Multisensory Cortical Signal Increases and Decreases During Vestibular Galvanic Stimulation (fMRI)

SANDRA BENSE, THOMAS STEPHAN, TAREK A. YOUSRY, THOMAS BRANDT, AND MARIANNE DIETERICH
1Department of Neurology and 2Department of Neuroradiology, Klinikum Grosshadern, Ludwig-Maximilians University, 81377 Munich, Germany

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Bense, Sandra, Thomas Stephan, Tarek A. Yousry, Thomas Brandt, and Marianne Dieterich. Multisensory cortical signal increases and decreases during vestibular galvanic stimulation (fMRI). J Neurophysiol 85: 886–899, 2001. Functional magnetic resonance imaging blood-oxygenation-level-dependent (BOLD) signal increases (activations) and BOLD signal decreases (“deactivations”) were compared in six healthy volunteers during galvanic vestibular (mastoid) and galvanic cutaneous (neck) stimulation in order to differentiate vestibular from ocular motor and nociceptive functions. By calculating the contrast for vestibular activation minus cutaneous activation for the group, we found activations in the anterior parts of the insula, the paramedian and dorsolateral thalamus, the putamen, the inferior parietal lobule [Brodmann area (BA) 40], the precentral gyrus (frontal eye field, BA 6), the middle frontal gyrus (prefrontal cortex, BA 46/9), the middle temporal gyrus (BA 37), the superior temporal gyrus (BA 22), and the anterior cingulate gyrus (BA 32) as well as in both cerebellar hemispheres. These activations can be attributed to multisensory vestibular and ocular motor functions. Single-subject analysis in addition showed distinctly nonoverlapping activations in the posterior insula, which corresponds to the parieto-insular vestibular cortex in the monkey. During vestibular stimulation, there was also a significant signal decrease in the visual cortex (BA 18, 19), which spared BA 17. A different “deactivation” was found during cutaneous stimulation; it included upper parieto-occipital areas in the middle temporal and occipital gyri (BA 19/39/18). Under both stimulation conditions, there were signal decreases in the somatosensory cortex (BA 2/3/4). Stimulus-dependent, inhibitory vestibular-visual, and nociceptive-somatosensory interactions may be functionally significant for processing perception and sensorimotor control.

INTRODUCTION

Vestibular galvanic stimulation (GVS) at the mastoid level acts on the eighth nerve (Goldberg et al. 1984) and elicits postural imbalance (Inglis et al. 1996), a rotational or tilt sensation, and tonic ocular torsion with superimposed nystagmus (Watson and Colebach 1998; Zink et al. 1998). GVS can be used to identify vestibular cortex structures provided that the differential effects of the associated auditory and somatosensory systems can be separated clearly enough. An experimental vestibular stimulus that selectively excites only the vestibular system is not currently available.

A previous fMRI study using fast low-angle shot (FLASH) sequences of the insular-thalamic region showed that GVS induced significant activations of the parieto-insular vestibular cortex (PIVC) and the posterior median thalamus (Bucher et al. 1998). According to monkey studies, both of these areas are involved in the processing of vestibular function (Grüsser et al. 1990a,b). However, the simultaneous activation of the transverse temporal (Heschl’s) gyrus indicates that the auditory systems are also involved. Likewise the bilateral activation of the medial part of the insula and the anterior-median thalamus indicates that the nociceptive system is involved too. Cutaneous galvanic pain stimulation (GPS) at the neck C5 level as a control (Bucher et al. 1998) also activated these nociceptive areas. Due to technical limitations, this FLASH study was limited to three sections in the insular-thalamic region and did not allow differentiation between signal increases and decreases. The only available study on whole-brain imaging during GVS ascribed multiple cortical areas to vestibular function (Lobel et al. 1998). Some of these areas probably reflect nonvestibular auditory and nociceptive functions since no control stimuli were used for both sensory stimuli.

On the basis of these previous works, we addressed two major questions in the present whole-brain functional magnetic resonance imaging (fMRI) study on GVS in normal subjects: what are the differential activation patterns during galvanic (nonvestibular) cutaneous, galvanic vestibular and cutaneous, and purely auditory stimulation and is not only “activation” [blood-oxygenation-level-dependent (BOLD) signal increase] but also simultaneous BOLD signal decrease (“deactivation”) evident under these conditions? “Deactivation” is of particular interest, since in an earlier positron emission tomography (PET) study on vestibular caloric irrigation, we found an increase in regional cerebral blood flow (rCBF) of the posterior insula (e.g., PIVC) with a simultaneous, significant, bilateral decrease in rCBF of the visual cortex covering Brodmann areas 17–19 (Wenzel et al. 1996).

METHODS

We examined six healthy, right-handed volunteers (3 females, 3 males; ages 25–43 yr, mean age, 33.3 yr) without any history of cochlear, vestibular, or CNS disorders. The study was approved by the

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local Ethics Committee of the Ludwig-Maximilians University, and all subjects gave their informed written consent.

MRI acquisition

Functional images were acquired on a standard clinical scanner (Siemens Vision, Erlangen, Germany) at a magnetic field strength of 1.5 T using a circularly polarized head coil and echo-planar imaging (EPI) with a T2*-weighted gradient-echo multislice sequence (TE = 66 ms, TR = 5,500 ms, voxel size 1.88 × 1.88 × 5 mm³). Twenty-four transversal slices with a matrix size of 128 × 128 pixels covered the whole brain and the upper parts of the cerebellum. Each scanning session comprised two successive time series consisting of 110 and 60 images, respectively, due to technical limitations of the scanner software. In both runs, a block design of five images at rest and five images during stimulation was used; the first 5 volumes of each run were discarded because of spin-saturation effects. In the first series, GVS at the mastoid and GPS at the neck C₅₀ level were interchangeably applied in blocks; in the second series acoustic stimulation (AS) artifacts, the forehead was also taped to the coil.

Galvanic stimulation

Animal studies have shown that externally applied galvanic currents modulate the tonic firing rate of vestibular afferents by acting directly on the vestibular afferents close to their postsynaptic trigger site (Goldberg et al. 1984). This broad-based stimulation is believed to act primarily on the fibers of the vestibular nerve. Galvanic vestibular stimulation in humans was performed in two runs by placing adhesive carbon electrodes over both mastoid processes: cathode always on the left side (n = 2), cathode always on the right side (n = 2), or cathode once on the left and once on the right side (n = 2). Galvanic pain stimulation (GPS) was used as a control by placing an additional pair paravertebrally at the neck C₅₀ level, which is far enough away from the upper cervical segments to ensure that no major muscle spindle afferents to the vestibular nuclei were stimulated. A battery-powered generator outside the Faraday cage produced rectangular electric DC (rise time of 2 mA/s) for periods of 27.5 s. To prevent radio frequency pickup and propagation by the wires, small LC filters tuned for resonance at 64 MHz and resistors (1 kΩ) were placed between the electrodes and connection cable to the stimulus generator. For safety reasons, subjects held a switch in their hand during the whole acquisition time, with which they could immediately interrupt the conduction to the electrodes. The individual electric current threshold to elicit vestibular effects and cutaneous pain varies considerably (1–4 mA), depending on the exact position of the electrode, the body position (upright or supine), and the skin resistance. Therefore we adjusted the current level of GVS for each subject according to the vestibular effects (perceived tilt) elicited, just before MRI acquisition, while the subject was already positioned on the scanner table. The current level of GPS was individually adjusted to match the intensity of pain during GVS.

Auditory stimulation

For auditory stimulation a special MR-safe headset (Resonance Technology, Northridge, CA) was connected to a conventional audio CD player. Repeated notes of ascending pitch (frequency 150 Hz to 6.3 kHz) were used as stimuli at a rate of six notes per second. They were presented without special instructions to the volunteers (non-directed listening). The headset largely attenuated the scanner background noise level (approximately 85 dB sound pressure level), which was the same under all test conditions.

In an earlier study, GVS at the mastoid level activated an area in the auditory cortex (Heschl’s gyrus), although it caused no auditory sensations in the subjects (Bucher et al. 1998). Because auditory sensations were absent, it was not possible to calibrate auditory stimulation. The DC GVS used in our study does not represent a localized physiological stimulation; it can spread into the inner ear and neighboring tissues and affect acoustic nerve fibers. Moreover this type of stimulation can activate not only areas in the primary auditory receiving cortex but also areas involved in integrative or associative auditory functions. For this reason, we chose repeated notes of ascending pitch to provide a broad base on which the activated areas could overlap during GVS.

Data analysis

Data processing was done on an UltraSPARC workstation (Sun Microsystems) using statistical parametric mapping (SPM96) (Friston et al. 1995b) implemented in MATLAB (Mathworks, Sherborn, MA). All volumes were realigned to the first one of each scanning session to correct for subject motion, and spatially normalized (Friston et al. 1995a) into the standard space of Talairach and Tournoux (1988). Prior to statistical analysis, each image was smoothed with a 6-mm (single subject) or 10-mm (group) isotropic Gaussian kernel to compensate for intersubject gyral variability and to attenuate high-frequency noise, thus increasing the signal to noise ratio. Statistical parametric maps were calculated on a voxel-by-voxel basis using the general linear model (Friston et al. 1995b) and the theory of Gaussian fields (Worsley and Friston 1995). SPM96 calculated the relative contributions of a delayed-box-car reference waveform as well as confounding variables (whole brain activity and low frequency variations) to the measured data. The delayed box car serves as a model of the expected hemodynamic response to the stimulus.

BOLD signal increases

Each scanning session consisted of four different conditions: GVS at the mastoid level, cutaneous GPS at the neck C₅₀ level, AS, and the rest condition without any stimulation. Statistical analysis was performed individually for the six subjects and group-wise (P ≤ 0.01, corresponding to Z ≥ 2.33). In an appropriate design matrix the following contrasts were specified: GVS–rest, GPS–rest, AS–rest, and GVS–GPS, to isolate vestibular from extravestibular nociceptive effects. Furthermore, conjunction analysis was performed both between GVS–rest and GPS–rest and between GVS–rest and AS–rest. The results from a conjunction analysis between two contrasts show only voxels that are common to the used contrasts and are not significantly different in these contrasts (Price and Friston 1997); conjunction analysis therefore makes it possible to check for jointly activated areas under different stimulation conditions. The results reported are based on an anatomically constrained hypothesis because the aim of the study was to separate the known areas reported in previous studies from the areas of nociceptive and auditory side effects due to GVS. Therefore uncorrected P-values were used for the contrasts mentioned in the preceding text and the conjunction analysis (P ≤ 0.001, corresponding to Z ≥ 3.09).

BOLD signal decreases

Task-induced BOLD MRI signal decreases were also measured, but their significance is still not clearly understood. In a comparative fMRI and PET study on visual optokinetic stimulation, we found a very similar activation pattern for signal increases and decreases in both techniques (Bense et al. 2000). This consistency supports the view that signal decreases with fMRI correlate with regional cerebral blood flow decreases in PET and may reflect functional deactivation (Fransson et al. 1999; Rauch et al. 1998). However, this correlation does not yet allow a conclusive statement about the neuronal activity.
Consequently we analyzed the contrasts rest–GVS and rest–GPS without an a priori hypothesis and considered only $P$ values corrected for multiple comparisons as significant ($P < 0.001$, corresponding to $Z \geq 3.09$).

Aguirre et al. (1998) recently demonstrated that the use of global scaling may lead to detection of false-negative signal changes if the signal in a voxel is less correlated with the task than the global brain signal itself. Therefore we also analyzed the data without the use of global scaling for comparison. Furthermore, the degrees of correlation of the global signal with the reference waveforms were computed.

For simplicity, we will use the term “deactivations” in quotation marks when referring to BOLD signal decreases.

**Anatomical localization**

To define the anatomical sites of activation and “deactivation” clusters derived by the different statistical approaches, we used the Talairach coordinates (Stephan et al. 1997; Talairach and Tournoux 1988) as well as defined anatomic landmarks (Naidich and Brightbill 1996a,b; Naidich et al. 1995; Yousry et al. 1997a,b). The anatomic-functional correlation was performed by a neuroradiologist experienced in the identification of cortical landmarks.

To the best of our knowledge, there is still no internationally agreed upon definition of insular and retroinsular regions available in the literature. The insula is anatomically divided into five gyri; three short (I–III), and 2 long insular gyri (IV and V). The region frontal to the central insular sulcus (arrow) is defined as the anterior insula; it includes the short insular gyri (I–III). The region posterior to the central insular sulcus is defined as the posterior insula; it includes the 1st (IV) and 2nd (V) long insular gyrus. The retroinsular territory is defined as the area posterior to the 2nd long insular gyrus.

**RESULTS**

Anodal stimulation, at the right (left) mastoid level led in all subjects to an apparent counterclockwise (clockwise) self-rotation of 90 to 360° around the nasal-occipital axis (from the viewpoint of the subject) and mild to moderate cutaneous pain sensations on the order of a pin-prick. Three subjects reported a slightly metallic taste. There were no recognizable postural reactions, no acoustic sensations, and no nausea during either GVS or GPS. The subjects denied substantial anxiety or stress.
Mode, build-up, and intensity of pain could not be distinguished by the subjects under either stimulation condition. During control pain stimulation at C5/C6 level, subjects did not mention any contraction of neck muscles, vestibular sensations, or head movements. Therefore we did not expect these neck muscles to contribute to the results. Even if the sacculocervical reflex (Halmagyi et al. 1995) was elicited by rapidly rising galvanic stimulation (which we did not use), the main muscle response would be expected in the sternocleidomastoid muscle. However, such a short-lived effect would be negligible in the average over one stimulus period (27.5 s). Moreover, no stimulus-correlated head movements were detected during data preprocessing. In the realignment process of statistical parametric mapping (SPM), the overall head movement across all scanning sessions was below 1.5 mm in translation and 1.5° in rotation for all individual subjects.

Activations during vestibular stimulation

Since GVS at the mastoid level not only activates vestibular but also nociceptive cortex areas, we concentrated on the contrast GVS–GPS. In the group analysis, this contrast included bilateral activation of the dorsolateral thalamus, anterior parts of the insula, the superior temporal gyrus (BA 22), the inferior parietal lobule (BA 40), the precentral/inferior frontal gyrus (BA 6/44), and the anterior cingulate gyrus (BA 32) was significant for one hemisphere only. The polarity of stimulation (either cathode left or right) did not influence the unilateral or bilateral activation patterns. For coordinates and Z-scores see Table 1.

FIG. 2. Activation areas obtained by statistical group analysis (n = 6) after subtracting cutaneous galvanic pain stimulation (GPS at neck C5/C6 level) from galvanic vestibular stimulation at mastoid level (GVS). GVS caused activation of the paramedian (not mapped) and dorsolateral thalamus (Th), putamen (Pu), anterior cingulate gyrus (not mapped), anterior insula (AI), cortical ocular motor centers including the frontal eye field [FEF, precentral gyrus, Brodmann area 6 (BA 6)] and prefrontal cortex (PFC, middle frontal gyrus, BA 46), motion-sensitive area in the middle temporal gyrus (MT/V5), the inferior parietal lobule (LPI, BA 40), the superior temporal lobe (G Ts, BA 22), the precentral/inferior frontal gyrus (G PrC/GFi, BA 6/44), and both cerebellar hemispheres (CH). Activation maps are superimposed onto selected transverse sections of a standard brain template and thresholded at \( P \leq 0.01 \), uncorrected (corresponding to \( Z \geq 2.33 \)). Corresponding Talairach coordinates and Z-scores are listed in Table 1.
Individual analysis indicated that all subjects showed an increased signal in the posterior insula or retroinsular region. Along the z-axis the individually circumscribed activations of the posterior insula, which had in the majority of cases a cluster size smaller than 20 voxels, ranged from 10 mm below to 10 mm above the AC–PC line. However, because of the considerable interindividual anatomical variation (Fig. 3), the vestibular area in the posterior insula (corresponding to the PIVC in monkeys) failed to show statistical significance in the group analysis (Fig. 2).

**Activations during auditory stimulation**

Although the subjects reported no auditory sensations with GVS, cochlear nerve stimulation might induce activation of auditory areas via the auditory portion of the eighth nerve. Nongalvanic AS caused broad bilateral activation not only in the primary auditory receptive cortex (transverse temporal gyrus of Heschl, BA 41) but also in its association and integration areas in the superior and medial temporal gyri (maxima BA 42/22/21), including parts of the inferior parietal lobule (BA 40). Additional activation foci were found in the posterior cingulate gyrus (BA 29), the superior temporal gyrus (BA 38), the anterior/paramedian thalamus, and the precentral gyrus (BA 6/4/8) (Table 2, Fig. 4, AS–rest).

Conjunction analysis of GVS and pure auditory stimulation ($P \leq 0.001$, uncorrected, Fig. 4, GVS–rest vs. AS–rest) showed common activations of the following areas bilaterally: superior temporal gyrus (BA 38/22), precentral gyrus (BA 6), inferior parietal lobule (BA 40), paramedian and dorsolateral thalamus, and both cerebellar hemispheres. The middle frontal gyrus (BA 46/9), the putamen, the anterior cingulate gyrus (BA 8/32), and the middle temporal gyrus (BA 37) were significantly activated unilaterally. The areas activated in common represent in part visual and ocular motor functions. The broad activation of the primary auditory cortex, its association and integration areas, overlap with the vestibularly activated areas in only a small part of the superior temporal gyrus (BA 42/22; 14 voxels) and in the depths of the transverse temporal (Heschl’s) gyrus adjacent to the posterior insula (BA 41; 23 voxels, Fig. 4, GVS–rest and AS–rest).

**Activations during pain stimulation**

GPS activates the anterior (BA 32) and posterior cingulate (BA 29) gyrus, anterior insula (short insular gyri I/II), middle/

<table>
<thead>
<tr>
<th>Table 1. Coordinates and Z-scores of activated brain areas for the contrast GVS–GPS</th>
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<tbody>
<tr>
<td>Brain Region, Abbreviation</td>
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<tr>
<td><strong>Subcortical</strong></td>
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<tr>
<td>Left putamen</td>
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<tr>
<td>Left paramedian thalamus</td>
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<tr>
<td>Right dorsolateral thalamus</td>
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<tr>
<td>Left dorsolateral thalamus</td>
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<tr>
<td>Left cerebellar hemisphere</td>
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<tr>
<td>Right cerebellar hemisphere</td>
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<tr>
<td><strong>Frontal</strong></td>
</tr>
<tr>
<td>Left anterior cingulate gyrus, BA 32</td>
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<tr>
<td>Right precentral gyrus, BA 6</td>
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<tr>
<td>Left precentral gyrus, BA 6</td>
</tr>
<tr>
<td>Left precentral gyrus/inferior frontal gyrus, BA 6/44</td>
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<tr>
<td>Right middle frontal gyrus, BA 9/46</td>
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<tr>
<td>Left middle frontal gyrus, BA 46</td>
</tr>
<tr>
<td>Right inferior frontal gyrus, BA 47/short insular gyrus I</td>
</tr>
<tr>
<td><strong>Temporal</strong></td>
</tr>
<tr>
<td>Left middle temporal gyrus, BA 37</td>
</tr>
<tr>
<td>Right superior temporal gyrus, BA 22</td>
</tr>
<tr>
<td>Left superior temporal gyrus, BA 22</td>
</tr>
<tr>
<td><strong>Parietal</strong></td>
</tr>
<tr>
<td>Left inferior parietal lobule/ supramarginal gyrus, BA 40</td>
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<td>Right inferior parietal lobule, BA 40</td>
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GVS, galvanic vestibular stimulation; GPS, galvanic pain stimulation; BA, Brodmann area.

Individual analysis indicated that all subjects showed an increased signal in the posterior insula or retroinsular region. Along the z-axis the individually circumscribed activations of the posterior insula, which had in the majority of cases a cluster size smaller than 20 voxels, ranged from 10 mm below to 10 mm above the AC–PC line.

**FIG. 3.** Examples of activation patterns of 3 representative subjects during galvanic vestibular stimulation at the mastoid level (GVS–GPS) superimposed onto the individual T1 images to show the great variation in the localization of the posterior insula and retroinsular activations. This activated area corresponds to the parieto-insular vestibular cortex (PIVC) in monkeys. Along the z-axis the small activation clusters (less than 20 voxels) ranged from 10 mm below to 10 mm above the AC-PC line, e.g., $x/y/z = 43/−16/11$. 
inferior frontal gyrus (BA 10/46/9), precentral gyrus (BA 6/44), inferior/superior parietal gyrus (BA 40/7), paramedian thalamus, pulvinar, and both cerebellar hemispheres. In addition, there was an unusual bilateral activation of the white matter between the anterior insula and the middle frontal gyrus (Table 3, Fig. 4, GPS–rest). Although BOLD signal changes were not significant in the group analysis, there was an unusual bilateral activation of the white matter between the anterior insula and the middle frontal gyrus (BA 41/68, 2, 8.10, 2319).

In the following, we attempt to attribute particular activated areas to multisensory vestibular or ocular motor functions. Therefore the analytic procedure comprises detailed comparisons between GVS and the rest condition and also between GVS and the auditory and nociceptive control stimuli. By this means we were able to separate areas involved in the processing of vestibular and ocular motor, auditory, and nociceptive functions. The second part of the discussion deals with a newly observed phenomenon: an inhibitory reciprocal vestibular-visual interaction.

**Activations related to ocular motor function**

The activations revealed by the group contrast GVS–GPS, which reduced the nociceptive part of GVS activation pattern as far as possible, can be attributed to multisensory vestibular and ocular motor functions (Fig. 2; Table 1).

In detail, the two separate activations in the precentral gyrus of the frontal lobe (BA 6) represent the frontal eye fields (FEF) (Paus 1996) and an area anterior to the FEF (BA 44/6). Activation of the FEF can be related to torsional eye movements induced by the vestibular stimulation. Other types of eye movements, such as optokinetic nystagmus (Dieterich et al. 1998), saccades (Anderson et al. 1994; Sweeney et al. 1996), and smooth pursuit eye movements (Petit et al. 1997, 1998) also activate this area. The second area anterior to this region might represent a second part of the FEF (Paus 1996) and correspond to a portion of the premotor cortex. This area was

**FMRI signal decreases ("deactivations")**

Negative BOLD MRI responses were calculated for GVS and GPS (P \( \leq 0.001 \), corrected for multiple comparisons). Comparison of the negative signal changes with and without the use of global scaling revealed that there were no additional clusters with global scaling. We also did not find a significant degree of correlation between the global signal and the reference waveforms used. However, the Z scores of the results were slightly different. We conclude that the global signal in our study does not behave as a confound, and therefore global scaling can be used in the statistical analysis.

Both contrasts, rest–GVS and rest–GPS, showed significant signal decreases in the central sulcus region, predominantly in the postcentral gyrus analogously to the primary somatosensory cortex (BA 2/3/4 left, BA 3/4/6 right). During GVS, further signal decreases were found in the visual cortex bilaterally (fusiform/inferior occipital gyrus, BA 18/19), sparing Brodmann area 17, and in the right precuneus near the interhemispheric fissure (BA 7). In contrast, GPS led to an additional signal decrease in the middle temporal/occipital gyrus (BA 19/39/18; Table 4, Fig. 5).

### DISCUSSION

There is no natural or noninvasive experimental stimulus available that selectively excites the vestibular system. The advantage of GVS over caloric vestibular stimulation is its short buildup and offset. Thus it is possible to alternate short periods of GVS with the rest condition in fMRI. GVS at the mastoid level not only induces a rotational or tilt sensation with tonic ocular torsion but also a mild cutaneous pain sensation (Watson and Colebach 1998; Zink et al. 1998). Interpretation of the complex activation pattern during GVS must also take into account that there is no primary vestibular cortex comparable to the striate visual cortex or Heschl’s auditory cortex. The vestibular cortex is part of a multisensory cortex, which involves other sensory modalities for spatial orientation, self-motion perception, and control of eye movements (Guldin and Grüsser 1998).

In the following, we attempt to attribute particular activated areas to multisensory vestibular or ocular motor functions. Therefore the analytic procedure comprises detailed comparisons between GVS and the rest condition and also between GVS and the auditory and nociceptive control stimuli. By this means we were able to separate areas involved in the processing of vestibular and ocular motor, auditory, and nociceptive functions. The second part of the discussion deals with a newly observed phenomenon: an inhibitory reciprocal vestibular-visual interaction.
also activated by eye movements during spatial attention tasks (Gitelman et al. 1999) or memory-guided saccades (W. Heide, personal communication). Fujii et al. (1998) reported that intracortical microstimulation of the FEF in the anterior wall of monkeys elicited contraversive saccades. The posterior arcuate area in monkeys (area 6pa) is part of the premotor area 6, which sends efferent axons to the vestibular nuclei as well as to the multisensory intracortical microstimulation of the FEF in the anterior wall of

Grüsser attributed premotor area 6 to the “inner vestibular circuit” (Guldin and Grüsser 1996).

Additional activations were located bilaterally in the middle frontal gyrus of the frontal lobe (BA 46, BA 9/46), which in part represents the prefrontal cortex (PFC) and is known to be involved in several ocular motor tasks, such as prosaccades and antisaccades (FMRI: Müri et al. 1998; PET: Sweeney et al. 1996), remembered or memory-guided saccades (PET: O’Sullivan et al. 1995; Sweeney et al. 1996), as well as visually guided saccades and fixation tasks (PET: Sweeney et al. 1996).

The activations of the anterior insula, thalamus, and putamen may be related to an efference copy of ocular motor

### TABLE 3. Coordinates, Z-scores, and cluster size of activated brain areas for GPS–rest

<table>
<thead>
<tr>
<th>Brain Region, GPS–rest</th>
<th>Coordinates (x, y, z)</th>
<th>Z-Score</th>
<th>Cluster Size, voxels</th>
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</thead>
<tbody>
<tr>
<td>Subcortical</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Left paramedian thalamus</td>
<td>-4, -8, 10</td>
<td>2.97</td>
<td>159</td>
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<tr>
<td>Right cerebellar hemisphere</td>
<td>14, 90, -30</td>
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<td>525</td>
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<td>Right cerebellar hemisphere</td>
<td>28, -82, -30</td>
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<td></td>
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<tr>
<td>Right cerebellar hemisphere</td>
<td>32, -72, -32</td>
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<td>Left cerebellar hemisphere</td>
<td>-16, -84, -24</td>
<td>2.57</td>
<td>27</td>
</tr>
<tr>
<td>Left pulvinar</td>
<td>-8, -32, 0</td>
<td>2.93</td>
<td>32</td>
</tr>
<tr>
<td>Cortical</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left anterior insula/white matter</td>
<td>-22, 36, 4</td>
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<td>208</td>
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<tr>
<td>Left middle/inferior frontal gyrus, BA 10/46</td>
<td>-42, 50, 12</td>
<td>3.89</td>
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<td>Left inferior occipital gyrus/Lef</td>
<td>-26, 22, -4</td>
<td>3.81</td>
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<tr>
<td>Right short insular gyrus</td>
<td>36, 18, 6</td>
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<td>-38, 8, 34</td>
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<td>-62, 20, 6</td>
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<td>Left inferior parietal gyrus, white matter</td>
<td>22, 44, 8</td>
<td>2.85</td>
<td>30</td>
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<td>Left posterior cingulate gyrus, BA 29</td>
<td>-2, -36, 22</td>
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<td>Left inferior parietal gyrus, BA 40</td>
<td>-46, -56, 52</td>
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<td>600</td>
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<td>-40, -56, 42</td>
<td>3.85</td>
<td></td>
</tr>
<tr>
<td>Left superior/inferior parietal gyrus, BA 7</td>
<td>-36, -74, 56</td>
<td>3.73</td>
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</table>

The highest maximum of each cluster is printed in bold.

![FIG. 4. The left 2 panels show the activation maps of the 2 control conditions, nongalvanic auditory stimulation (AS–rest) and cutaneous pain stimulation at neck C5/6 level (GPS–rest), contrasted with the rest condition and thresholded at P ≤ 0.01 uncorrected (group analysis, corresponding to Z ≥ 2.33). AS–rest: AS mainly activates the primary auditory receptive cortex (transverse gyrus of Heschl), and its association and integration areas in superior and medial temporal convolutions and parts of the inferior parietal lobule (BA 40). Additional activation foci are found in the posterior cingulate gyrus (not mapped), anterior/paramedian thalamus, and precentral gyrus bilaterally, including the frontal eye fields (not mapped) (BA and Z-scores in Table 2). GPS–rest: GPS mainly activates the paramedian thalamus, pulvinar, the PFC (middle/inferior frontal gyrus, not mapped), inferior/superior parietal gyrus (not mapped), anterior and posterior cingulate gyrus, parts of the anterior insula (short insular gyrus II), and the cerebellar hemispheres (see BA and Z-scores in Table 3). The right 2 panels show the conjunction analysis of the control conditions with the galvanic vestibular stimulation (GVS–rest vs. GPS–rest, GVS–rest vs. AS–rest, P ≤ 0.001, uncorrected, corresponding to Z ≥ 3.09). GVS–rest vs. AS–rest showed common activations bilaterally in the superior temporal gyrus (BA 38/22), precentral gyrus (BA 6, not mapped), inferior parietal lobule (BA 40), paramedian and dorsolateral thalamus, and both cerebellar hemispheres. The middle frontal gyrus (BA 46/9, not mapped), the putamen, the anterior cingulate gyrus (BA 8/32, not mapped), and the middle temporal gyrus (BA 37) were significantly activated unilaterally. GVS–rest vs. GPS–rest showed joint activations bilaterally in the cerebellar hemispheres, widespread in the frontal lobe (inferior/superior frontal gyrus, anterior insula (short insular gyrus II), middle frontal gyrus (BA 9/46)), precentral gyrus (BA 6, not mapped), the anterior and posterior cingulate gyrus, the putamen, the anterior/paramedian, and dorsolateral thalamus (not mapped) as well as in the left inferior parietal lobule (BA 40, not mapped).]
signals. In particular, the activations of the thalamus and putamen fit the concept of an efferent basal ganglia-thalamocortical (ocular) motor loop proposed by Alexander et al. (1986). Moreover, the thalamus is considered a complex relay station for efferent ocular motor pathways in the paramedian thalamus (subnuclei ventralis lateralis, dorsomedialis, pulvinaris) (Bucher et al. 1997) and for vestibular afferents conveyed to vestibular cortex areas via the ventroposterior subnucleus (Akbarian et al. 1992). The activation pattern here (anterior insula, basal ganglia, thalamus) corresponds to that of activations during optokinetic stimulation [optokinetic nystagmus (OKN)] (Bucher et al. 1997) and voluntary saccades (Petit et al. 1993). The fact that the anterior part of the insula was activated during OKN, but not when OKN was suppressed by fixation of a stationary target indicates its attribution to ocular motor function (Dieterich et al. 1998). On the one hand, this view is also supported by earlier studies in monkeys, which showed an extensive efferent pathway from the anterior insula directly across the external capsules into the putamen and the globus pallidus (Showers and Lauer 1961). On the other, these areas were found to be activated in several experimental and clinical pain studies using PET and fMRI in humans (Bucher et al. 1998; Coghill et al. 1994; Derbyshire and Jones 1998; Hsieh et al. 1995; Tolle et al. 1999). Dostrovsky and Craig (1996) were able to characterize electrophysiologically nociceptive neurons in the ventral medial nucleus of the thalamus of monkeys, emphasizing the multisensory function of these neurons. Thus, despite the subtraction analysis used (GVS–GPS), we cannot completely exclude the possibility of additional pain-related activations.

The activations that can be related to the ocular motor system were the two cortical structures, the prefrontal (FEF) and the middle frontal gyrus (PFC), as well as the anterior median insula, thalamus, and putamen, which are elements of the descending pathways to the brain stem. However, some of these areas are activated by a variety of sensory stimuli and motor tasks. Therefore registration of activation in these areas must not necessarily reflect the actual execution of eye movements. They could simply reflect the stimulus-induced readiness of the ocular motor system to execute eye movements. A number of imaging and electrophysiological studies show that imagination of sensory motor tasks causes activations similar to that caused by the actual performance (Bodis-Wollner et al. 1997; Hollinger et al. 1999; Lang et al. 1994; Law et al. 1997).

Activations related to multisensory vestibular function

Experimental studies in monkeys (Grüsser et al. 1990a,b) and cats (Jiwiwa et al. 1991), clinical lesion studies in patients

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FIG. 5. Statistical parametric maps showing significant BOLD magnetic resonance imaging (MRI) signal decreases ($P \leq 0.001$ corrected, corresponding to Z $\geq 3.09$, group analysis) obtained by subtracting stimulation from rest condition. These contrasts may reflect cerebral deactivation. Both contrasts, rest−GVS and rest−GPS, showed significant signal decreases in the central sulcus region, predominantly in the postcentral gyrus (GPoC) analogous to the primary somatosensory cortex (BA 2/3/4 left, BA 3/4/6 right). GVS showed significant signal decreases of the visual cortex bilaterally (VC, fusiform/ inferior occipital gyrus, BA 18/19; left, top 3 sections, $z = -15$ to $-5$) sparing Brodmann area 17, and in the right precuneus (PCu) near the interhemispheric fissure (BA 7). In contrast, GPS led to a signal decrease in upper parts of the tempo-occipital cortex areas (middle temporal/occipital gyrus, GTm/Go, BA 18/19/39; right, bottom 3 sections, $z = 15$ to $+5$). The abbreviations are according to the atlas of Talairach and Tournoux (1988).
(Brandt and Dieterich 1999; Brandt et al. 1994, 1995), and activation studies in healthy subjects (Bottini et al. 1994; Bucher et al. 1997, 1998; Dieterich et al. 1998, 1999)—all indicate that the posterior insula and the retrolimbic areas are the human homologue of the PIVC in monkeys. In the current study, the small individual activations regularly found in posterior insular and retrolimbic areas varied in their location. These activations did not reach the level of significance in the group analysis obviously because of the considerable anatomical variation between the individual subjects (Figs. 2 and 3). The neurons of PIVC in the monkey brain are multisensory and respond not only to vestibular but also to various kinds of visual and somatosensory stimulations (Grüsser et al. 1990a,b). This was further demonstrated in earlier human studies using optokinetic (fMRI: Bucher et al. 1997; Dieterich et al. 1998), caloric (PET: Bottini et al. 1994; Dieterich et al. 1999), or galvanic vestibular stimulation (fMRI: Bucher et al. 1998). All these studies localized PIVC around the bicommissural line of Talairach (AC-PC) level (e.g., Talairach coordinates between −5 and +5 mm along the z-axis). The only other study on GVS using EPI sequences attributed the PIVC to an activation area in the temporo-parietal junction 20 mm above the AC-PC level (x/y/z = −64/−36/+20) (Lobel et al. 1998). These coordinates, however, correspond better to lower parts of BA 40, which we attribute to monkey area 7 and not to PIVC. Lobel and co-workers did not describe activation of the posterior or anterior parts of the insula, which we found in both individual (posterior) and group analyses (anterior).

We did not find any activation in areas corresponding to areas 2v and 3a, which are also parts of the inner vestibular circuit in monkeys. To the best of our knowledge, no human brain activation study so far was able to unequivocally show activations of the multisensory vestibular cortex areas 2v and 3a.

Activations in the inferior parietal lobule (BA 40) and the anterior cingulate gyrus were also seen during caloric vestibular stimulation in PET studies (Bottini et al. 1994; Dieterich et al. 1999). Both areas have intimate connections to the PIVC and belong to the inner vestibular circuit (Guldin and Grüsser 1996). After injection of tracer substances into different parts of the brain stem vestibular nuclear complex of monkeys, labeled cells were observed not only in the PFC, area 6pa, and dorsal to the prearcuate gyrus but also in the ventral bank of the anterior cingulate gyrus (Akbarian et al. 1994). Monkey studies revealed two multisensory areas in the parietal lobe, visual and vestibular, named visual temporal sylvian area (Guldin and Grüsser 1996) and area 7b (Faugier-Grimaud and Ventre 1989). The location is comparable to parts of our activation in BA 40. To complicate matters, the inferior parietal lobule and the anterior cingulate cortex are also involved in human pain [Casey et al. 1996; Derbyshire et al. 1997, 1998; Hsieh et al. 1995; current study (GPS–rest)], in auditory (in the current study the inferior parietal lobule is part of the bilateral big activation clusters with their maxima in the temporal lobe) and ocular motor processing (Dieterich et al. 1998; Paus et al. 1993) as well as in manual and speech responses (Paus et al. 1993). The involvement of these areas in several sensory functions might indicate that they also play a role in orientation in space (BA 40) (Griffiths et al. 1998; Weeks et al. 1999) and in the motivational-affective system (cingulum, BA 40) (Bushnell et al. 1995).

The activation of the middle temporal gyrus (BA 37) corresponds best with the human homologue of the motion-sensitive area MT/MST in the monkey (Desimone and Ungerleider 1986; Dubner and Zeki 1971; Lagae et al. 1994; Wurtz and Newsome 1985). It also receives vestibular input (Thier and Erickson 1992) and is the origin of direct fibers to the vestibular nuclei (Faugier-Grimaud and Ventre 1989; Jeannerod 1996). In humans, this structure is also known to play an important role in eye movement and visuomotor processing such as object motion perception (Barton et al. 1996; Brandt et al. 1998a; Dupont et al. 1994; Zeki et al. 1991) and self-motion perception (Brandt et al. 1998; Cheng et al. 1995; de Jong et al. 1994).

Bilateral activation in the cerebellar hemispheres was found during all stimuli used and can be related to attention (Allen et al. 1997; Kim et al. 1999), timing (Jueptner et al. 1995; Penhune et al. 1998), learning (Raymond et al. 1996), and ocular motor processing (Dieterich et al. 1999; Heide et al. 1999; Nitschke et al. 1996, 1999).

The conjunction analysis allowed us to check for jointly activated areas under two stimulus conditions. The results showed for the conjunction between the contrasts GVS–rest and AS–rest, only two small overlaps in the insular area in the depths of the transverse temporal and in the superior temporal gyrus. There was no jointly activated area in the short or long insular gyri. This supports the view that GVS only represents a weak stimulus for the auditory system. In contrast, significant activations in the frontal eye field, prefrontal cortex, inferior parietal lobule (BA 40), the paramedian thalamus, and the cerebellar hemispheres also appeared not only in the conjunction analysis between GVS and AS but also between GVS and GPS (Fig. 4). Activations of these ocular motor centers might represent a basic network involved in orientation in space which is activated by different sensory stimuli.

Despite the obvious difficulties of selectively attributing one specific function to one specific area, we identified the posterior and retrolimbic regions, parts of the inferior parietal lobule (BA 40), and premotor area 6 as areas mainly involved in processing of multisensory vestibular function.

**Concurrent “deactivations” of the visual and the somatosensory cortex areas**

It is becoming increasingly apparent that relative deactivations may be as important for brain function as are activations. A PET study using caloric stimulation demonstrated not only an activation of the PIVC but also a highly significant decrease in rCBF of the visual cortex (Wenzel et al. 1996). Brandt et al. (1998) were able to add to this example of an inhibitory vestibular-visual interaction in their recent demonstration of a visual-vestibular interaction using large-field motion patterns that induce apparent self-motion perception. They found that during activation of parieto-occipital areas in the visual cortex, there was a simultaneous rCBF decrease of the posterior insula (PIVC) bilaterally. This mechanism of a reciprocal inhibitory interaction theoretically allows the dominant sensorial weight to be shifted from one modality to the other, depending on which mode of stimulation prevails (Brandt and Dieterich 1999).

The first evidence of stimulus-dependent circumscribed “deactivations” came from PET studies (Shulman et al. 1997;
Such “deactivations” are detected on fMRI when calculating negative BOLD signal changes (Allison et al. 2000; Fransson et al. 1999; Rauch et al. 1998). Despite the considerable disparities in earlier reports comparing PET and fMRI data (Sadato et al. 1998; Schloesser et al. 1998), recent studies draw attention to similarities (Votaw et al. 1999). In our study using global scaling, we found negative BOLD responses during GVS in the form of a bilateral “deactivation” in the visual cortex (fusiform gyrus/inferior occipital gyrus, BA 18/19), sparing BA 17. These responses occurred independently of whether global scaling was applied or not. The finding of “deactivations” in the visual cortex agrees well with findings of an earlier PET study on caloric irrigation (Wenzel et al. 1996). While Wenzel and co-workers used the extreme stimulus of ice water stimulation and found a “deactivation” of BA 17–19, we used the comparatively weak galvanic stimulus and found that the striate visual cortex, BA 17, was spared. This difference may also be related to the relatively poor spatial resolution of PET.

On analogy with the inhibitory vestibular-visual interaction, we found an inhibitory nociceptive-somatosensory interaction during both kinds of stimulation, GVS and GPS. The “deactivated” areas involved the somatosensory cortex bilaterally (BA 2/3/4 left, BA 3/4/6 right) and occurred simultaneously with...
activations of nociceptive areas in the frontal lobe and the anterior insula (short insular gyrI/II bilaterally). In agreement with our findings, Apkarian et al. (1992) in an earlier Tc99m-HMPAO study observed a decrease in rCBF in the contralateral somatosensory cortex during persistent pain stimulation that they interpreted to be cortical inhibition. While using nonvestibular neck stimulation (GPS), we saw additional “de-activations” in the precuneus (BA 7) and upper parieto-occipital areas in the middle temporal and occipital gyrus (BA 19/39/18, Fig. 5, Table 4). This was seen also during GVS, if a lower level of significance was used.

In conclusion, GVS not only elicits a complex pattern of activations that can be related to ocular motor and vestibular function, but it also interacts with other sensory systems by means of circumscribed “de-activations” within the visual or somatosensory cortex (Fig. 6). Intersensory inhibitions may provide a basic mechanism for spatial orientation and self-motion perception. In case of inappropriate or misleading input from two afferent sensory systems, visual-vestibular or nociceptive-somatosensory, a perceptual mismatch can be avoided by suppressing the input from one sensory system.

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