Functional MRI of Galvanic Vestibular Stimulation

ELIE LOBEL,[1,2] JUSTUS F. KLEINE,[3] DENIS LE BIHAN,[1,2] ANNE LEROY-WILLIG,[1] AND ALAIN BERTHOZ[2]

[1]*Service Hospitalier Frédéric Joliot, Commissariat à l'Énergie Atomique, 91406 Orsay, France;* [2]*Laboratoire de Physiologie de la Perception et de l'Action, Collège de France, 75005 Paris, France; and* [3]*Department of Physiology, Freie Universität, 14195 Berlin, Germany*

Lobel, Elie, Justus F. Kleine, Denis Le Bihan, Anne Leroy-Willig A, and Alain Berthoz. Functional MRI of galvanic vestibular stimulation. *J. Neurophysiol.* 80: 2699–2709, 1998. The cortical processing of vestibular information is not hierarchically organized as the processing of signals in the visual and auditory modalities. Anatomic and electrophysiological studies in the monkey revealed the existence of multiple interconnected areas in which vestibular signals converge with visual and/or somatosensory inputs. Although recent functional imaging studies using caloric vestibular stimulation (CVS) suggest that vestibular signals in the human cerebral cortex may be similarly distributed, some areas that apparently form essential constituents of the monkey cortical vestibular system have not yet been identified in humans. Galvanic vestibular stimulation (GVS) has been used for almost 200 years for the exploration of the vestibular system. By contrast with CVS, which mediates its effects mainly via the semicircular canals (SCC), GVS has been shown to act equally on SCC and otolith afferents. Because galvanic stimuli can be controlled precisely, GVS is suited ideally for the investigation of the vestibular cortex by means of functional imaging techniques. We studied the brain areas activated by sinusoidal GVS using functional magnetic resonance imaging (fMRI). An adapted set-up including LC filters tuned for resonance at the Larmor frequency protected the volunteers against burns through radio-frequency pickup by the stimulation electrodes. Control experiments ensured that potentially harmful effects or degradation of the functional images did not occur. Six male, right-handed volunteers participated in the study. In all of them, GVS induced clear perceptions of body movement and moderate cutaneous sensations at the electrode sites. Comparison with anatomic data on the primate cortical vestibular system and with imaging studies using somatosensory stimulation indicated that most activation foci could be related to the vestibular component of the stimulus. Activation appeared in the region of the temporoparietal junction, the central sulcus, and the intraparietal sulcus. These areas may be analogous to areas PIVC, 3aV, and 2v, respectively, which form in the monkey brain, the ''inner vestibular circle''. Activation also occurred in premotor regions of the frontal lobe. Although undetected in previous imaging-studies using CVS, involvement of these areas could be predicted from anatomic data showing projections from the anterior ventral part of area 6 to the inner vestibular circle and the vestibular nuclei. Using a simple paradigm, we showed that GVS can be implemented safely in the fMRI environment. Manipulating stimulus waveforms and thus the GVS-induced subjective vestibular sensations in future imaging studies may yield further insights into the cortical processing of vestibular signals.

INTRODUCTION

The knowledge of the cortical areas involved in the processing of vestibular information is important because of the fundamental role of the vestibular system in motion perception, body orientation, eye movement, and posture control (reviewed in Berthoz 1996). Interest in this knowledge recently has been increased by the discovery that vestibular stimulation induces a remission of spatial neglect resulting from parietal lobe lesions (Vallar et al. 1990) and that vestibular cortex lesions impair the perception of verticality (Brandt et al. 1994).

In the present work, we used functional magnetic resonance imaging (fMRI) to study the areas of the cerebral cortex involved in the perceptual and motor effects of stimulation of the vestibular organs using galvanic vestibular stimulation (GVS). This is the first time that GVS was used with fMRI because we were able to implement it in this electromagnetic environment without any danger for the subjects. Previously, several areas in man have been identified to be activated by caloric vestibular stimulation (CVS: irrigation of the external ear canal with cold or warm water) using functional brain imaging (Bottini et al. 1994; Lobel et al. 1996b; Vitte et al. 1996). These areas correspond well to areas described in the monkey (reviewed in Guldin and Grüsser 1998). CVS is well known in medical practice, but it has several drawbacks for a brain imaging experiment: its postural and ocular effects are mediated predominantly by the semicircular canals, with little or no otolithic component (Barany 1907; Gentine et al. 1990); it has a slow reaction time: maximal nystagmus velocity may be reached only 80 s after stimulation and vestibular sensations can take up to 15 min to disappear (Proctor 1988), thus preventing the rapid alternation of periods with and periods without stimulation; it provokes movement of the volunteer; and with fMRI, it provokes magnetic susceptibility artifacts due to the susceptibility difference between air and water (Lobel et al. 1996b).

Clinicians early in this century were interested in GVS for the functional exploration of vestibular organs (Babinski 1903; Dohlmann 1929), and they used some specific pathologies to show that the induced postural effects were indeed of vestibular origin (Blonder and Davis 1936). More recently the clinical relevance of GVS was evaluated (Pfaltz and Koike 1968; Sekitani and Tanaka 1975; Watanabe et al. 1989). Quantitative methods for measuring the postural effects, attributed to vestibulo-spinal or vestibulo-reticulospinal descending influences, were proposed (Baldissera et al. 1990; Iles and Pisini 1992; Johansson et al. 1995; Njokiktjien and Folkerts 1971), and nystagmic eye movements have been measured in humans (Brantberg and Magnusson 1990; Pfaltz 1967). Finally the influence of cognitive factors on

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked ''*advertisement*'' in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

the galvanic motor or perceptual effects have been used as a tool for the study of the relations between the body scheme and the vestibular system (Fitzpatrick et al. 1994; Popov et al. 1986) and adaptation to microgravity (Shulhenko et al. 1983). Some limits to the interest of the method were established (Coats 1972), and nowadays it is not extensively used in the clinic by contrast with CVS.

However, for a functional brain imaging experiment, GVS has several advantages over CVS: it generally is recognized that GVS stimulates both canals and otolith afferents as compared with CVS, which mainly stimulates the semicircular canals (Goldberg et al. 1984); GVS has a fast reaction time: vestibular stimulation (VS) builds up after the onset and ceases after the offset of current with a 1- to 2-s lag, thus making it possible to alternate short (e.g., 30 s) periods of rest and stimulation; and the intensity of the delivered current can be adjusted individually to reach a precise level of VS.

Recently, new interest in this method developed because of the difficulties in measuring otolithic deficits. Even the most recent functional tests of otolith function, such as the off-vertical-axis rotation test (OVAR), remain unsatisfactory, and new methods are required (Darlot et al. 1988a,b). In parallel, neurophysiological studies have provided information concerning the mechanisms of action of GVS. Goldberg et al. (1984), recording from afferent fibers in the squirrel monkey, provided evidence that GVS acts directly on the spike trigger site of the primary vestibular neuron. GVS, by bypassing the mechanoelectrical transduction process in the vestibular hair cells, thus elicits indistinguishable responses in both semicircular canal and otolith afferents. In addition, it was demonstrated that GVS can induce modifications in both the canal induced VOR and in otolith-related nystagmic eye movements during OVAR (Angelaki and Perachio 1992; Angelaki et al. 1993).

However, no information is yet available concerning the cortical areas involved in the various perceptual or motor effects elicited by GVS. The purpose of the present study therefore was to use GVS to obtain a more complete description of the areas involved in vestibular processing. We used a specially designed stimulator using sinusoidal galvanic stimulation (Dzendolet 1963; Von Romberg et al. 1951). In this first study, we chose binaural stimulation to minimize cutaneous or nociceptive side effects. The perceptual effects of the stimulation were tested for each subject before the fMRI experiment.

It is clear that in the present set of data both somatosensory and vestibular stimulation were present as in normal clinically applied galvanic stimulation. In any case, most of the vestibular areas recognized so far have been found to be activated by multisensory inputs. Further studies are in progress to try to separate these two components of the stimulation.

METHODS

This study was approved by the Institutional Ethics Committee for Biomedical Research. Six right-handed male volunteers, aged 20–30 yr, healthy and devoid of ear problems, participated in this experiment after giving their informed consent.

Galvanic stimulation

Stimulus waveforms were generated by a function generator (Hewlett-Packard 33120 A) and fed via optocouplers into two channels of a specially constructed battery-driven current-controlled amplifier (Dipl.-Ing. Nitert, FU Berlin). The current signals reached the subjects via high-impedance carbon fiber electrodes (Bruker, Germany). To increase the contact area at the electrode sites and thereby reduce somatosensory side effects, three triplets of electrodes were used that were placed on either mastoid and on the back between the scapulae and made up two independently controlled circuits. The stimuli in all experiments consisted of 1.0-Hz sinusoids, which were 180° out of phase in the two circuits, resulting in synergistic stimulation of the left and right labyrinth. Current flow was measured as the voltage drop across resistors placed in series with the test subjects and continuously monitored on oscilloscopes during the experiments.

For fMRI, the generators were placed outside the Faraday cage, and the current leads entered the cage through low-pass filters (frequency cut: 1 MHz), which prevented radio frequency (RF) propagation through the cage. A second filterbox placed next to the subject contained small LC filters tuned for resonance at 125 MHz (Larmor frequency) and prevented RF pick-up by the electrodes. The leads of the carbon electrodes were twisted carefully together to reduce loop surface as much as possible. Several preliminary experiments were performed to ensure the safety and the quality of the installation (Lobel et al. 1997).

Psychophysical experiments

To determine the individual susceptibility to galvanically induced vestibular sensations and the sensitivities for undesired side effects, such as pain at the electrode sites or nausea, all participants were subjected to pretests 1 day before the fMRI experiment. To accustom them to the stimulation, subjects were tested first while sitting upright in a dark room with their eyes closed in an armchair equipped with a head support. Sinusoidal GVS was applied (see above), and the stimulus amplitude slowly increased from 0 mA until the subject first had a clear perception of body movement. Stimulus amplitude then was increased further to the level where heat sensation at the electrode sites started to become unpleasant or painful. Most subjects perceived a slight metallic taste at high stimulus amplitudes but prominent nausea did not occur. Finally stimulus intensity was lowered again until the vestibular sensation disappeared. By repeating the entire procedure several times, approximate threshold values for vestibular sensations and painful side effects could be established reliably in all subjects. Likewise threshold values were determined with the subjects in the supine position while they were lying with their head free on a firm mattress. Vestibular thresholds in the seated and the supine position differed by no more than 0.2 mA in all subjects and ranged from 1.2 to 1.6 mA. (mean 1.5 mA). Pain thresholds were somewhat more variable and ranged from 3.5 to 4.7 mA (mean 4.1 mA). The stimulus intensity for the fMRI experiment was set at 0.5 mA less than the individual pain threshold. Thus for each subject, stimulus amplitude in the fMRI experiment was at ~2.5 times, at least 2 times, the vestibular threshold value as determined during the pretest.

fMRI experiments

Experiments were performed on a 3 Tesla whole-body system (Bruker), equipped with a quadrature bird-cage RF coil and a head-gradient coil insert designed for echoplanar imaging (EPI). Involuntary head movements inside the magnet were prevented by taping the subject's head on the forehead and firmly restraining it on either side with foam pads. For noise protection, the subjects were earplugged and wore ear protectors. During the functional experiment, the volunteers were placed in complete darkness, with their eyes closed, and submitted for 5 min to alternations of periods without and periods with GVS (32.7 s per period). To keep a constant focus of attention, the subjects continuously performed

rhythmic fingertapping with their right index finger throughout both stimulation and rest periods. After image acquisition, they were asked to give detailed descriptions of what they had perceived during the experiment.

Data acquisition

Sets of high-resolution images (voxel: $1 \times 1 \times 2.5$ mm^3) were acquired for anatomic identification. Functional images were acquired with a T2∗-weighted single-shot gradient-echo EPI sequence (TE = 40 ms, TR = 4,670 ms, voxel = $4 \times 4 \times 5$ mm^3, 14–18 slices, 63 repetitions). The functional slab was centered on the lateral sulcus: the field of view of the global analysis we performed (see next section) includes the inferior half of the frontal and parietal gyri as well as the superior temporal gyrus and the superior part of the occipital lobe.

Data analysis

Data were analyzed individually and groupwise for the six subjects using the SPM96 software. The first four functional volumes (1st 18 s) were discarded to make sure the steady-state signal was reached. The functional volumes then were corrected for movement, normalized into the standard space defined by the Montreal National Institute template, and spatially smoothed with a 8 mm fwhm Gaussian filter (Friston et al. 1995). Statistical parametric maps were calculated using a multilinear regression analysis based on a hemodynamic modelization of the two states of the experiment and including global signal change and low frequencies (<1/120 Hz) as confounding covariates (Worsley and Friston 1995). For the two contrasts (GVS-control) and (control-GVS), activated clusters >5 voxels were obtained by thresholding at $z > 3.09$ ($P < 0.001$ uncorrected) for group analysis and at $z > 2.58$ or 1.64 ($P < 0.005$ or 0.05) for individual analysis. Statistical significance then was determined for each cluster using a correction for multiple comparisons based on cluster level and cluster extent (Poline et al. 1997).

For individual data (see RESULTS and Fig. 3), activated clusters that did not reach statistical significance also were reported. These data were used to obtain additional information on the anatomic location of activation foci identified in the group analysis.

RESULTS

Preliminary experiments

Preliminary experiments first were performed on phantoms and then on a volunteer's leg. No loss of signal was observed in the vicinity of the electrodes when comparing images with or without current. No additional noise was measured in the images with the GVS installation turned on. No detectable current was induced by gradient commutation. LC filters reduced RF pickup from ~5 mA (leading to painful cutaneous stimulation) to <200 μA (undetected by the volunteer), and when tested on a volunteer's leg, no RF sensation was induced at increasing levels of RF power (≤3 times the level used for imaging).

Consequently, all further experiments were performed safely, and no volunteer reported heating of the skin.

Psychophysical results

The vestibular sensations induced by GVS during the pretests were similar in all subjects. They consistently experienced small-amplitude (5–15°) oscillations of the entire body at stimulus frequency about an approximately midsagittal axis, which was perceived variably as passing through the body somewhere between the head and the upper abdomen. The orientation of this axis relative to the body did not change essentially when the body was brought from the seated to the supine position. These illusory vestibular phenomena are equivalent to those reported in previous studies making use of sinusoidal GVS (Grüsser and Kleine 1995; Von Romberg et al. 1951).

Inside the magnet during f MRI, all participants had qualitatively similar sensations as in the pretests. However, the perception of illusory body oscillation was generally less intense. The subjects spontaneously attributed this to the rigid head fixation and to the noise generated during image acquisition, which was still prominent despite our sound-reducing measures. Nevertheless, all subjects reported to have had distinct sensations of body movement during the periods of GVS and not during the resting periods. The build-up and the cessation of the vestibular sensation were perceived as quick and took <2 s from the onset and offset, respectively, of stimulation in all subjects. Somatosensory side effects at the electrode sites were present in all subjects and were described mostly as a moderate heating sensation. All subjects except one perceived a slight metallic taste during GVS. Nausea, as in the pretests, did not occur.

fMRI results

The comparison of the GVS condition with the control condition showed significant increase of MR signal (activation) during GVS in seven cortical areas, and significant

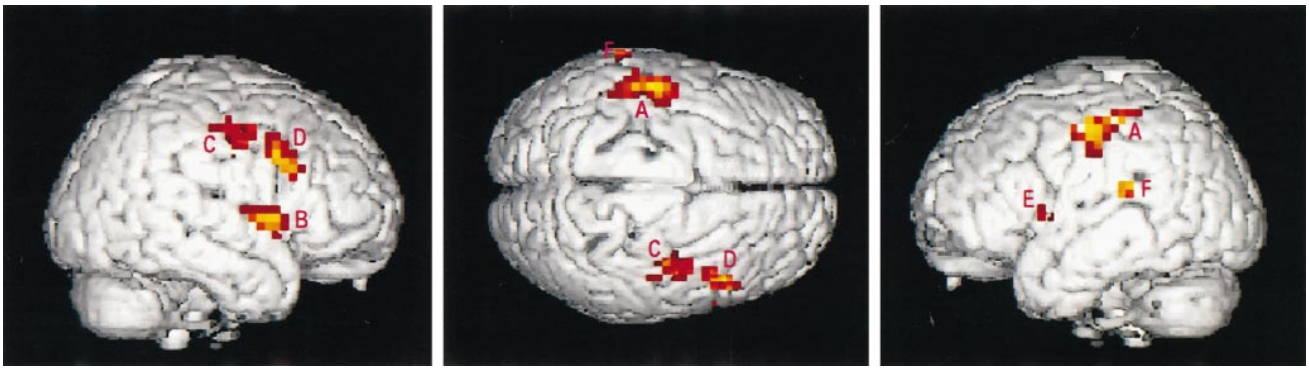


FIG. 1. Areas of significant activation (group analysis). Foci of activation are reported on a 3-dimensional reconstruction of a standardized brain. From *left* to *right*: right hemisphere view, superior view, left hemisphere view. Letters correspond to codes in Table 1. Talairach coordinates for each area are given in Table 1.

TABLE 1. *Areas of significant signal change in the comparison of the GVS condition with the control condition (group analysis)*

Region of Activation	Code	Talairach Coordinates, *x, y, z*	Number of Voxels	Corrected Cluster *P* Value
Activations				
Left postcentral g. and intraparietal s.	A	−48, −12, 48 −52, −28, 52	52	0.001
Right inferior precentral and frontal g.	B	56, 12, 0	26	0.002
Right central s.	C	40, −12, 44	44	0.002
Right middle precentral and frontal g.	D	48, 16, 36	30	0.004
Left inferior frontal g.	E	−64, 8, 4	9	0.02
Left posterior lateral s.	F	−64, −36, 20	11	0.06
Deactivations				
Transverse frontopolar g.	G	−4, 68, −8	28	0.03

Data analysis procedure is presented in METHODS. For each cluster of activation or deactivation, the coordinates of the most significant voxels in the cluster, the extent of the cluster, and the corrected *P* value are given. g., gyrus; s., sulcus.

decrease of MR signal (deactivation) during GVS in one area. Areas with significant signal change are shown in Figs. 1, 2, and 4, and presented in Table 1 with their location and their statistical significance.

TEMPORO-PARIETAL JUNCTION ACTIVATION. *Group analysis.* Significant activation was found in the left temporo-parietal junction (TPJ; area F), but was not seen in the right hemisphere. This activation was located in the posterior part of the lateral sulcus, on its external banks, and overlaps both the posterior part of the superior temporal gyrus and the inferior part of the supramarginal gyrus in the parietal lobe.

Individual analysis. Individual analysis indicates that five volunteers (*V1*–*V5*) showed an increased signal in the TPJ region (see Fig. 3). This activation was located in the posterior part of the lateral sulcus, except in *V3* where it appeared more posteriorly in the angular gyrus (significant at $P < 0.05$ corrected). The lateralization pattern appearing in the group analysis was not found at the individual level because four volunteers showed an increased signal in the right TPJ (significant at $P < 0.05$ corrected in *V5*).

CENTRAL SULCUS ACTIVATION. *Group analysis.* Activation was found in the right central sulcus (area C). This activation is large (44 voxels) and highly significant (corrected $P = 0.002$). The most significantly activated voxel was located in the depth of the central sulcus (~2 cm inside the sulcus), at about the level of the middle frontal gyrus. The area of activation also extended into the adjacent postcentral and precentral gyri.

In the left hemisphere, area A shows a highly significant activation extremum in (−48, −12, 48), adjacent to the central sulcus, in the anterior part of the left postcentral gyrus.

Individual analysis. In three volunteers (*V1*–*V3*), individual analysis indicated a significant ($P < 0.05$ corrected) and bilateral activation in the depth or on the banks of the central sulcus, at the level of the middle frontal gyrus (see Fig. 3). *V4* and *V5* also showed increased signal in this area at $z > 1.64$ in the left and in the right hemisphere, respectively (not appearing in Fig. 3 for *V5*).

PARIETAL LOBE ACTIVATION. *Group analysis.* Activation was found in only one area of the parietal lobe, unilaterally in the left hemisphere (area A). This area was very large (52 voxels), showing the highest level of significance of all areas in this study (corrected $P = 0.001$) and presented two significant extrema (see Table 1).

Area A was located mainly on the lateral surface of the left postcentral gyrus but also extended posteriorly, and the second extremum was found in the most anterior part of the intraparietal sulcus. As previously stated, area C in the right hemisphere extended into the postcentral gyrus, and thus we cannot exclude bilateral activation of the postcentral gyrus. However area A extended much more posteriorly, and the activation in the intraparietal sulcus was observed in the left hemisphere only.

Individual analysis. The lateralized pattern also was suggested by the individual analysis, which showed significant activation foci ($P < 0.05$ corrected) in the left parietal lobe only (*volunteers V1*–*V3*). In these three volunteers, the activation was located at the most anterior part of the left intraparietal sulcus, whereas in *V6* increased signal (at $z > 1.64$) appeared more posteriorly in the left parietal lobe (see Fig. 3). At $z > 1.64$, two volunteers also showed increased signal in the right parietal lobe (*V1* and *V5*, not appearing in Fig. 3).

FRONTAL LOBE: INFERIOR FRONTAL GYRUS. *Group analysis.* Bilateral activation was found on the lateral surface of the frontal lobe (area B in the right hemisphere, area E in the left). These activations were highly significant with a corrected *P* value of 0.002 for B and of 0.02 for E.

In both hemispheres, the activation was located in the most inferior and posterior part of the inferior frontal gyrus, i.e., in the pars opercularis. In the right hemisphere, the activation was wider (24 voxels) and also appeared to extend

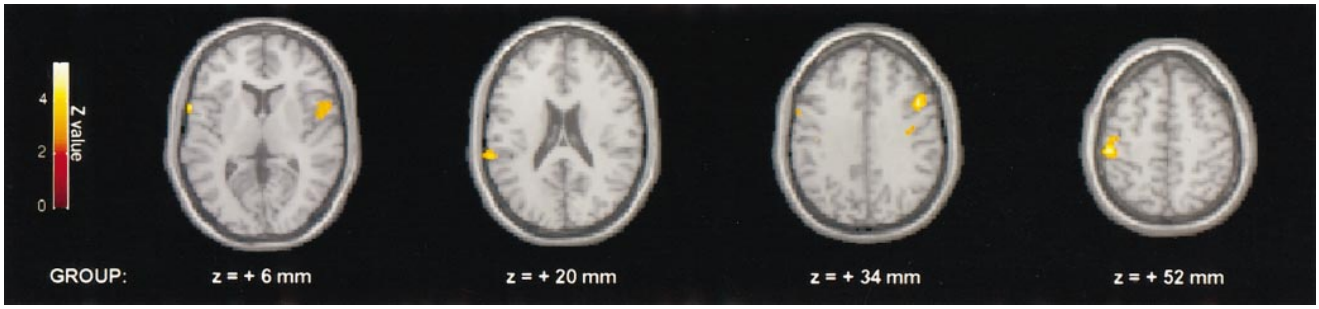


FIG. 2. Axial slices showing significant activation foci (group analysis). Foci are reported on axial slices of a standardized brain (right side of the brain is right side of image). Distance from the bicommissural plane (*z* coordinate) is indicated below each slice.

into the frontal operculum as well as into the inferior part of the precentral gyrus. However, in both hemispheres, the most significantly activated voxels were located inside the inferior frontal gyrus (see coordinates in Table 1).

Individual analysis. Five volunteers show an increased signal in the posterior part of the right inferior frontal gyrus (significant at $P < 0.05$ corrected for *V5*, not appearing in Fig. 3 for *V2*). In the left hemisphere, significant activation was found only in *V1*.

FRONTAL LOBE: INTERSECTION OF PRECENTRAL SULCUS AND INFERIOR FRONTAL SULCUS. *Group analysis.* In the right hemisphere, significant activation was also found dorsal to the previous area, in the vicinity of the intersection of the precentral sulcus and of the inferior frontal sulcus (area D, corrected $P = 0.004$). This large activation (30 voxels) was located ~1 cm inside the sulcus and overlapped the cortex of the precental gyrus and of the inferior and middle frontal gyri. In the left hemisphere, increased signal also appeared in the same region (at $z > 3.09$), but it did not reach statistical significance.

Individual analysis. In the right hemisphere, individual analysis showed in five volunteers a signal increase in this area (significant at $P < 0.05$ corrected for *V1*). In the left hemisphere, only *V1* showed an increased signal (at $z > 1.64$) in the corresponding region.

OTHER ACTIVATIONS. In the group analysis, the middle cingulate sulcus also showed an increased signal at the uncorrected threshold, but this increase did not reach statistical significance. The voxel with highest z value in this cluster was located in (0,0,48).

''DEACTIVATIONS'': GROUP ANALYSIS. In addition to these areas of activation, one region showed significant ''deactivation,'' i.e., decrease of the MR signal during GVS. This deactivation (corrected $P = 0.03$) was found in the most anterior part of the frontal lobe (area G, see Fig. 4).

It was located around the interhemispheric fissure and was located in the middle and inferior parts of the frontopolar gyrus. It also extended into the medial wall of the frontal lobe. The group analysis showed a more intense deactivation in the left hemisphere, with 20 of 28 voxels located in the left hemisphere.

Other areas showing a signal decrease at uncorrected threshold were found (ventral medial frontal gyrus, posterior cingulum), but the signal changes did not reach statistical significance.

DISCUSSION

Variability of individual activations

The group results of this study indicates that in humans a large set of areas is activated by GVS, including in particular the TPJ, the intraparietal sulcus, and the premotor regions of the frontal lobe. At the individual level, there exists however more variability (see Fig. 3), and three factors at least may contribute to this interindividual variability.

First, image acquisition requires the head to be rigidly fixated. This necessarily will lead to sensory conflicts between proprioceptive information signaling stability of the head and GVS-elicited vestibular signals indicating head movement. According to animal experiments, convergence of polysensory signals related to self-motion or object motion appears to be a fundamental property of cortical vestibular areas. Interindividual differences in the weighing of conflicting sensory signals may not only cause hardly controllable differences in the intensity of movement sensation but also lead to variability in the measurable blood-flow changes. Second, unlike in the vestibular periphery, in which all neurons will be either activated or inhibited by GVS, a variable number of type I and type II neurons can be found in cortical vestibular areas, which will respond with an increase or decrease in discharge, respectively, to a given vestibular stimulus. For example, Buettner and Büttner (1978) reported an almost equal number of type I and type II responses (26 vs. 25) to yaw rotation in vestibular neurons from area 2v of the rhesus monkey. The simultaneous occurrence of inhibitory and excitatory responses in a cortical vestibular region may end up in a relatively small net increase in neuronal activity and, therefore, blood flow. A third factor, specifically relevant for GVS, is related to the different galvanic sensitivities of regular and irregular vestibular afferents (Goldberg et al. 1984). Irregular units are highly sensitive with respect to galvanic stimulation, whereas regular afferents are only slightly modulated even by high-amplitude stimuli. There are about three times more regular than irregular units in the mammalian vestibular nerve (Baird et al. 1988; Goldberg et al. 1990), and it has been shown that regular units contribute significantly to both vestibulo-ocular and vestibulo-spinal output pathways of secondary neurons in the vestibular nuclei (Highstein et al. 1987). Therefore, it appears likely that regular afferents also participate in the mediation of vestibular information from the periphery to the cortex. The low galvanic sensitivity of regular afferents will be reflected in a low amplitude of the transmitted signals because only moderate stimulus amplitudes could be applied in our experiments.

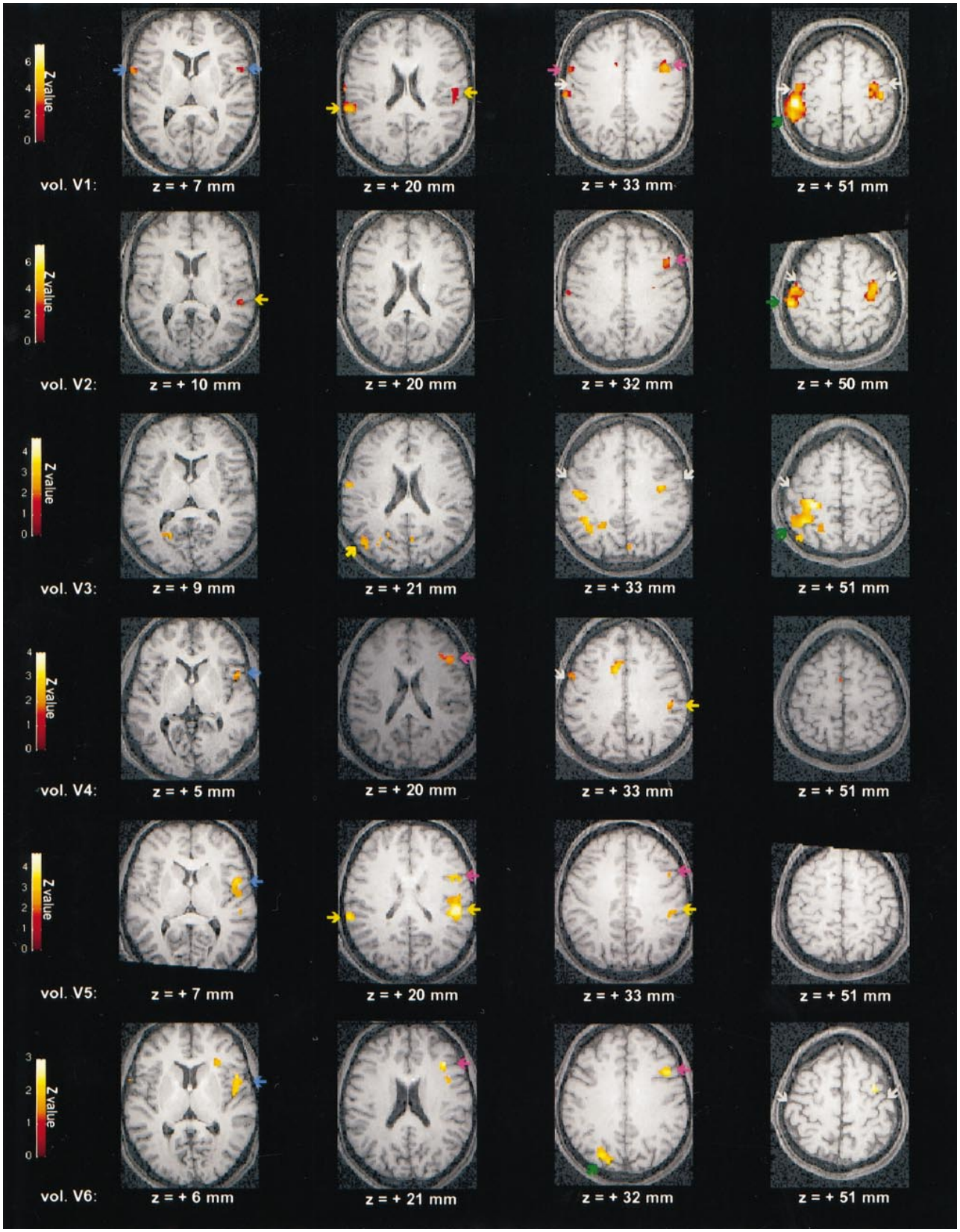
Thus on one hand, the observed interindividual variability may result from specific properties of the stimulus and of the peripheral and cortical vestibular system. On the other hand, averaging across subjects will increase the predictably low contrast-to-noise ratio in the data and enable the reliable detection of activations. Accordingly, the following discussion will put the focus on group results.

TPJ activation

In the group analysis, activation appeared in the left TPJ (area F). The individual analysis allocates this focus to the posterior end of the lateral sulcus and also shows in four volunteers a signal increase in the right hemisphere.

This area corresponds closely to a polysensory vestibular field, which recently was discovered in several primate species and designated parieto-insular vestibular cortex (PIVC) by Grüsser and co-workers (Grüsser et al. 1983, 1990; for review, see Guldin and Grüsser 1998). The PIVC is located deep in the lateral sulcus, posterior to the insular cortex. It is one of the primate areas in which neurons responding to vestibular stimulation have been found and appears to be a core area of the primate cortical vestibular system. Most vestibular neurons in the PIVC also receive an optokinetic and/or somatosensory input.

A positron emission tomography (PET) study in humans (Bottini et al. 1994) showed two distinct areas in the TPJ region contralaterally activated by cold CVS: a posterior



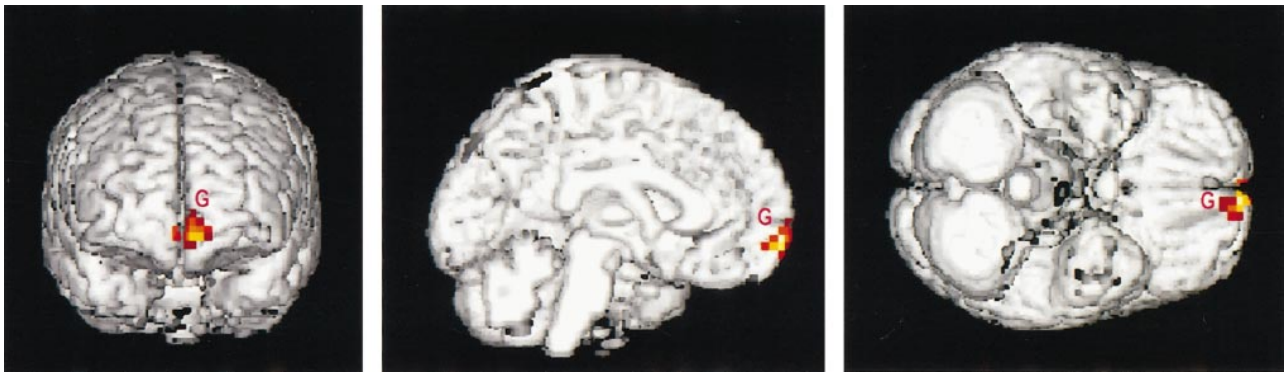


FIG. 4. Area of significant deactivation (group analysis), reported on a 3-dimensional reconstruction of a standardized brain. From *left* to *right*: anterior view, paramedian sagittal view, inferior view. Letters correspond to codes in Table 1. Talairach coordinates are given in Table 1.

insula region and a more superficial posterior lateral sulcus activation. The authors proposed that the posterior insula region be the human's equivalent of the PIVC. To our knowledge, this was the first functional imaging study pointing to a vestibular function of the human's posterior insula. Posterior insula activation, however, had been found in other functional imaging experiments using nonvestibular stimuli such as painful hot stimulation of the arm (Casey et al. 1996; Coghill et al. 1994; Talbot et al. 1991).

Until then, experiments concerning the human vestibular cortex had pointed to the involvement of the superficial part of the superior temporal or inferior parietal gyri. Penfield (1957) and Smith (1960), using electrical microstimulation of the brain in epileptic patients during surgery, evoked vestibular sensations when the electrode was placed on the external banks of the lateral sulcus, at a depth-excluding insular stimulation. Friberg et al. (1985), using SPECT and warm CVS, showed contralateral activation also coming from the superficial part of the TPJ.

In our group and individual data, no significant insular activation was found. Area F is closer to the area found by Bottini et al. (1994) in the lateral sulcus, although the location they report is 1.5 cm deeper in the sulcus. It cannot be confounded with the auditory cortex which is located almost 2 cm deeper in the lateral sulcus, in Heschl's gyrus according to several studies (Johnsrude et al. 1997; Wise et al. 1991; Zatorre et al. 1992). Area F, in the posterior part of the lateral sulcus, therefore could be the human equivalent of the monkey's PIVC region.

Central sulcus activation

In the right hemisphere, the group analysis showed an activation centered in the depth of the central sulcus and extending into the adjacent postcentral and precentral gyri (area C). In the left hemisphere, activation also was found in the postcentral gyrus (anterior part of area A). This pattern was confirmed by the analysis of individual results, which showed significant bilateral activation of this region in three volunteers.

Such an activation could be expected. In several species including monkeys, there exists a bilateral vestibular projection to the central sulcus, inside area 3a (Ödkvist et al. 1973a,b, 1974). This vestibular area is small and located within the arm field of the somatosensory cortex. A bilateral projection is in good agreement with our data because areas A and C are located in and around the central sulcus, where area 3a usually is located in humans according to architectonic data (K. Zilles, personal communication) and because areas A and C are at the level of the hand somatosensory cortex located between $z = +40$ mm and $z = +57$ mm in Talairach coordinates according to several studies (Coghill et al. 1994; Fox et al. 1987; Kawashima et al. 1994; Stephan et al. 1995; Walter et al. 1992).

Activation in areas A and C cannot be due to the finger-tapping task (FT) in which subjects were involved because FT was performed continuously during the whole experiment and should be subtracted out by the comparison of the two conditions. Even if differences in rhythm or attention during FT could have led to differences in the two conditions, such FT-related activations would be located unilaterally in the left motor cortex because FT was performed with the right index finger only.

Areas A and C are distinct from the frontal eye fields (FEF), which are located 1.4 cm more anterior in the right hemisphere and 1.9 cm more anterior in the left (review in Paus 1996). They are also distinct from the neck somatosensory area, which is situated above the hand area (Penfield and Rasmussen 1950). It is therefore unlikely that the activation could be related to the somatosensory component of the stimulus.

It appears that the region we found can be the homologue in humans of the vestibular projection to area 3a described in animals. The specific role played by this area is not well

FIG. 3. Individual foci of activation. For each volunteer, foci are reported on normalized individual axial slices (right side of the brain is right side of image). The distance from the bicommissural plane (z coordinate) is indicated below each slice. Activations maps were obtained with thresholding at $z > 2.58$ ($P < 0.005$ uncorrected) and cluster size >5 voxels for volunteers *V1, V2, V3,* and *V5.* For volunteers *V4* and *V6,* whose activations were less significant, we used a lower threshold: $z > 1.64$ ($P < 0.05$ uncorrected) and cluster size >5 voxels. Some of the depicted foci are not significant at $P < 0.05$ corrected: this is explained in METHODS, and significance is indicated in RESULTS. Each colored arrow indicates a specific focus of activation: blue, inferior frontal gyrus; yellow, temporo-parietal junction; pink, middle frontal gyrus or middle precentral gyrus; green, intraparietal sulcus. White arrows indicate the position of the central sulcus. vol., volunteer.

understood, but its high degree of convergence of vestibular and proprioceptive input could make it an important relay to ensure correct performance of directional movements.

Parietal lobe activation

An important result of this study is the unilateral activation in the left posterior parietal lobe. Group analysis as well as individual analysis showed a significant activation of an area centered around the anterior part of the left intraparietal sulcus (posterior part of area A).

Activation in this area was expected. Foerster (1936) reported that electrical stimulation of the anterior intraparietal sulcus in epileptic patients results in typical vestibular sensations of being rolled with apparent motion of the visual surroundings. In the cat, a short-latency vestibular projection to the parietal lobe was then demonstrated by Walzl and Mountcastle (1949). A homologous area also was identified in the monkey within the lower bank of the anterior tip of the intraparietal sulcus in a specific architectonic area called 2v, located posteriorly to SI neurons responding to hand or mouth stimulation (Fredrickson et al. 1966). Many neurons in area 2v receive deep somatic afferents (Schwarz and Fredrickson 1971) or respond to optokinetic stimulation (Buettner and Büttner 1978). In cats and in monkeys, vestibular projections to the parietal lobe are mainly contralateral, although a weak ipsilateral projection also exists (Fredrickson et al. 1966; Kornhuber and DaFonesca 1964).

Although an activation in the region of the intraparietal sulcus could be predicted based on these previous studies, the asymmetry in the activation pattern is an unexpected but fairly robust result, which also is reflected largely by the individual data (except for *V5* who shows signal increase in the right parietal lobe but not in the left). Given that the observed asymmetry does reflect an underlying functional lateralization, it could indicate a specialization of the human left parietal lobe in the processing of self-motion-related information. In line with this argument is a PET study that compared blood flow during coherent and incoherent wide-field visual motion, in which a similar asymmetry was observed (Cheng et al. 1995). However, such an interpretation apparently contradicts a wealth of evidence pointing to a specialization of the right hemisphere in spatial information processing.

The region of the intraparietal sulcus (IPS) is known to be involved in coordinate transformations, from retino- to cranio- or spatiotopic coordinates and also from sensory to motor coordinates (reviewed in Andersen 1994). Our results suggest that the most anterior part of the IPS is a specific region where vestibular information is processed and where it could be integrated with spatial information from other sensory modalities, particularly visual motion signals, which can be found in the IPS (Colby et al. 1993; Dupont et al. 1994).

Frontal activations

One of the most interesting results of this study is the bilateral activation in the frontal premotor regions during GVS (areas B, D, and E). No such activations have yet been reported in previous PET experiments on vestibular stimulation.

This activation is distinct from the FEF, which is localized >2.5 cm away, in the depth of the precentral sulcus at its intersection with the superior frontal sulcus (Lobel et al. 1996a; Paus 1996). In humans, Israël et al. (1995) reported that lesions of the middle and inferior posterior frontal gyri, as well as lesions of the medial anterior frontal gyrus (SEF), result in specific impairments in a task of vestibular-guided memory saccades in the dark. Furthermore, in a recent study of evoked potentials induced by selective stimulation of the vestibular nerve in humans during surgery, it was shown that three dipoles could be modeled in the frontal lobe 10 ms after the stimulation (Baudonnière et al. 1996).

Based on old (Brodmann 1909) and recent (Zilles et al. 1995) cytoarchitectonic studies, the activations we find correspond to Brodmann's area 44 (BA44) or to the most ventral part of BA6, with a possible anterior extension of area D onto the intersection with BA9/BA44. According to their location, these frontal activations appear to be homologous to the monkey vestibular region in the anterior ventral part of premotor area 6. This region sends direct corticofugal projections to the vestibular nuclei and also projects strongly to areas PIVC and 3aV (Akbarian et al. 1993, 1994), which together with area 2v form a key circuitry in the primate cortical vestibular system (Guldin et al. 1992).

Up to now, functional imaging studies failed to demonstrate the existence of this vestibular area in humans. Because these studies used CVS, one may speculate that the frontal activations we find are related to the stronger modulation of otolith afferent activity brought about by GVS. In fact, the vestibular part of area 6 is certainly among the candidate regions for a representation of otolithic signals in the primate cortex (Akbarian et al. 1993). However, our simple paradigm did not allow to separate the effects of GVS on otolith and semicircular canal afferents, and it can therefore not be decided, based on the present data, whether these frontal activations are due to an otolithic component of the galvanic stimulus or result from other methodological differences between our and the previous imaging studies. Nevertheless, the present finding of an activation focus in the region of area 6 is an important result, indicating that a vestibular region also exists in the human premotor cortex and increasing the evidence for a close correspondence between the cortical vestibular system in human and in nonhuman primates.

Finally, the asymmetrical pattern of activation our bilateral stimulation evoked in this area may be related to the general specialization of the right hemisphere in spatial behavior and can be compared with the right-sided hemispheric dominance of lesions provoking spatial hemineglect (reviewed in Bisiach and Vallar 1988). In the right hemisphere, lesions to this particular frontal region can indeed result in neglect symptoms (Husain and Kennard 1996). Furthermore recent f MRI experiments have shown that in healthy volunteers the computation of the subjective midsagittal plane, a basic egocentric spatial reference that can be strongly disturbed in spatial hemineglect, involves a bilateral activation of the same region of the lateral premotor frontal cortex with a much stronger activation in the right hemisphere (Galati et al. 1997).

Negative BOLD responses ("deactivations")

A focus of significantly negative BOLD response appeared in the transverse frontopolar gyrus (area G). According to

the Talairach and Tournoux atlas (Talairach and Tournoux 1988), this focus is located at the border between BA10 and BA11. Focal signal decreases during the ''stimulation'' relative to the ''resting'' condition frequently have been observed in functional imaging studies, but the interpretation of this phenomenon remains controversial (Le Bihan and Dohi 1995). However, recent findings suggest that it could correspond to a decrease in cerebral blood flow, i.e., represent a true ''deactivation'' (McKinstry et al. 1998).

The present finding of a signal decrease in the prefrontal cortex is interesting because it may indicate the involvement of this region in the processing of vestibular information, as already suggested by a recent study of vestibularly evoked potentials in which input to this region was observed (Baudonnière et al. 1996). However, there is no anatomic or single unit data supporting this hypothesis, and it may be worth studying this area in future vestibular animal experiments.

Conclusion

GVS led to activation in the region of the TPJ, the central sulcus, and the intraparietal sulcus, which may correspond to areas PIVC, 3aV, and 2v, respectively, in the monkey. Because of their dense reciprocal connections, these areas are thought to form a key vestibular circuitry in the primate cortex, which has been labeled as the ''inner vestibular circle'' (Guldin et al. 1992).

In addition, activation was found in the frontal premotor region, presumably analogous to the anterior ventral part of area 6, which by anatomic investigations has been identified as a vestibular region in several primate species (review in Guldin and Grüsser 1998). One may speculate, that the observed activation could be related to the modulation of otolith afferent activity elicited by GVS because previous studies using caloric stimulation failed to show an increase in activity in this area. Clearly, single-unit recordings from the various candidate areas, including areas 6, T3 and the cingulate cortex, must be performed to clarify the question of a cortical representation of the otolith organs in the primate brain. In any case, our study increases the evidence indicating a very similar organization of the cortical vestibular system in human and nonhuman primates.

Using a simple paradigm we showed that GVS can be implemented safely in the f MRI environment. Manipulating stimulus waveforms and thus the GVS-induced subjective vestibular sensations in future imaging studies may yield further insights into the cortical processing of vestibular signals.

The authors thank Dr. W. Guldin for helpful comments, Dipl. Ing. N. Nitert for the construction of the stimulator, E. Giacomini for help in adapting the stimulator to the MRI environment, and Dr. P.-F. Van de Moortele for development and improvement of high-quality EPI magnetic resonance imaging; the contribution of Prof. O. J. Grüsser in the initiation of this research is also acknowledged.

This work was supported by a ACC Action Concertée Sciences de la Vie and Galilée grants from the French Ministry of Research. E. Lobel was supported in part by a grant from the Institut de Formation Supérieure Biomédicale.

Address for reprint requests: A. Berthoz, LPPA, Collège de France, 11 place Marcelin Berthelot, 75005 Paris, France.

Received 23 February 1998; accepted in final form 7 July 1998.

REFERENCES

AKBARIAN, S., GRÜSSER, O.-J., AND GULDIN, W. O. Corticofugal projections to the vestibular nuclei in squirrel monkeys: further evidence of multiple cortical vestibular fields. *J. Comp. Neurol.* 332: 89–104, 1993.

AKBARIAN, S., GRÜSSER, O.-J., AND GULDIN, W. O. Corticofugal connections between the cerebral cortex and brainstem vestibular nuclei in the macaque monkey. *J. Comp. Neurol.* 339: 421–437, 1994.

ANDERSEN, R. A. Coordinate transformations and motor planning in posterior parietal cortex. In: *The Cognitive Neurosciences,* edited by M. S. Gazzaniga. Cambridge, MA: MIT Press, 1994, p. 519–532.

ANGELAKI, D. E. AND PERACHIO, A. A. Contribution of irregular semicircular canal afferents to the horizontal vestibuloocular response during constant velocity rotation. *J. Neurophysiol.* 69: 996–999, 1993.

ANGELAKI, D. E., PERACHIO, A. A., MUSTARI, M. J., AND STRUNK, C. L. Role of irregular otolith afferents in the steady-state nystagmus during off-vertical axis rotation. *J. Neurophysiol.* 68: 1895–1900, 1992.

BABINSKI, J. Sur le mécanisme du vertige voltaïque. *C. R. Soc. Biol. (Paris)* 55: 350–353, 1903.

BAIRD, R. A., DESMADRYL, G., FERNANDEZ, C., AND GOLDBERG, J. M. The vestibular nerve of the chinchilla. II. Relation between afferent response properties and peripheral innervation patterns in the semicircular canals. *J. Neurophysiol.* 60: 182–203, 1988.

BALDISSERA, F., CAVALLARI, P., AND TASSONE, G. Effects of transmastoid electrical stimulation on the triceps brachii EMG in man. *Neuroreport* 1: 191–193, 1990.

BARANY, R. New methods of examination of the semicircular canals and their practical significance. *Ann. Ophthalmol.* 16: 755–861, 1907.

BAUDONNIÈRE, P. M., DE WAELE, C., TRAN BA HUY, P., AND VIDAL, P.-P. Réponses évoquées vestibulaires avant et après neurectomie vestibulaire unilatérale chez l'homme. In: *Le Cortex Vestibulaire,* edited by M. Collard, M. Jeannerod, and Y. Christen. Paris: Irvinn, 1996, p. 95–108.

BERTHOZ, A. How does the cerebral cortex process and utilize vestibular signals. In: *Disorders of the Vestibular System,* edited by R. W. Baloh and G. M. Halmagyi. Oxford, UK: Oxford Univ. Press, 1996, p. 113–125.

BISIACH, E. AND VALLAR, G. Hemineglect in humans. In: *Handbook of Neuropsychology,* edited by F. Boller and J. Grafman. Amsterdam: Elsevier, 1988, p. 195–222.

BLONDER, E. J. AND DAVIS, L. The galvanic falling reaction in patients with verified intracranial neoplasms. *JAMA* 107: 411–412, 1936.

BOTTINI, G., STERZI, R., PAULESU, E., VALLAR, G., CAPPA, S. F., ERMINIO, F., PASSINGHAM, R. E., FRITH, C. D., AND FRACKOWIAK, R.S.J. Identification of the central vestibular projections in man: a positron emission tomography activation study. *Exp. Brain Res.* 99: 164–169, 1994.

BRANDT, T., DIETERICH, M., AND DANEK, A. Vestibular cortex lesions affect the perception of verticality. *Ann. Neurol.* 35: 403–412, 1994.

BRANTBERG, K. AND MAGNUSSON, M. Galvanically induced asymmetric optokinetic after-nystagmus. *Acta Otolaryngol. (Stockh.)* 110: 189–195, 1990.

BRODMANN, K. *Vergleichende Lokalisationslehre der Grosshinrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues.* Leipzig: Barth, 1909.

BUETTNER, U. AND BÜTTNER, U. W. Parietal cortex activity in the alert monkey during natural vestibular and optokinetic stimulation. *Brain Res.* 153: 392–397, 1978.

CASEY, K. L., MINOSHIMA, S., MORROW, T. J., AND KOEPPE, R. A. Comparison of human cerebral activation patterns during cutaneous warmth, heat pain, and deep cold pain. *J. Neurophysiol.* 76: 571–582, 1996.

CHENG, K., FUJITA, H., KANNO, I., MIURA, S., AND TANAKA, K. Human cortical regions activated by wide-field visual motion: an $H_2{}^{15}O$ PET study. *J. Neurophysiol.* 74: 413–427, 1995.

COATS, A. C. Limit of normal of the galvanic body-sway test. *Acta Otolaryngol. (Stockh.)* 81: 410–416, 1972.

COGHILL, R. C., TALBOT, J. D., EVANS, A. C., MEYER, E., GJEDDE, A., BUSHNELL, M. C., AND DUNCAN, G. H. Distributed processing of pain and vibration by the human brain. *J. Neurosci.* 14: 4095–4108, 1994.

COLBY, C. L., DUHAMEL, J. R., AND GOLDBERG, M. E. Ventral intraparietal area of the macaque: anatomic location and visual response properties. *J. Neurophysiol.* 69: 902–914, 1993.

DARLOT, C., DENISE, P., DROULEZ, J., COHEN, B., AND BERTHOZ, A. Eye movements induced by off-vertical axis rotation (OVAR) at small angles of tilt. *Exp. Brain Res.* 73: 91–105, 1988a.

DARLOT, C., DENISE, P., DROULEZ, J., COHEN, B., AND BERTHOZ, A. Motion perceptions induced by off-vertical axis rotation (OVAR) at small angles of tilt. *Exp. Brain Res.* 73: 106–114, 1988b.

DOHLMANN, G. Experimentelle Untersuchungen über die galvanische vestibuläre Reaktion (Abstract). *Acta Otolaryngol. Suppl. (Stockh.)* 8: 48, 1929.

DUPONT, P., ORBAN, G. A., DE BRUYN, B., VERBRUGGEN, A., AND MORTELMANS, L. Many areas in the human brain respond to visual motion. *J. Neurophysiol.* 72: 1420–1424, 1994.

DZENDOLET, E. Sinusoidal electrical stimulation of the human vestibular apparatus. *Percept. Mot. Skills* 17: 171–185, 1963.

FITZPATRICK, R., BURKE, D., AND GANDEVIA, S. C. Task-dependent reflex responses and movement illusions evoked by galvanic vestibular stimulation in standing humans. *J. Physiol. (Lond.)* 478: 363–371, 1994.

FOERSTER, O. Sensible corticale Felder. In: *Handbuch der Neurologie,* edited by O. Bumke and O. Foerster. Berlin: Springer, 1936, p. 358–449.

FOX, P. T., BURTON, H., AND RAICHLE, M. E. Mapping human somatosensory cortex with positron emission tomography. *J. Neurosurg.* 67: 34–43, 1987.

FREDRICKSON, J. M., FIGGE, U., SCHEID, P., AND KORNHUBER, H. H. Vestibular nerve projection to the cerebral cortex of the rhesus monkey. *Exp. Brain Res.* 2: 318–327, 1966.

FRIBERG, L., OLSEN, T. S., ROLAND, P. E., PAULSON, O. B., AND LASSEN, N. A. Focal increase of blood flow in the cerebral cortex of man during vestibular stimulation. *Brain* 108: 609–623, 1985.

FRISTON, K. J., ASHBURNER, J., FRITH, C. D., POLINE, J. B., HEATHER, J. D., AND FRACKOWIAK, R.S.J. Spatial registration and normalization of images. *Hum. Brain Mapping* 3: 165–189, 1995.

GENTINE, A., EICHHORN, J.-L., KOPP, C., AND CONRAUX, C. Modelling the action of caloric stimulation of the vestibule. I. the hydrostatic model. *Acta Otolaryngol. (Stockh.)* 110: 328–333, 1990.

GOLDBERG, J. M., DESMADRYL, G., BAIRD, R. A., AND FERNANDEZ, C. The vestibular nerve of the chinchilla. IV. Discharge properties of utricular afferents. *J. Neurophysiol.* 63: 781–790, 1990.

GOLDBERG, J. M., SMITH, C. E., AND FERNANDEZ, C. Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J. Neurophysiol.* 51: 1236–1256, 1984.

GRÜSSER, O.-J. AND KLEINE, J. F. The effect of binaural galvanic stimulation in man. *Soc. Neurosci. Abstr.* 21: 135, 1995.

GRÜSSER, O.-J., PAUSE, M., AND SCHREITER, U. A new vestibular area in the primate cortex. *Soc. Neurosci. Abstr.* 9: 749, 1983.

GRÜSSER, O.-J., PAUSE, M., AND SCHREITER, U. Localization and responses of neurones in the parieto-insular vestibular cortex of awake monkeys (*Macaca fascicularis*). *J. Physiol. (Lond.)* 430: 537–557, 1990.

GULDIN, W. O., AKBARIAN, S., AND GRÜSSER, O.-J. Cortico-cortical connections and cytoarchitectonics of the primate vestibular cortex: a study in squirrel monkeys (*Saimiri sciureus*). *J. Comp. Neurol.* 326: 375–401, 1992.

GULDIN, W. O. AND GRÜSSER, O.-J. Is there a vestibular cortex? *Trends Neurosci.* 21: 254–259, 1998.

HIGHSTEIN, S. M., GOLDBERG, J. M., MOSCHOVAKIS, A. K., AND FERNANDEZ, C. Inputs from regularly and irregularly discharging vestibular nerve afferents to secondary neurons in the vestibular nuclei of the squirrel monkey. II. Correlation with output pathways of secondary neurons. *J. Neurophysiol.* 58: 719–738, 1987.

HUSAIN, M. AND KENNARD, C. Visual neglect associated with frontal lobe infarction. *J. Neurol.* 243: 652–657, 1996.

ILES, J. F. AND PISINI, J. V. Vestibular-evoked postural reactions in man and modulation of transmission in spinal reflex pathways. *J. Physiol. (Lond.)* 455: 407–424, 1992.

ISRAËL, I., RIVAUD, S., GAYMARD, B., BERTHOZ, A., AND PIERROT-DESEILLIGNY, C. Cortical control of vestibular-guided saccades in man. *Brain* 118: 1169–1183, 1995.

JOHANSSON, R., MAGNUSSON, M., AND FRANSSON, P. A. Galvanic vestibular stimulation for analysis of postural adaptation and stability. *IEEE Trans. Biomed. Eng.* 42: 282–292, 1995.

JOHNSRUDE, I. S., PAUS, T., ZATORRE, R. J., PERRY, D. W., WARD, G. P., AND EVANS, A. C. The location of auditory activation foci relative to Heschl's gyri (Abstract). *Neuroimage* 5: S177, 1997.

KAWASHIMA, R., ROLAND, P. E., AND O'SULLIVAN, B. T. Activity in the human primary motor cortex related to ipsilateral hand movements. *Brain Res.* 663: 251–256, 1994.

KORNHUBER, H. H. AND DAFONESCA, J. S. Optovestibular integration in the cat's cortex: a study of sensory convergence on cortical neurons. In: *The Oculomotor System,* edited by M. B. Bender. New York: Harper and Row (Hoeber), 1964, p. 239–279.

LEBIHAN, D. AND DOHI, M. Can f MRI detect decreased neuronal activity (Abstract)? *Proc. Soc. Magn. Reson.* 1: 452, 1995.

LOBEL, E., BERTHOZ, A., LEROY-WILLIG, A., AND LE BIHAN, D. f MRI study of voluntary saccadic eye movements in humans (Abstract). *Neuroimage* 3: S396, 1996a.

LOBEL, E., LE BIHAN, D., LEROY-WILLIG, A., AND BERTHOZ, A. Searching for the vestibular cortex with functional MRI (Abstract). *Neuroimage* 3: S351, 1996b.

LOBEL, E., KLEINE, J., LE BIHAN, D., GIACOMINI, E., BERTHOZ, A., AND LEROY-WILLIG, A. FMRI of the vestibular cortex with galvanic stimulation: a feasibility study (Abstract). *Proc. Soc. Magn. Reson.* 1: 450, 1997.

MCKINSTRY, R. C., OJEMANN, J. G., SNYDER, A. Z., AKBUDAK, E., OLLINGER J. M., BURTON, H., MCDERMOTT, K. B., DAVIS, T. L., RAICHLE, M. E., AND CONTURO, T. E. BOLD- f MRI changes in regions of rCBF-PET increases and decreases during vibrotactile stimulation (Abstract). *Proc. Soc. Magn. Res.* 1: 512, 1998.

NJOKIKTJIEN, C. AND FOLKERTS, J. F. Displacement of the body's centre of gravity at galvanic stimulation of the labyrinth. *Confin. Neurol.* 33: 46–54, 1971.

ÖDKVIST, L. M., RUBIN, A. M., SCHWARZ, D.W.F., AND FREDRICKSON, J. M. Vestibular and auditory cortical projection in the guinea pig (*Cavia porcellus*). *Exp. Brain Res.* 18: 279–286, 1973a.

ÖDKVIST, L. M., RUBIN, A. M., SCHWARZ, D.W.F., AND FREDRICKSON, J. M. Vestibular cortical projections in the rabbit. *J. Comp. Neurol.* 149: 117–120, 1973b.

ÖDKVIST, L. M., SCHWARZ, D.W.F., FREDRICKSON, J. M., AND HASSLER, R. Projection of the vestibular nerve to the area 3a arm field in the squirrel monkey. *Exp. Brain Res.* 21: 97–105, 1974.

PAUS, T. Location and function of the human frontal eye-field: a selective review. *Neuropsychologia* 34: 475–483, 1996.

PENFIELD, W. Vestibular sensation and the cerebral cortex. *Ann. Otol. Rhinol. Laryngol.* 66: 691–698, 1957.

PENFIELD, W. AND RASMUSSEN, T. *The Cerebral Cortex of Man: a Clinical Study of Localization of Function.* New York: Macmillan, 1950.

PFALTZ, C. R. Recherches nystagmographiques sur la réaction galvanique vestibulaire. *Rev. Neurol. (Paris)* 117: 309–315, 1967.

PFALTZ, C. R. AND KOIKE, Y. Galvanic test in central vestibular lesions. *Acta Otolaryngol. (Stockh.)* 65: 161–168, 1968.

POLINE, J.-B., HOLMES, A., WORSLEY, K., AND FRISTON, K. J. Making statistical inferences. In: *Human Brain Function,* edited by R.S.J. Frackowiak, K. J. Friston, C. D. Frith, R. J. Dolan, and J. C. Mazziotta. San Diego, CA: Academic, 1997, p. 85–106.

POPOV, K. E., SMETANIN, B. N., GURFINKEL, V. S., KUDINOVA, M. P., AND SHLYKOV, V. I. Spatial perception and vestibulomotor reactions in man. *Neirofiziologiia* 18: 779–787, 1986.

PROCTOR, L. R. Clinical experience with a short-acting, adjustable caloric stimulation. In: *Vestibular Disorders,* edited by H. O. Barber and J. A. Sharpe. Chicago: Year Book Medical Publishers, 1988, p. 87–96.

SCHWARZ, D.W.F. AND FREDRICKSON, J. M. Rhesus monkey vestibular cortex: a bimodal primary projection field. *Science* 172: 280–281, 1971.

SEKITANI, T. AND TANAKA, M. Test for galvanic vestibular responses—survey of experimental and clinical investigation for the last 20 years. *Bull. Yamaguchi Med. Sch.* 22: 439–452, 1975.

SHULHENKO, J. B., GOGILADZE, G. I., AND KOZLOVA, V. G. Binaural galvanic stimulation of labyrinths used to the imitation of vestibular afferentation in the weightlessness. *Space Biol. Aerospace Med.* 17: 86–88, 1983.

SMITH, B. H. Vestibular disturbances in epilepsy. *Neurology* 10: 465–469, 1960.

STEPHAN, K. M., FINK, G. R., PASSINGHAM, R. E., SILBERSWEIG, D., CEBALLOS-BAUMANN, A. O., FRITH, C. D., AND FRACKOWIAK, R.S.J. Functional anatomy of mental representation of upper extremity movements in healthy subjects. *J. Neurophysiol.* 73: 373–386, 1995.

TALAIRACH, J. AND TOURNOUX, P. *Co-Planar Stereotaxic Atlas of the Human Brain.* Stuttgart: Georg Thieme Verlag, 1988.

TALBOT, J. D., MARRETT, S., EVANS, A. C., MEYER, E., BUSHNELL, M. C., AND DUNCAN, G. H. Multiple representation of pain in human cerebral cortex. *Science* 251: 1355–1358, 1991.

VALLAR, G., LOBEL, E., GALATI, G., BERTHOZ, A., PIZZAMIGLIO, L., AND LE BIHAN, D. A fronto-parietal system for computing the egocentric spatial frame of reference in humans. *Exp. Brain Res.* In press.

VALLAR, G., STERZI, R., BOTTINI, G., CAPPA, S. F., AND RUSCONI, M. L. Temporary remisssion of left hemianesthesia after vestibular stimulation. A sensory neglect phenomenon. *Cortex* 26: 123–131, 1990.

VITTE, E., DEROSIER, C., HASBOUN, D., CARITU, Y., AND BERTHOZ, A. Activation of the hippocampal formation by vestibular stimulation: a fMRI study. *Exp. Brain Res.* 112: 523–526, 1996.

VON ROMBERG, G., VON HOLST, E., AND DODEN, W. Über Zusammenhänge zwischen Wahrnehmung und objektivem Geschehen bei Wechselstromreizung des Vestibularapparates und optokinetischer Pendelreizung der Retina. *Pflügers Arch.* 254: 98–106, 1951.

WALTER, H., KRISTEVA, R., KNORR, U., SCHLAUG, G., HUANG, Y., STEINMETZ, H., NEBELING, B., HERZOG, H., AND SEITZ, R. J. Individual somatotopy of primary sensorimotor cortex revealed by intermodal matching of MEG, PET, and MRI. *Brain Topogr.* 5: 183–187, 1992.

WALZL, E. M. AND MOUNTCASTLE, V. B. Projection of vestibular nerve to cerebral cortex of cat. *Am. J. Physiol.* 159: 595, 1949.

WATANABE, Y., ASAI, M., KINOSHITA, A., AND MIZUKOSHI, K. Retro-labyrinthine disorders detected by galvanic body sway responses in routine equilibrium examinations. *Acta Otolaryngol. (Stockh.)* 468: 343–348, 1989.

WISE, R., CHOLLET, F., HADAR, U., FRISTON, K. J., HOFFNER, E., AND FRACKOWIAK, R. S. J. Distribution of cortical neural networks involved in word comprehension and word retrieval. *Brain* 114: 1803–1817, 1991.

WORSLEY, K. J. AND FRISTON, K. J. Analysis of fMRI time-series revisted—again. *Neuroimage* 2: 173–181, 1995.

ZATORRE, R. J., EVANS, A. C., MEYER, E., AND GJEDDE, A. Lateralization of phonetic and pitch discrimination in speech processing. *Science* 256: 846–849, 1992.

ZILLES, K., SCHLAUG, G., MATELLI, M., LUPPINO, G., SCHLEICHER, A., QU, M. S., DABRINGHAUS, A., SEITZ, R. J., AND ROLAND, P. E. Mapping of human and macaque sensorimotor areas by integrating architectonics, transmitter receptor, MRI and PET data. *J. Anat.* 187: 515–537, 1995.