RESEARCH NOTE

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Activation of the hippocampal formation by vestibular stimulation: a functional magnetic resonance imaging study

Abstract Functional MRI (f-MRI) is a non-invasive technique developed to permit functional mapping of the brain with a better temporal and spatial resolution than that offered by PET techniques. In our study, f-MRI was performed using blood oxygenation level dependent (BOLD) contrast imaging based on the magnetic properties of hemoglobin. This method relies on changes in the blood supply to the brain that accompany sensory stimulation or changes in cognitive state. All the images were obtained at 1.5 T on a Signa GEMS without ultrafast imaging. The vestibular stimulation was cold irrigation of the external auditory meatus (caloric stimulation). A population of normal healthy volunteers without a history of vestibular dysfunction was studied. The hippocampal formation as well as the retrosplenial cortex and the subiculum were activated by vestibular stimulation, suggesting that this activation may be related to spatial disorientation and a sensation of self-rotation experienced by the subjects during vestibular stimulation. The other results are similar to those obtained using PET.

Introduction

The existence of cortical vestibular projections in humans has been postulated on the basis of electrical stim-

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ulation (Penfield and Rasmussen 1957) and clinical studies on epileptic patients (Smith 1960). Measurement of cerebral blood flow with xenon-133 after unilateral caloric stimulation revealed a vestibular projection probably localized in the superior temporal gyrus and posterior to the auditory area (Friberg et al. 1985). Another study (Bottini et al. 1994), using positron emission tomography (PET), has identified areas activated by cold vestibular stimulation in the temporo-parietal junction, the posterior insula, the putamen, the anterior cingulate cortex and in the primary sensory cortex contralaterally. These projections, with the exception of the putamen, are similar to those first described in the monkey (Grüsser et al. 1990).

In this report we show for the first time, with functional magnetic resonance imaging (f-MRI), that caloric vestibular stimulation induces activity in the human hippocampal formation.

Methods

In our study, f-MRI was performed by using blood oxygenation level dependent contrast imaging based on the magnetic properties of hemoglobin (Ogawa at al. 1992). Imaging was carried out on a 1.5-T GE Signa MRI system without ultrafast imaging. Conventional gradient-echo three-dimensional T1-weighted [slice thickness 2 mm, field of view (FOV) 22 cm, flip angle 20°, separation 0, repetition time (TR) 23 ms, echo time (TE) 9 ms, matrix 256×256] localizer scans were first performed. Functional images were acquired in Spoiled GRASS Gradient Echo sequences (SPGR) (slice thickness 5 mm, FOV 32 cm, flip angle 40°, separation 0, TR 70 ms, TE 60 ms, matrix 256×128).

The vestibular stimulus was unilateral irrigation of either the right (one of ten subjects) or the left external auditory meatus (caloric stimulation) with 30 ml of cold water (12°C). Functional images were recorded 30 s after the end of the irrigation (corresponding to the maximum of the vestibular-induced nystagmus). Subjects were asked to fixate a target inside the magnet during vestibular stimulation and during f-MRI acquisition.

Three axial-oblique slices parallel to the longitudinal hippocampal axis defined by the line tangential to the ventral border of the subiculum (hippocampal axial plane, HAP) (Bronen and Cheung 1991) were analyzed. Three sagittal planes at Talairach coordinates (Talairach and Tournoux 1988) a–b (G.21, D.20), b (G.25,
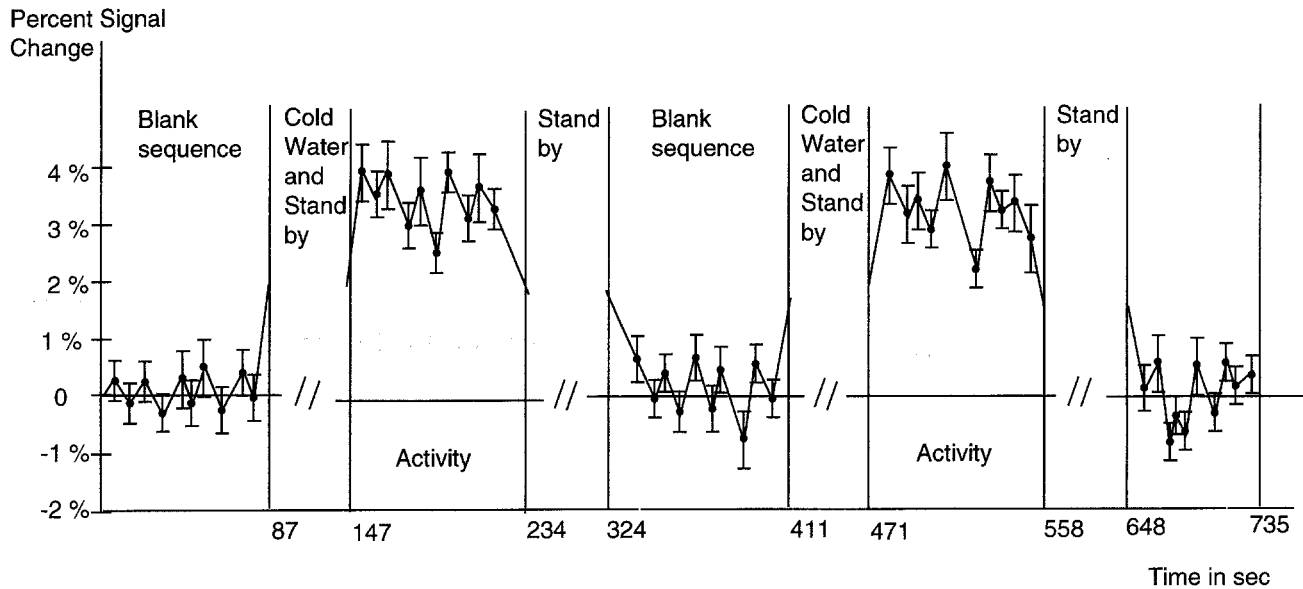
Percent Signal
Change

Fig. 1 Example of the recording of a functional (f-MRI) signal in successive sequences during caloric stimulation and rest. For each level of slice, the paradigm of the f-MRI sequence was as follows: ten acquisitions (blank sequence), unilateral irrigation of the external auditory meatus with 60 ml of cold water (12°C) during 30 s, ten acquisitions 30 s after the end of the irrigation (corresponding to "the active sequence" at the culmination of the vestibular induced nystagmus), ten acquisitions 90 s later (blank sequence). During the active sequence the subjects were asked to fixate a target in the magnet and were observed during the task. This paradigm was repeated twice for each level of slice. A total of 50 images per slice was collected

D.24) and b–c (G.33, D.30) and three coronal planes at Talairach coordinates E (–16), E–F (–24) and F (–32) were studied. Since we did not use ultrafast imaging, f-MRI acquisitions were performed plane after plane. We used a standard GEMS head coil and the head of each subject was immobilized with a neck support and a forehead restraining band.

The anatomical images, which are in exact registration with the activation images, were later used as the bases images on which to overlay activation maps.

Calculation and image manipulation were carried out on a SPARC 10 workstation (Sun Microsystems). The analysis was carried out using the mathematics of vector spaces. Because single simple image subtraction can neglect useful information contained in the time response of the activation-induced signal change and, therefore, be ineffective in differentiating artifactual from activation-induced signal change enhancement, a thresholding technique has been developed to analyze the signal. This technique compares the shape of the response of a pixel with the shape of a reference waveform as the decision criterion. This thresholding technique suppressed the noise and also the spurious correlation in pixels with very large signal changes arising from vessels. This method of image processing involves thresholding by shape as characterized by the correlation coefficient (C) of the data with respect to a reference waveform followed by formation of a cross-correlation image (Bandettini et al. 1993; Derosier et al. 1994) after removal of the linear drifts of the signal with respect to time. The correlation coefficient is a measure of the correspondence of the shapes of the reference waveform and the functional waveform:

$$c = \frac{\sum_{n=1}^{N} (fi - \mu f)(ri - \mu r)}{\left|\sum_{n=1}^{N} (fi - \mu f)^2\right|^{1/2} \left|\sum_{n=1}^{N} (ri - \mu r)^2\right|^{1/2}} \quad (1)$$

where fi is the time-course function in a given pixel and can be considered to be an N-dimensional vector. A reference waveform or vector is denoted by ri. The average values of vectors f and r are μf and μr, respectively. The reference waveform is a square wave ideal vector. The delay between the induced signal enhancement and neuronal activation is taken into consideration by adjustment of the phase of the reference waveform. The signal process is the same as averaging all images during the interleaved "on" periods and subtracting the averages of all images during the interleaved "off" periods.

To be significant, only the pixels of regions activated by the vestibular stimulation with a correlation coefficient C exceeding 0.66 were selected. The measured MRI signal changes are shown in Fig. 1. A percentage signal change exceeding 2.3% was consid-

ered as significant. The areas activated by the vestibular stimulation were then superimposed on the anatomical images. There was no significant artifact due to any motion that could produce false activation patterns in f-MRI.

Ten healthy volunteers without a history of vestibular dysfunction or motion sickness susceptibility underwent the f-MRI after informed consent. The experiments were conducted according to the rules of the ethics committee in the Neuroradiology Department of the Val de Grâce Hospital. All subjects experienced true vertigo after vestibular stimulation (i.e., cold water irrigation). To avoid vestibular induced nystagmus, the f-MRI was recorded while the subject was fixating a visual target.

Results

As described previously (Friberg et al. 1985; Bottini et al. 1994), we found that cold caloric stimulation induces activity in Brodmann's areas 39, 40, 41, 42 and in the posterior insular cortex mostly contralaterally to the stimulation. In our study the putamen was activated mainly ipsilaterally to the stimulation (seven subjects). Furthermore, Brodmann's area 7 in the superior parietal lobe on the convex surface of the brain was activated as well as the retrosplenial cortex (isthmus of the cingulum) but ipsilaterally. These activations will be described in a further publication. The present report focuses on the findings concerning the hippocampal formation.

Activity in the hippocampal formation was mainly localized (eight subjects) ipsilateral to the side receiving
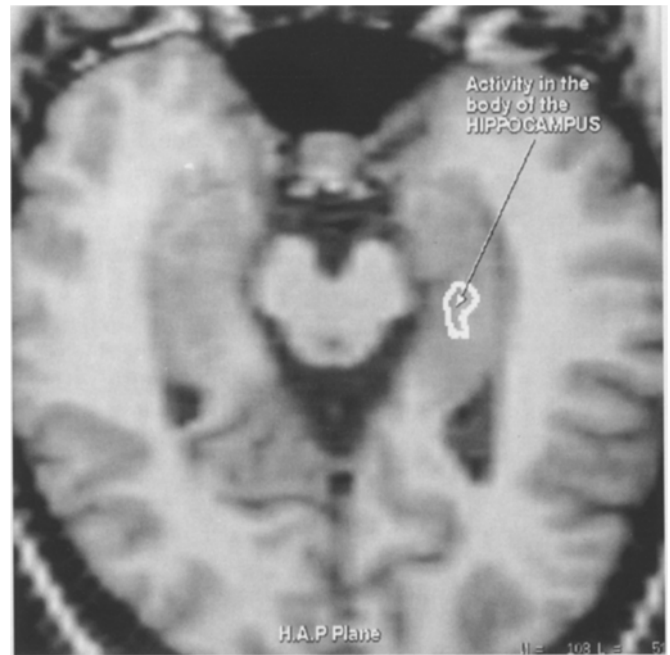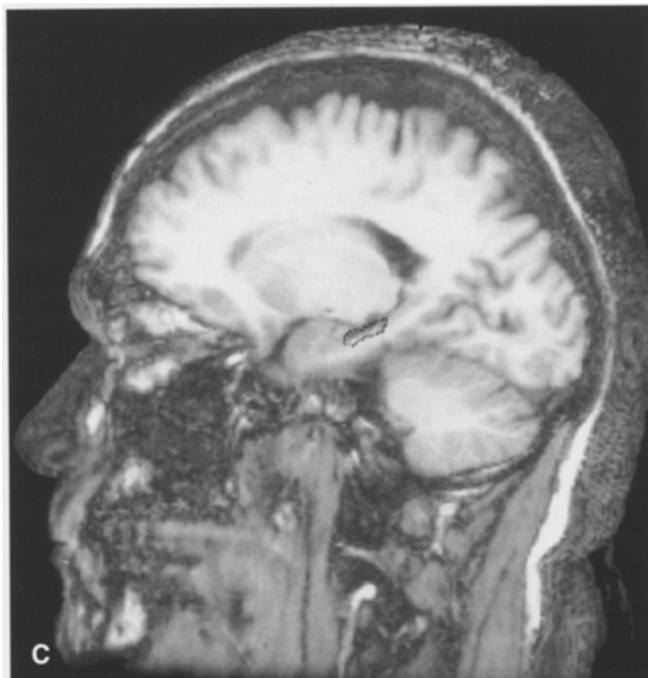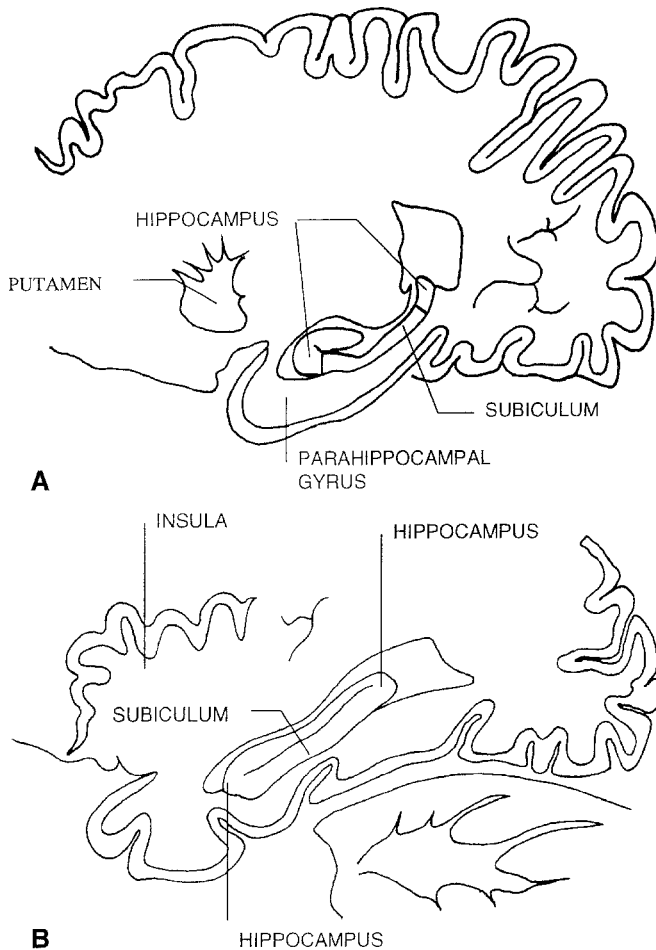
Fig. 3 Hippocampal axial plane. Activity is located in the body of the left hippocampus

the vestibular stimulation and was reproducible (three subjects underwent f-MRI three times with similar results). The activity in the hippocampal formation was present when the subject was fixating a target, showing that this activation was not due to ocular movements. The complex shape of the hippocampal formation (Duvernoy 1992), including the dentate gyrus and the hippocampus (cornu ammonis), requires careful morphological analysis of the activated regions (Naidich et al. 1988). Given the precision of our technique, this activity was restricted to the hippocampus (cornu ammonis) and/or the subiculum (Fig. 2). The mean of the correlation coefficient of the activated pixels of the hippocampal formation was 0.75 ± 0.05. Compared with the threshold correlation coefficient (i.e., 0.66) this activity was statistically significant, with $P=0.001$. The mean percentage signal change was 3.2 ± 0.8 for the ten subjects.

Discussion

Our finding of activation of the hippocampal formation during caloric vestibular stimulation is consistent with re-

Fig. 2A–C Morphology of the hippocampal formation (Naidich et al. 1988). A The hippocampal fissure separates the subiculum inferiorly from the hippocampus peripherally. B The subiculum and the hippocampus are localized respectively interferiorly and at the edges of the hippocampal fissure. C Three-dimensional (3D) reconstruction of the head. The anatomical images were acquired using gradient-echo 3D T1-weighted sequences. The activation images were acquired in exact registration with the anatomical images. After left cold caloric stimulation, activity is clearly shown in the left subiculum (*delineated area*)

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cent neurophysiological evidence in animal studies showing an influence of vestibular activity on these structures.

In the rat the hippocampus is known to be activated by multisensory cues in spatial tasks and, in addition, firing of the cells of the hippocampus is modulated by vestibular stimulations (review in Eichenbaum et al. 1989; Wiener and Berthoz 1993; MacNaughton et al. 1994; Sharp et al. 1995; Wiener et al. 1995). In addition, hippocampal theta wave activity has recently been shown to be increased during whole-body rotation (Gavrilov et al. 1995). Structures belonging to the hippocampal complex such as the postsubiculum contain head-direction cells that are probably influenced by vestibular and visual inputs (Taube et al. 1990a,b) and receive inputs from the anterior thalamus to signal head direction (Blair and Sharp 1995). These cells code for the direction of the head in space irrespective of where the animal is in a room. This head-direction system seems to be very dependent upon active exploration of space.

In the nonhuman primate, hippocampal cells recorded during whole-body motion and responding to whole-body motion even in the absence of visual cues appeared to be driven by vestibular inputs (O'Mara et al. 1994).

The anatomical pathways for vestibular-evoked hippocampal activation are not clear; however, in the monkey (Grüsser et al. 1990) vestibular information may reach the hippocampus through the subiculum via projections from the parietotemporal cortex (PIVC), the cingulate cortex and the posterior parietal cortex.

In humans, recent studies concerning hippocampal activation studied by PET during visual memory tasks (Kapur et al. 1995) have revealed a dissociation between the left and right side and have suggested an involvement of right hippocampal regions in processing of faces and of left hippocampal regions when explicit memory for faces is required. However, no data are available concerning vestibular evoked activity. Because the above data on animals suggest a role of vestibular cues in the updating of spatial coding during whole-body motion, the f-MRI activity in the hippocampal formation could be due to a rotational vertigo and spatial disorientation experienced by the subjects after a vestibular caloric stimulation, which may in turn induce a need to re-establish spatial coherence and activate several structures involved in the representation and memory of spatial orientation. It is of particular interest that lesions of the perihippocampal regions and subiculum have been found to produce topographical disorientation (Habib and Sirigu 1987).

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