In the first set bilateral activation of the insula, inferior frontal gyrus and inferior precentral gyrus and left activation of the medial frontal gyrus was observed in more than four subjects. In three subjects or fewer, activations of the inferior parietal lobule, superior temporal gyrus, and postcentral gyrus were found. These results confirm the previous identification of vestibular cortical areas but, in addition, indicate new areas in the frontal and hippocampal regions.

A recent direct electrophysiological study has confirmed the existence of additional areas involved in vestibular processing at short latency (Baudonniére *et al*. 1997). Activation by electrical stimulation of the vestibular nerve pre-operatively in patients undergoing vestibular surgery evoked field potentials in five main areas: the ipsilateral temporoparietal region or so-called parietoinsular vestibular cortex, the controlateral posteroparietal cortex and inferior parietal lobule, the controlateral supplementary motor area and possibly its specialized subarea for eye movements (the supplementary eye field in the dorsomedial frontal cortex), an ipsilateral prefrontal area, and finally ventromedial prefrontal areas known to have connections with the limbic system.

These data give some indication as to the areas of the cortex in which one may find deficits in tasks involving the contribution of the vestibular system to perception, memory, or the control of movement. This knowledge has been used to study the deficits of vestibular memory about self-motion in patients with focal cortical lesions. These results are briefly reviewed in the next section.

(*c*) *The vestibular memory contingent saccade task*

To study the role of several cortical areas in vestibular memory, a new psychophysical test of passive body-rotation estimation, the 'vestibular memory contingent saccade' (VMCS) paradigm, has been used (Bloomberg *et al*. 1988). The seated subject is first presented with an earth-fixed visual target and is then rotated by turning the chair about its swivel base (oriented along the earth-vertical axis). During the rotation, the subject has to fixate another target, which remains at a fixed position with respect to the head (head-fixed target), to suppress the vestibulo-ocular

reflex (VOR). After a delay of about 2 s, the subject is required to make a saccade toward the 'memorized' earth-fixed target, in complete darkness. The results showed that humans can correctly match the amplitude of a preceding head rotation with a voluntary ocular saccade of equal but opposite amplitude (figure 2). The amplitude of a passive body rotation in darkness can therefore be correctly estimated by the brain; this information can also be adequately stored, and further retrieved and used by the oculomotor system. This is also true for rotations in different planes of three-dimensional space (Israël e*t al*. 1993*c*).

In another experiment (Israël *et al*. 1991) the duration of vestibular information storage was studied in greater detail by using delays of less than 20 s, as well as 1 and 5 min. The results showed that the amplitude of a passive rotation detected by the vestibular system can be accurately memorized for as long as 5 min (figure 3). At such long delays, however, smaller rotation angles (less than 20 °) are overestimated (i.e. lead to an undershoot).

From these results the involvement of the hippocampus and cortical structures (frontal and parietal lobes) in the representation of self-rotation detected by the vestibular system (Berthoz 1989) was inferred. Further research aimed to discover which areas of the cortex were particularly important in the VMCS. Those areas of the cortex that are activated during saccade generation, or that have been suggested to be involved either in visuospatial delay tasks and working memory or in the processing of vestibular signals, were chosen.

(*d*) *Deficits in the vestibular memory tasks in patients with cortical and hippocampal lesions*

The working hypothesis was that lesions in two areas of the brain would account for the main deficits in the VMCS task. These areas were: (i) the prefrontal cortex because of its known involvement in 'visual representational memory' (Quintana & Fuster 1993; Goldman-Rakic 1987) and which it is proposed should be also involved in what is here called 'vestibular representational motion memory'; and (ii) the parietoinsular cortex.

The vestibular memory contingent saccade task was applied to 24 neurological patients with various cortical lesions and to 18 age-matched control subjects (Israël *et al*. 1992, 1995; Pierrot-Deseilligny *et al*. 1993) (figure 4). Anticipation and latency, direction errors and accuracy of the first saccade, stability of eye position in darkness, and final eye position were quantified. Patients were divided into small groups with lesions affecting the following cortical areas : left or right frontal eye field (FEF), left or right prefrontal cortex (area 46 of Brodmann) (PFC), left supplementary eye field (SEF), left or right posterior parietal cortex (PPC) and right parieto-temporal cortex (PTC) (i.e. the vestibular cortex). There were some abnormalities in the results of the right FEF group, concerning anticipation, direction errors and latency of the first saccade, but no differences from controls in the accuracy of the first saccade or of the final eye position. Results in the left FEF group were normal. Accuracy of the first saccade was bilaterally impaired in the SEF group. Final eye position was also inaccurate in the SEF group. In both PFC groups, significant and generally bilateral abnormalities existed for all parameters tested.

(i) *Parietal lesions*

The only deficit that was found in patients with PPC lesions was a slightly increased percentage of anticipated responses in the right PPC group. In the monkey the PPC is involved in spatial attention and integration (Andersen 1995; Barash *et al*. 1991; Colby *et al*. 1995; Duhamel *et al*. 1992). PPC cells receive direct projections from different cortical visual areas and have eye and head position gain fields; some of them also receive vestibular information (Kawano *et al*. 1980, 1984).

The parietal cortex is clearly involved in the control of visual memory-guided saccades. In a previous study in patients with parietal lesions, performance of a similar vestibular-driven paradigm was markedly impaired (Tropper *et al*. 1990). The exact limits of the lesions, which were much larger than those of the patients in the present study, were not indicated, thus reducing the validity of any comparison between the two studies.

Finally, the absence of marked deficits in the results of the present study after PPC lesions suggests that the PPC is not crucial for this paradigm. Vestibular integration probably takes place elsewhere.

(ii) *Parietotemporal cortex lesions*

The right PTC group was found to be deficient in the spatial aspects of saccade performance, showing a decrease in first saccade accuracy, an increase in direction errors, and a decrease in the duration during which eye position in darkness was accurate to within 50%. The fact that the right PTC group was markedly impaired reflects the vestibular input of the task. Although this result was expected, to our knowledge this is the first behavioural demonstration, together with the observation of deficits in the perception of the subjective vertical (Brandt *et al*. 1994), that the PTC is the probable equivalent in humans to the parietoinsular vestibular cortex in the monkey. Despite the difficulty of extrapolating from monkey to human cortex, because PPC lesions did not result in impairment in the present study, it is suggested that vestibular processing is carried out in the PTC or in a nearby area, and the integrated information sent directly to the frontal lobe. This answers the third question about the relative contribution of the PPC and PTC in this vestibular-guided task: the PPC is not crucial in the control of such a task.

These results suggest that (i) the PFC is involved in the memorization of saccade goals, probably encoded in spatiotopic coordinates since PFC patients were impaired in both vestibular- and visual-memory guided tasks; (ii) the SEF, but not the FEF, is involved in the control of accuracy of these vestibular-derived goal-directed saccades, whereas the reversed pattern of results was

found for the visual-derived saccades; and (iii) the PTC (i.e. the vestibular cortex), but not the PPC, is involved in the control of vestibular memory-guided saccades, the reverse pattern again being found for visually derived saccades. This represents two different cortical networks, with only the PFC in common. The network found here with the VMCS paradigm may be specific to the vestibular input, or else could be a pathway used for all non-retinotopic (craniotopic and spatiotopic) saccades, as the SEF has been found to be involved in sequences of visual memory-guided saccades, i.e. visual-derived saccades encoded in craniotopic coordinates (Gaymard *et al*. 1990, 1993).

In conclusion, a new network is here suggested for the cortical control of vestibular memory-guided saccades, which, although still speculative, is different from that of visual memory-guided saccades (Israël *et al*. 1995): the cortical pathway involved in the control of vestibular-guided saccades includes the PTC, which could be involved in the integration of vestibular and other sensory information to reconstruct head movement in space. Patients with PPC lesions showed impairment in the visual memory-guided saccade task, but not in the vestibular-guided saccade task (Pierrot-Deseilligny *et al*. 1993). The PTC would then play in the vestibular task a role similar to that played by the PPC in the visual task. After integration, vestibular information could be sent to and stored in the PFC, where 'spatial' memory could be organized. The vestibular saccade could then be triggered by the SEF, via the superior colliculus (SC) rather than by the FEF in visual memory-guided saccades, as it has recently been shown that additional channels beside those coursing through the FEF and SC are utilized to access the saccade generator of the brainstem: patients with FEF lesions exhibited impairment in the visual memory-guided saccade task, but not in the vestibular-guided saccade task, whereas the contrary was observed for patients with SEF lesions, who were impaired in the vestibular but not in the visual task. Therefore, the networks corresponding to these two tasks could both pass through the PFC, which would store the processed (integrated) information and select the next step.

(iii) *The role of the hippocampus in vestibular memory*

Given that vestibular stimulation can activate the hippocampal regions in humans, it would be interesting to see whether the VMCS task is impaired in hippocampal patients. This was not tested. A recent report indicates, however, that patients with hippocampal lesions show deficits in sequences of visually guided memory saccades (Müri *et al*. 1994) and Wiest *et al*. (1996) have found a clear deficit in a whole-body return task. They exposed ten patients with temporal-lobe epilepsy and unilateral hippocampal atrophy and ten age-matched controls to random rotational displacements away from the centre position in darkness. They required them to perform the whole-body return task (Metcalfe & Gresty 1992). They found a hypometry in the return angle towards the side ipsilateral to the lesion. This question remains, however, open to future investigation.

4. MENTAL NAVIGATION ALONG MEMORIZED ROUTES

The neurobiological mechanisms of spatial navigation have been studied extensively in rodents. However, very little is known concerning the cerebral structures involved in the memory of routes in primates and humans.

In primates, only two research groups have reported data concerning the activity in the hippocampus and related structures during navigation or spatial tasks. T. Ono and his collaborators (Tamura *et al*. 1992*a*,*b*), in the hippocampus of the monkey, have found neurones that were activated when the animal was moving actively or passively to a given location in the room. These cells therefore had properties similar to those of place cells. In addition, some of these neurons were activated when a task (visual object recognition, motor task) was performed at a given location in the room: an association was made between task and place. This group has also suggested that hippocampal neurones are influenced by the meaning of the object–place association for the monkey (either reward or punishment). E. T. Rolls has recently proposed that in the hippocampus and parahippocampus of the monkey there is a diversity of cells; some were called view cells and were activated when the animal was paying attention to an object at a particular location in space (Miyashita *et al*. 1989; Rolls 1991). Given that he did not find any place cells, he concluded that the primate hippocampus was coding objects in place in allocentric coordinates. Recently, he has discovered cells that are activated when the animal is looking at a particular place in a cue control room independently of the location of the animal in the room. These cells have been named 'space cells'. They seem to code an area of space 'out there' in allocentric coordinates independently of where the animal is. It is important to note that these cells seem to keep some of their properties in total darkness and therefore have an activity related to memorized object-in-place location. However, nothing is known of the exact processing occurring in the hippocampus of the monkey that gives rise to this type of coding.

In humans, several strategies can be used to remember topographic routes, for example if one tries to recall the route from home to office or laboratory. The brain can use a survey strategy and try to imagine a map of the environment and mentally visualize the route on this map. This neural basis for this survey type of strategy has been studied in humans (Mellet *et al*. 1995). On the other hand, subjects can try to remember the sequence of turns and walks in relation to visual landmarks and eventually to other cues or actions associated with the route. This type of memory can be subserved by several types of cognitive strategies (Amorim *et al*. 1997).

A clear dissociation has been found between these different strategies in patients with brain lesions. Several studies have demonstrated impairment in topographic memory, and a dissociation has been claimed between the ability to recognize familiar landmarks (Whiteley & Warrington 1978; Incisa della Rocchetta *et al*. 1996), sometimes leaving the capacity to describe well-known routes relatively intact, and the ability to

describe routes with recognition landmarks relatively unaffected (Pallis 1955; Paterson 1994). Sometimes patients can also describe routes and recognize landmarks but they still lose their way because landmarks no longer convey directional information (Hécaen *et al*. 1980). The hippocampus is not necessarily the only area involved in these spatial memory deficits: Habib (1987), for instance, has shown that lesions in patients with topographic memory loss were restricted to the parahippocampus and the subiculum but did not extend to the hippocampus. By contrast, patient R. B., who had a severe anterograde amnesia following selective damage to the hippocampus, did not report getting lost in his neighbourhood (Zola-Morgan *et al*. 1986).

The patient studied by Incisa della Rocchetta *et al*. (1996) had a severe deficit in describing familiar routes in her environment but no difficulty in identifying countries from outline maps and in naming a city within a country when it was identified by a dot. Both episodic and semantic memory were impaired in this patient. The suggestion is that this patient has a specific deficit for category-specific knowledge of inanimate objects (hills, buildings, etc.). There seems to be a specific coding of topographic objects distinct from other classes of object; there could also be a separation between the objects that require locomotion to reach them, and other objects.

One should therefore be careful before ascribing to any particular area of the cortex a crucial role in spatial memory. It seems more likely that this function is distributed over several areas, each making a distinct contribution. For example, the frontal cortex seems to be involved in visual spatial memory (Courtney *et al*. 1996) and in mental recall of complex environments (Guariglia *et al*. 1993).

It therefore seemed interesting to explore the areas of the brain involving recall of an actual locomotor route, mostly in view of the difficulty encountered by other investigators in activating the hippocampus. The brain structures activated during a mental navigation task, in which the emphasis was put on memory of self-motion associated with visual landmark recall during route navigation, were therefore investigated.

The details of the experiments are given by Ghaem *et al*. (1997) and the main features of this task are therefore only summarized here. Subjects were driven to a totally unfamiliar urban environment and were asked to walk along a previously selected route in the city of about 800 m in length (figure 5). The subjects walked three times along the route and were asked to remember the route and in particular seven prominent visual landmarks (tower, petrol station, telephone box, etc.). The first two times the subject was guided by the experimenter and the third time the subject walked under supervision. Time of locomotion was recorded. The day after this learning session and 4–6 h before PET acquisition, the subjects executed two tasks, which were repeated in the PET apparatus.

(*a*) *MSR task*

In this mental simulation of routes the subject was instructed verbally to indicate the name of two landmarks, chosen by the experimenter, between which he or she was supposed to walk mentally. The subject pressed a button upon the mental arrival to the final landmark and the sequence was repeated with another set of two landmarks. This also allowed the mental locomotion time to be measured and compared with the previously recorded actual time in the real environment.

(*b*) *VIL task*

In this visual recall task the subject was instructed to mentally visualize a landmark and keep it in memory upon hearing its name through the earphones.

(*c*) *Results*

The results indicated that there was a strong correlation between the time taken to 'walk' mentally between two segments and the real time of locomotion in the city during both the training session ($r = 0.99$, $p = 0.0003$) and the PET session ($r = 0.92$, $p = 0.024$), suggesting that subjects were doing the required task. The following main areas were activated during these tasks when compared with the rest condition.

MSR task: there was bilateral activation of the dorsolateral cortex, the posterior hippocampal areas, the posterior cingulate gyrus, the supplementary motor area, the right middle hippocampal areas, the left precuneus, the middle occipital gyrus, the fusiform gyrus and the lateral premotor area. VIL task: there was bilateral activation of the middle hippocampal regions, the left inferior temporal gyrus, the left posterior hippocampal regions, the precentral gyrus and the right posterior cingulate gyrus. When these two conditions were subtracted (MSR minus VIL) activation of only the left hippocampal regions, precuneus and insula was observed.

(*d*) *Discussion*

The activation of the right hippocampal areas is important: this is the first time that the hippocampus has been shown to be activated in a 'navigation' spatial task (three reports were presented simultaneously: Aguirre *et al*. (1996), Maguire *et al*. (1996) and Ghaem *et al*. (1996)). It is coherent with the literature on the effects of lesions, which show a dominance of the right hippocampus in spatial deficits. There is a definite difference in the location of these activations (middle, posterior, anterior) within the hippocampal formation. However, the resolution of the PET images is not sufficient for a definition of the precise part of the hippocampal formation activated during this task. It is hoped that current work in which the experiment has been repeated will allow more detailed description of the exact areas involved.

A surprising result was the activation of the left hippocampus and the fact that it was the only side activated after the MRS minus VIL subtraction. This is in contrast with the current view attributing to the left hippocampus a major role in the processing of verbal material. One explanation could be that in these experiments the instructions for the mental route task

were given verbally. However, the instructions to recall a visual landmark in the VIL condition were also verbal and the two effects may have subtracted from each other. It is proposed that there is a potential involvement of the left hippocampus in the combination of visuospatial and body-position information, which is important for navigation. The activation of the insula may be related to the fact that subjects had to remember the turns of their body during the memorized locomotory task. Activation of the insula has been found during tasks requiring mental repositioning of the body with respect to external objects (Bonda *et al*. 1995). One may therefore, as do Ghaem *et al*. (1997), suggest that there may be two subsystems involved in the processing of spatial memory and that the left hippocampus could be particularly involved when memories including the relation between whole-body movements and the environment have to be recalled.

5. CONCLUSION

These three studies confirm the idea that there is a class of spatial memory, which I propose to call 'topokinetic' memory, which involves several brain structures (parietal and parietoinsular cortex, insula, cingulate cortex, hippocampal formation, dorsolateral frontal cortex, etc.) involved in the processing of self-generated eye or locomotor movements. It seems that the design of tasks requiring the recall of some previously generated movements is important if one wants to study spatial memory in relation to real physiological functions and not to artificial tasks based upon the wrong idea that the brain is essentially designed to process visual information and not first of all action involving self generated movement which will be detected by a combination of visual, vestibular and idiothetic cues together with efferent copies from motor commands. New paradigms have therefore still to be designed to study this problem adequately and understand the contribution of each of these areas to the memory of movement.

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