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Human Vestibular Cortex as Identified with Caloric Stimulation in Functional Magnetic Resonance Imaging

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Anatomic and electrophysiological studies in monkeys have yielded a detailed map of cortex areas receiving vestibular afferents. In contrast, comparatively little is known about the cortical representation of the human vestibular system. In this study we applied caloric stimulation and fMRI to further characterize human cortical vestibular areas and to test for hemispheric dominance of vestibular information processing. For caloric vestibular stimulation we used cold nitrogen to avoid susceptibility artifacts induced by water calorics. Right and left side vestibular stimulation was repetitively performed inducing a nystagmus for at least 90 s after the end of the stimulation in all subjects. Only the first 60 s of this nystagmus period was included for statistical analysis and compared with the baseline condition. Activation maps revealed a cortical network with right hemispheric dominance, which in all subjects comprised the temporoparietal junction extending into the posterior insula and, furthermore, the anterior insula, pre- and postcentral gyrus, areas in the parietal lobe, the ventrolateral portion of the occipital lobe, and the inferior frontal gyrus extending into the inferior part of the precentral sulcus. In conclusion, caloric stimulation in fMRI reveals a widespread cortical network involved in vestibular signal processing corresponding to the findings from animal experiments and previous functional imaging studies in humans. Furthermore, this study demonstrates a strong right hemispheric dominance of vestibular cortex areas regardless of the stimulated side, consistent with the current view of a rightward asymmetrical cortical network for spatial orientation.

INTRODUCTION

For a long time, vestibular research has concentrated on labyrinthine, brainstem, and cerebellar structures to elucidate vestibular function. Spatial orientation and perception of movement, however, require processing of vestibular information at the cortical level, but comparatively little is known about the cortical representation of the vestibular system. Animal experiments have shown that there is no primary vestibular cortex that obtains projections exclusively from vestibular afferents (Guldin and Grüsser, 1998). Instead, several multimodal sensory areas have been identified, which integrate vestibular, visual, and somatosensory signals (Faugier-Grimaud and Ventre, 1989; Fredrickson *et al.*, 1966; Guldin and Grüsser, 1998; Odkvist *et al.*, 1974). In humans, these areas have been partly confirmed by intraoperative cortical stimulation (Foerster, 1936; Penfield, 1957), by clinical studies in patients with acute cortical lesions (Brandt *et al.*, 1994), and by functional imaging using positron emission tomography (PET) (Bottini *et al.*, 1994). Previous imaging studies in humans provided evidence that vestibular afferents project predominantly to the right hemisphere but separate stimulation of both vestibular organs has not been performed so far to test for this hypothesis.

Imaging of the cortical vestibular system with functional magnetic resonance imaging (fMRI), the most useful tool in functional imaging today, has been difficult to accomplish. Since caloric irrigation of the ears with hot and cold water is burdened with artifacts due to the paramagnetic properties of water, some authors have used galvanic (electrical) stimulation of the mastoids (Bucher *et al.*, 1998; Lobel *et al.*, 1998, Bense *et al.*, 2001). Galvanic vestibular stimulation, however, differs from caloric stimulation in several aspects:

1. In previous fMRI studies, galvanic stimulation has been applied to both right and left vestibular nerves simultaneously, so that the cortical response to unilateral vestibular activation could not be studied.
2. Galvanic stimulation evokes primarily ocular torsion, wheras the induced torsional and horizontal nystagmus is rather weak (Zink *et al.*, 1998) compared with the usual horizontal nystagmus velocity of 10 to

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20°/s resulting from caloric stimulation; this corresponds to a subjective illusion of tilt around the naso-occipital axis (Bense *et al.*, 2001) during galvanic stimulation, while caloric stimulation induces a constant sensation of rotation.

3. With galvanic stimulation probably all branches of the vestibular nerve are activated, originating from each of the five suborgans of the laryrinth, but it is controversial whether galvanic stimulation affects predominantly otolith afferents (Watson *et al.*, 1998) or fibers from the semicircular canals (Schneider *et al.*, 2000). In contrast, caloric stimulation affects primarily the horizontal semicircular canal.

For this study, we implemented caloric vestibular activation in fMRI with gas instead of water to stimulate each vestibular organ separately. Thereby, we intended to further characterize cortical vestibular areas and to test for hemispheric dominance of vestibular information processing.

METHODS

Subjects

Five individuals (four men, one woman, age range 24–36 years) participated in the study; none had a history of vestibular or neurological dysfunction. All subjects were right-handed according to a modified version of the Edinburgh Inventory for Handedness. The study was approved by the local ethics committee. Informed consent was obtained from each participant prior to investigation.

Data Acquisition

Imaging was performed on a 1.5-T Siemens Vision echo-planar system with a standard head coil. The head was immobilized by vacuum pads to minimize movement artifacts. Functional scans were acquired in 16 slices covering the supratentorial parts of the brain except for the orbitofrontal cortex in an oblique orientation in runs of 304 images per slice using a T2*-weighted FID echo-planar-imaging sequence (TR = 2 s, TE = 60 ms, flip angle = 90°). Slice thickness was set at 5 mm (skip 0.5 mm between slices) with 4 × 4-mm in-plane resolution (field of view = 256 × 256 mm, imaging matrix = 64 × 64). With every functional session we collected a high-resolution T1-weighted 3D-MP RAGE dataset (TR = 9.7 ms, TE = 4 ms, flip angle = 90°, field of view = 256 × 256 mm, voxel size 1 × 1 × 1 mm, 190 slices) to transform the EPI data into three-dimensional space and to perform statistical analysis from scans that were taken on different days (four to six sessions per subject). For visual control of the spatial transformation process a 2D T1-weighted scan (TR = 900 ms, TE = 14 ms, voxel size 2 × 2 × 5 mm, 16 slices) in the same orientation as the functional data complemented each experiment. In the first session, high-resolution 3D-Flash datasets (TR = 20 ms, TE = 5 ms, flip angle = 30°, field of view = 256 × 256 mm, voxel size 1 × 1 × 1 mm, 190 slices) were acquired instead of the MP RAGE to generate an individually reconstructed and inflated cortical surface as a detailed anatomical reference.

Stimulus

Caloric stimulation was applied with cold nitrogen through a plastic tube into the external ear canal. The resulting gas temperature was 5–7°C at the end of the tube. The flow of nitrogen was adjusted to the individual threshold for vestibular sensations, which was identified outside the scanner. Caloric nystagmus was recorded once for each participant outside the scanner with horizontal electro-oculography (EOG) in complete darkness. Nystagmus slow-phase velocities were measured by hand from the graph paper by averaging 10 representative slow phases during peak intensity of caloric nystagmus for each direction. Since former studies showed considerable interindividual variability of cortical activation (Bucher *et al.*, 1998; Lobel *et al.*, 1998), we performed an individual analysis of the data instead of a group analysis. Each subject underwent 6 to 10 runs comprising two caloric irrigation cycles of 60 s each for each stimulation side. Functional scans were acquired in complete darkness and participants had their eyes closed to prevent even minimal changes of visual input during nystagmus. After the scans, the participants were asked about their perception of motion.

Data Analysis

Imaging data were analyzed using the Brainvoyager 3.9 software package (R. Goebel, Max Planck Society, Germany). The first 4 volumes of each functional run were discarded to allow for signal equilibration, resulting in a total of 300 volumes for statistical analysis. The two-dimensional slice time courses were converted into three-dimensional volume time courses by coregistration with the three-dimensional anatomical data sets from the same session and interpolation to the resolution of 1 mm^3. Coregistration was based on the scanner slice position parameters for the functional and anatomical measurements and was visually controlled using the T1 scans, which were taken in the same orientation as the EPI datasets. After 3D-Motion correction, spatially smoothing with a Gaussian kernel (FWHM = 2 mm) and linear drift removal, the statistical maps for the individual subject were computed with the general linear model (GLM). This required a *Z* transformation of the time courses prior to multiple regression analysis. Since motion perception can induce compensatory head movements only functional runs that showed a displacement of less than 2 mm in

TABLE 1

Cortical Areas of the Right Hemisphere Activated in Response to Unilateral Caloric Stimulation

	Participant									
	a		b		c		d		e	
Cortical area	Right[a]	Left	Right	Left	Right	Left	Right	Left	Right	Left
A. Parieto-insular	+	+	+	+	+	+	+	+		+
B. Anterior insula	+	+	+	+	+	+	+	+	+	+
C. Post. sup. temporal sulcus	+	+	+	+				+	(+)[b]	+
D. Post. sup. temporal gyrus	+	+	+	+						+
E. Dorsolateral parietal area	+	+	+	+	+	+				
F. Inferior temporal sulcus		+	+	+					(+)	+
G. Occipital lateral gyrus	+	+	+	+		(+)		+		+
H. Central sulcus	+	+	+	+		+	+	+		+
I. Frontoparietal operculum	+	+	+	+	+	+	+		+	
J. Precentral sulcus	+	+	+	+		+	+	+		+
K. Dorsolateral prefrontal	+	+	+	+	+	+		+		
L. Posterior cingular sulcus	+	+	+	+	+	+	+	+	+	+
M. Anterior cingular gyrus	+	+	+	+	+	+	+	+	+	

[a] Stimulated side.

[b] (+) refers to a BOLD signal increase in fewer than 176 neighboring interpolated voxels at our significance level of $P < 10^{-9}$.

either direction before motion correction were included. The statistical maps were thresholded at $P < 10^{-9}$.

Three dimensional cortex reconstruction was performed by segmenting and tessellating the gray–white matter boundary and by inflating (Carman *et al.*, 1995; Van Essen *et al.*, 1998) the resulting surface mesh on the basis of the Flash data. The EPI volume time courses of later sessions were realigned by an automatic intensity-based process between the 3D-MP RAGE and the 3D-Flash scan. The statistical maps for the individual subject of all functional runs could then be calculated and overlaid on the individually reconstructed surface.

To produce activation maps, baseline measurements were compared with the 60-s period after termination of stimulus application, when the caloric nystagmus peaked as confirmed by the EOG measurements outside the scanner. By excluding the stimulation period from statistical analysis nonvestibular influences such as somatosensory and auditory stimuli were minimized. Between the functional runs we paused for 4 min to allow the vestibular excitation to subside.

RESULTS

Motion Perception and Nystagmus

All subjects reported moderate to strong vestibular sensations, which they usually described as being tilted toward the nonstimulated side. Self-motion perception started by the end of the caloric stimulation and in all subjects caloric stimulation led to motion perception for about 90 s after the end of the stimulus. No subject reported pain, nausea, sweating, or emotional discomfort. Corresponding to the reported self motion perception EOG recordings revealed a buildup of nystagmus usually during the last third of the stimulation period. Nystagmus lasted about 90 s with a mean peak slow-phase velocity of 19.8°/s (SD = 5.0°/s).

BOLD Signal Increases

Regardless of the stimulated side there was a strong right hemispheric dominance in all subjects with respect to the number of areas as well as their cluster size at the chosen statistical threshold. An exception was the medial surface of each hemisphere. In the following, clusters activated in at least one hemisphere in at least three subjects are described. The capital letters in parentheses in this section refer to Tables 1 and 2 and Figs. 1 and 2.

Insula. We found a large area of signal increase of the junction of parietal and insular cortex extending from the lateral sulcus into the posterior part of the insula (A). A second significant spot of activation was usually situated on the short gyri of the anterior insula (B). These areas could be identified in all participants (Fig. 2; Tables 1, 2).

Temporoparietal region. Four main foci were observed. One was found in the posterior part of the superior temporal sulcus extending into medial temporal gyrus in some subjects (C). Four participants had a significant signal increase on the posterior bank of the superior temporal gyrus (D), whereas the dorsolateral parietal cortex (E) at the junction of the postcentral and intraparietal sulci was activated in only three par-

TABLE 2

Cortical Areas of the Left Hemisphere Activated in Response to Unilateral Caloric Stimulation

	Participant									
	a		b		c		d		e	
Cortical area	Right[a]	Left	Right	Left	Right	Left	Right	Left	Right	Left
A. Parieto-insular	+	+	+	+	+			+		+
B. Anterior insula	+	+	+	+		+	+	+	+	+
C. Post. sup. temporal sulcus	+		+			+		+	(+)[b]	+
D. Post. sup. temporal gyrus	(+)		+					+		+
E. Dorsolateral parietal area			+	+						
F. Inferior temporal sulcus			+		+				(+)	+
G. Occipital lateral gyrus		+	+	+		(+)		+		+
H. Central sulcus	+	+	+	+	+	+	+			+
I. Frontoparietal operculum	+	+	+	+	+	+	+	+	+	
J. Precentral sulcus			+	+	+	+		+		+
K. Dorsolateral prefrontal		+	+	+				+		
L. Posterior cingular sulcus	+	+	+	+	+	+	+	+	+	+
M. Anterior cingular gyrus	+	+	+	+		+	+	+	+	

[a] Stimulated side.

[b] (+) refers to a BOLD signal increase in fewer than 176 neighboring interpolated voxels at our significance level of $P < 10^{-9}$.

ticipants. Furthermore, four participants showed an activation focus in the inferior temporal sulcus (F).

Occipital lobe. Four participants had a significant spot of activation in the occipital cortex covering the anterior portion of the occipital lateral gyrus (G). In the fifth participant we also observed activation in this area, but it failed to reach the cluster size criterion of significance.

Central region. Cortical activations were observed on the pre- and postcentral gyri around the central sulcus (H).

Frontal lobe. In the frontal lobe we found three main foci of BOLD signal increase. One was situated in the frontoparietal operculum of the inferior frontal gyrus extending into the anterior insula in some subjects (I). Additional significant areas could be observed, in the precentral sulcus (J) and in the dorsolateral prefrontal cortex (K).

Medial surface of the brain. Activation on the medial surface of the brain was found in both hemispheres in the posterior part of the cingular sulcus (L) and in the middle part of cingular gyrus (M). In contrast to the previously described foci a consistent hemispheric dominance could not be observed.

Variability between the subjects. Individual reconstruction of the cortical surfaces revealed interindividual differences in the sulcal and gyral configuration. Variations were also found with respect to the cluster size at the chosen statistical threshold. For illustration, the unfolded right insular cortex is displayed separately for each participant in Fig. 2.

DISCUSSION

Using caloric vestibular stimulation and susceptibility-sensitive fMRI we found activation of a large-scale cortical network with dominance of the right hemisphere, irrespective of the stimulated side. We observed distinct spots of activation in the parieto-insular cortex, around the central sulcus, and in parietal, temporal, occipital, and frontal areas. In the following we discuss how these widespread cortical activations can be interpreted with respect to vestibular cortical maps derived from animal work and previous studies in humans.

Temporoparietal Junction and Insula

In all subjects activation could be identified at the temporoparietal junction, which in some subjects extended into the posterior insular cortex (for details on variability of individual activations see Fig. 2). This area corresponds closely to the parieto-insular vestibular cortex (PIVC), which has been described in several monkey species (Grüsser *et al.*, 1990; Guldin and Grüsser, 1998). PIVC has been postulated to be the core region within the vestibular cortical system with respect to its strong interconnections with other vestibular cortex areas including Brodman areas 3aV, 2v, and 6, as well as with the vestibular nuclei in the brain stem (Guldin and Grüsser, 1998). More than 50% of PIVC neurons receive vestibular input (Guldin and Grüsser, 1998). Other neurons of this area respond to optokinetic or somatosensory stimuli characterizing PIVC as a multimodal sensory area (Grüsser *et al.*,

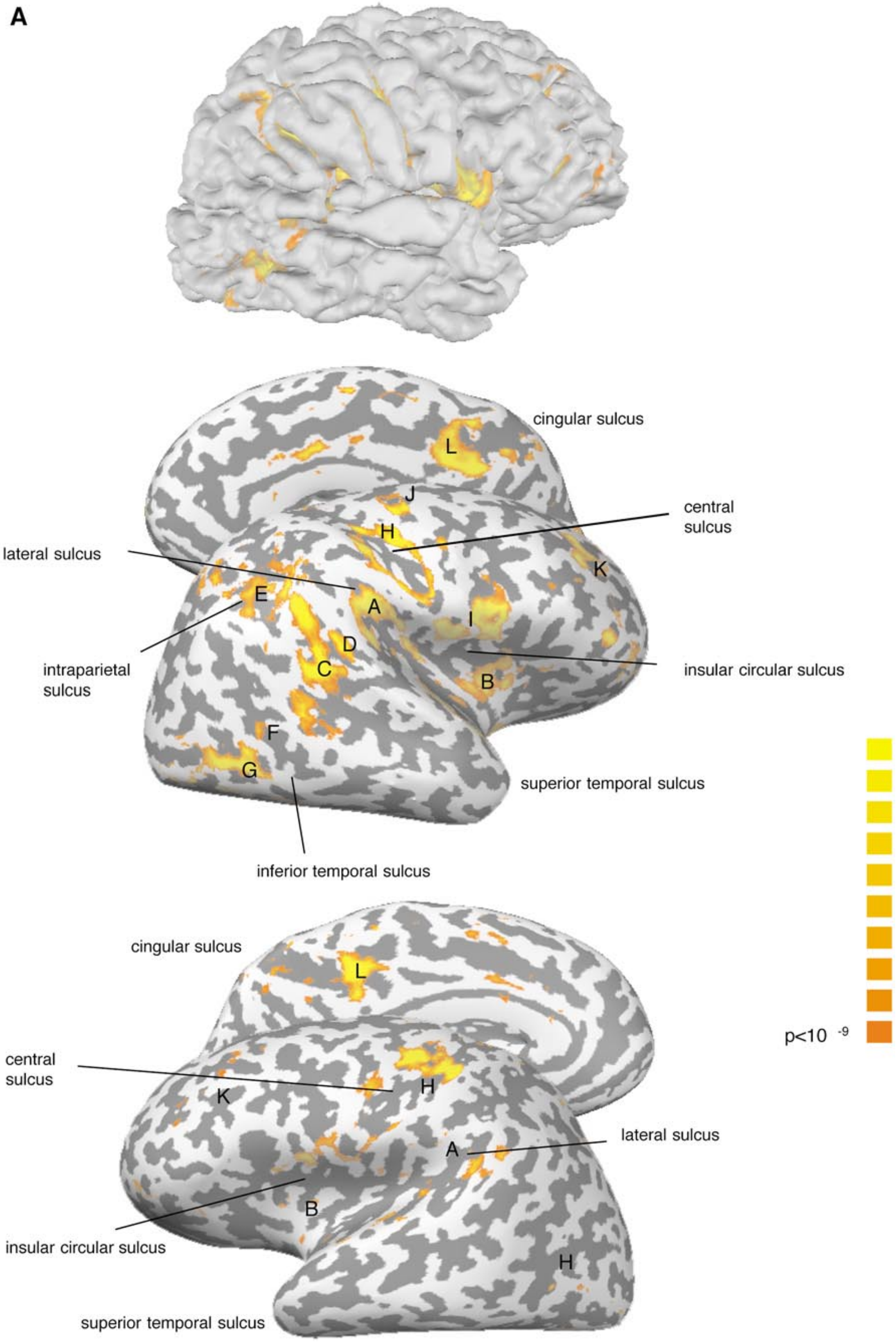


FIG. 1. Data of participant a are shown at a threshold of $P < 10^{-9}$. The light and dark gray stripes symbolize the sulcal and gyral patterns of the individual unfolded hemisphere, which is shown from lateral and medial perspectives. (A) Vestibular caloric stimulation, left ear; (B) vestibular caloric stimulation, right ear. Upper row: right hemisphere; lower row: left hemisphere.

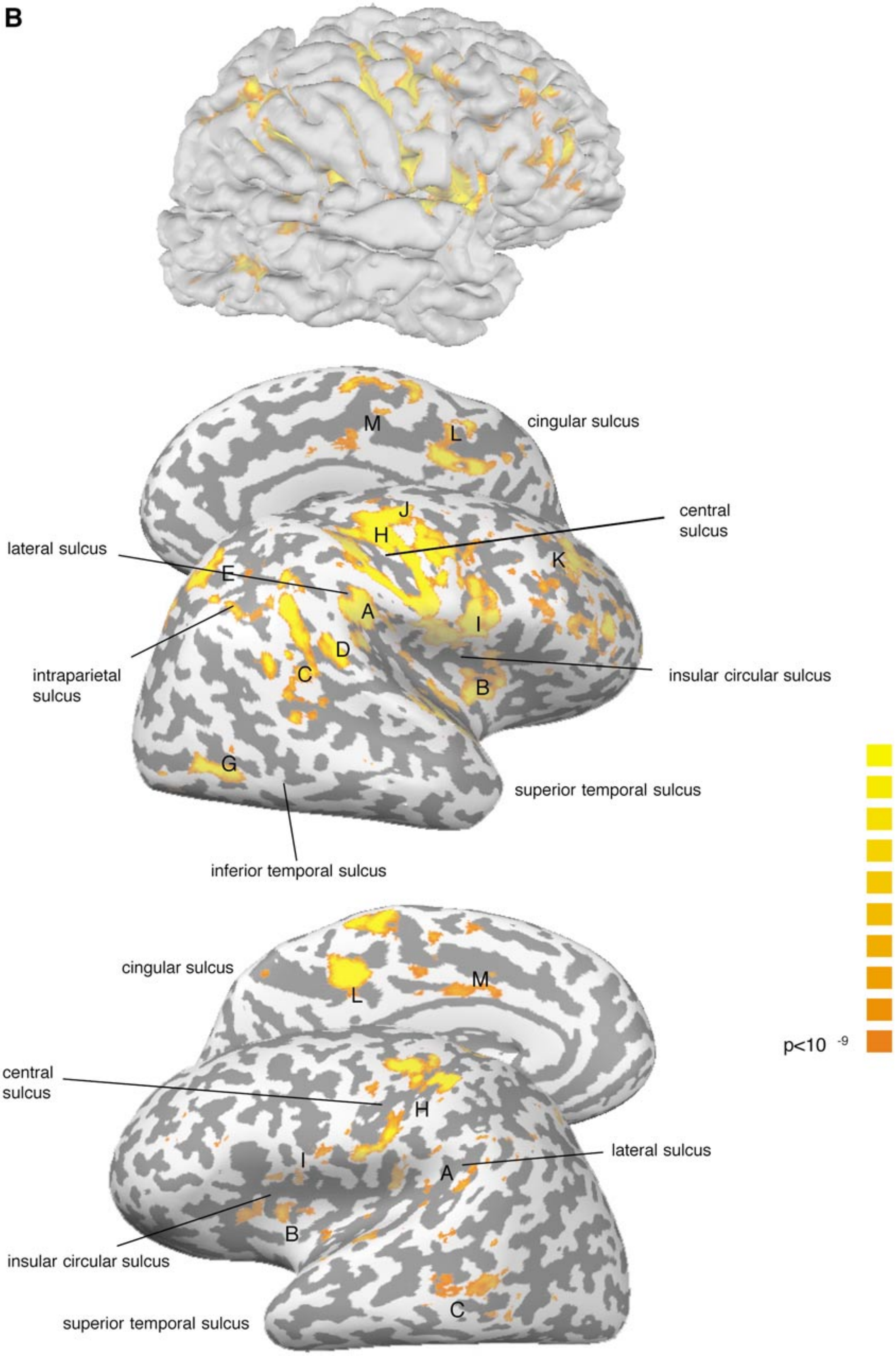
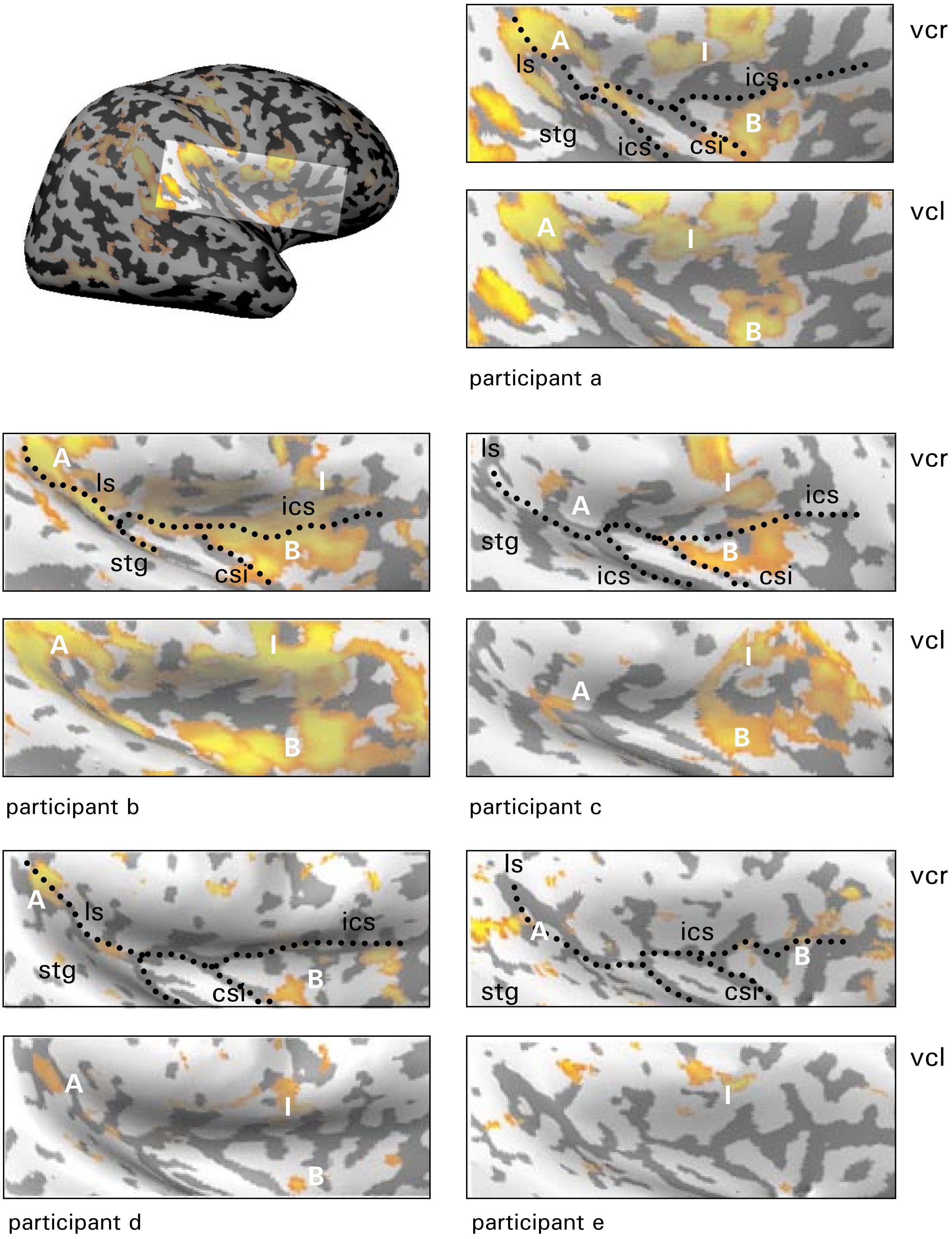


FIG. 1—*Continued*



participant a

participant b

participant c

participant d

participant e

FIG. 2. Spatial variation of activation in insula region. Data of the right hemisphere are shown for vestibular caloric stimulation of the left (vcl) and right (vcr) ears thresholded at $P < 10^{-9}$. For anatomical orientation the insular sulcal pattern is stressed with a dotted line. Anatomical landmarks: ls, lateral sulcus; stg, superior temporal gyrus; ics, insular circular sulcus; csi, central sulcus of insula.

1990). Optokinetic activation of PIVC has also been shown in humans using fMRI (Dieterich *et al.*, 1998). Brandt and colleagues (1994) demonstrated that acute lesions centered on the posterior insula cause vestibular dysfunction, namely, contraversive tilting of the subjective visual vertical. Our result of PIVC activation is further corroborated by previous imaging studies reporting blood flow increases in the temporoparietal junction and posterior insula as measured by PET during caloric stimulation (Bottini *et al.*, 1994) and during galvanic stimulation (Bucher *et al.*, 1998; Lobel *et al.*, 1998, Bense *et al.*, 2001). The interindividual anatomic variation of PIVC (Fig. 2) may account for the failure to demonstrate PIVC activation in the group analysis in some galvanic vestibular studies (Dieterich and Brandt, 2000).

We observed activation not only of the posterior insula, but also of the anterior insula in our subjects. While animal studies have failed to demonstrate a vestibular input to this area, the anterior insula can be activated by optokinetic stimulation (Dieterich *et al.*, 1998), which interacts closely with the vestibular system. Further, a recent study investigating the human neural network of spatial attention demonstrated activations bilaterally in the anterior insula (Kim *et al.*, 1999). The anterior insula is also known to correspond to both pain and painless thermal stimuli (Davis *et al.*, 1998). Although our caloric stimulus was not painful and we excluded the stimulation period itself from statistical analysis to avoid interference with the somatosensory and auditory stimulation caused by the air flow, an enduring temperature stimulus can be assumed. Therefore, activation of the anterior insula cannot be reliably ascribed to vestibular mechanisms.

Temporoparietal Areas

The visual posterior sylvian area (VPS) is situated posterior to PIVC in the inferior parietal lobe in the squirrel monkey. About 30% of the VPS neurons were found to be vestibularly driven, while most of the neurons receive optokinetic or visual input (Guldin and Grüsser, 1998). The neighboring area 7 also receives vestibular afferents (Faugier-Grimaud and Ventre, 1989), but vestibularly driven units in this area were found to be very rare (Guldin and Grüsser, 1998). Area 2v is another parietal region receiving vestibular afferents and is located in the rhesus monkey at the anterior end of the intraparietal sulcus (Akbarian *et al.*, 1994; Fredrickson *et al.*, 1966). In humans the region around the intraparietal sulcus is also referred to as parietal eye field and activated during eye movements (Muri *et al.*, 1996). There is evidence that this region is involved in spatial attention beyond the mere control of eye movements (Kim *et al.*, 1999). Even if it may be tempting to extrapolate the results from monkeys to activation focuses observed in the parietal lobe of our subjects, we hesitate to do so with respect to the variance of cortical anatomy between different species. We think that further studies are required involving stimuli from vestibular and other sensory modalities to clarify the human functional anatomy of these presumably multisensory areas.

Electrical stimulation of the superior temporal gyrus in awake humans causes sensations of rotation (Penfield, 1957). Similarly, focal epileptic seizures arising from the posterior temporal lobe may manifest with rotational vertigo and nystagmus (Furman *et al.*, 1990). An early human functional study revealed a consistent focal activation in the superior temporal region during vestibular activation (Friberg *et al.*, 1985). A recent galvanic study demonstrated activations in the superior temporal gyrus and as well in the middle temporal gyrus (Bense *et al.*, 2001). Therefore, we think that the temporal areas activated in our study can be attributed to the human vestibular cortical network.

Occipital Lobe

Interestingly, we observed activation ventrolaterally in the occipital lobe in the lateral occipital gyrus. In this location an area has been identified as the homologue of monkey MT/V5 (Tootell *et al.*, 1995; Zeki *et al.*, 1991). This region is now referred to as hMT/V5 + or MT/MST complex since it comprises also the adjacent area MST, which is closely linked to MT. The principal function of the MT/MST complex is visual motion detection and encoding of optic flow. Area MST seems to receive also semicircular canal signals in primates (Bremmer *et al.*, 1999; Thier and Erickson, 1992), which may serve to compensate for head movements in the encoding of optic flow (Andersen *et al.*, 1999). It is unlikely that changes in retinal input caused by vestibular nystagmus are responsible for MT/MST activation in our participants, since they had their eyes closed in darkness inside the scanner.

Central Region

Activation around the central sulcus may indicate the close link of the vestibular system to the somatosensory system. Vestibular projections to area 3a have been found in primates. Beside vestibular-driven neurons in the neck area of area 3a (Akbarian *et al.*, 1994; Guldin *et al.*, 1992) vestibular input to the arm area of area 3a has been described (Odkvist *et al.*, 1974). Around 40% of the units in the 3a neck region are driven by vestibular stimuli (Guldin and Grüsser, 1998), and cytoarchitectonically this region may extend into area 4. Compared with the circumscribed areas reported in the animal literature (Akbarian *et al.*, 1994; Guldin *et al.*, 1992; Odkvist *et al.*, 1974) the extension of the activation spots in this region appeared to be relatively large in some of our subjects.

Again, an enduring temperature sensation by the caloric stimulus, which may have contributed to this activation in the central region, cannot be excluded, although the activations seem to be outside the somatosensory representation field of the ear canal.

Frontal Lobe Activations

Frontal activations were found in the pars opercularis of the inferior frontal gyrus extending to the inferior part of the precentral sulcus. This activation comprises Brodman area 44 and the caudal part of Brodman area 6. Lobel *et al.* (1998) found activation spots in a similar location in their study with galvanic vestibular stimulation. Presumably these activations are homologous to the premotor area in monkeys, which is interconnected with the PIVC and VPS (Akbarian *et al.*, 1993, 1994). In humans an acute right-sided lesion of Brodman area 44 is known to cause visual neglect (Husain and Kennard, 1996). Activation of the dorsolateral prefrontal cortex, which is involved in eye movement control and attentional tasks (Funahashi *et al.*, 1991) as well as in spatial attention (Kim *et al.*, 1999), coincided with activation of the frontal eye field (FEF), which is located in the vicinity of the precentral sulcus and in the depth of the caudal-most part of the superior frontal sulcus (Paus, 1996). This activation of the FEF may be associated with nystagmus, although a vestibular nystagmus does not depend on involvement of the FEF. Such activation either may reflect a feedback signal encoding eye position during vestibular nystagmus or, beyond mere oculomotor control, may indicate the involvement of the network of spatial attention with its cortical epicenters located in the posterior parietal cortex, the frontal eye fields, and the cingulate gyrus (Mesulam, 1999).

Cingular Gyrus Activations

Both the anterior and posterior parts of the cingular gyrus were activated during vestibular-stimulation. In the squirrel monkey corticocortical connections of the so-called “inner cortical vestibular circuit” comprising PIVC, 3aV, and area 2 to the anterior cingulate cortex have been shown (Guldin *et al.*, 1992). Parts of the cingulate cortex participate in the cortical network monitoring head and body movements in space. A similar role in spatial and particularly visuospatial attention has been established in humans (Corbetta *et al.*, 1993; Kim *et al.*, 1999; Mesulam, 1999).

Asymmetries of Vestibular Activation

Unlike previous investigators, we applied unilateral vestibular stimulation on either side in all participants, which allowed insight into the hemispheric specialization of vestibular information processing. Regardless of the stimulated side we found a reproducible strong right hemispheric dominance of the activated vestibular cortical network. This is consistent with the current model of a distributed network for the representation and exploration of space with hemispheric dominance on the right (Mesulam, 1981, 1999). Recently, functional imaging revealed further experimental evidence for such an asymmetric large-scale neural network of spatial attention, which in many aspects overlaps with the vestibular network found in this study (Kim *et al.*, 1999). Interestingly, vestibular stimulation can transiently reverse impairment of spatial exploration in unilateral neglect syndrome (Cappa *et al.*, 1987; Rubens, 1985). In addition to vestibular input such a network has to integrate and process visual and somatosensory information to construct an internal representation of space (Brandt and Dieterich, 1999).

Our study has shown that caloric stimulation can be successfully employed in the MRI scanner to visualize vestibular functions at the cortical level. This approach may be useful for both physiological and clinical research as it combines the advantages of unilateral vestibular stimulation with a safe imaging procedure that can be repeatedly applied. In addition, caloric stimulation in fMRI seems to be a particularly sensitive method for labeling of vestibular areas: this study has shown significant activation of human cortex areas that are probably homologous to the major cortical areas that have been found to receive vestibular input in several primate species (Guldin and Grüsser, 1998). In addition, our approach allowed us to explore systematically the laterality of the vestibular cortical network, revealing a strong right hemispheric dominance.

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