J Neurophysiol 89: 2639–2646, 2003;
10.1152/jn.00599.2002.

Cortical Projection of Peripheral Vestibular Signaling

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Submitted 24 July 2002; accepted in final form 24 January 2003

Emri, Miklós, Mihály Kisely, Zsolt Lengyel, László Balkay, Teréz Márián, László Mikó, Ervin Berényi, István Sziklai, Lajos Trón, and Ágnes Tóth. Cortical projection of peripheral vestibular signaling. *J Neurophysiol* 89: 2639–2646, 2003; 10.1152/jn.00599.2002. The cerebral projection of vestibular signaling was studied by using PET with a special differential experimental protocol. Caloric vestibular stimulation (CVS)-induced regional cerebral blood flow (rCBF) changes were investigated in two populations. Butanol perfusion scans were carried out on six healthy volunteers and on six patients following the removal of tumors from the right cerebello pontine angle. The complete loss of the vestibular function postoperatively allowed a comparison of the rCBF changes in the populations with or without this input and offered a promising functional approach whereby to delineate the cortical region most responsive to pure vestibular input. The activations by left-sided and right-sided CVS were determined for both the healthy volunteers and the patient population. Statistical analysis of the data obtained following left-sided CVS did not reveal any cerebral region for which there was a significant difference in CVS-induced response by these two populations. In the case of right-sided CVS, however, the statistical comparison of the CVS-related responses demonstrated a single contralateral area characterized by a significantly different degree of response. This cortical area corresponds to part of the cortical region described recently which can be activated by both CVS and neck vibration. It appears to be anatomically identical to the aggregate of the somatosensory area SII and the retroinsular cortex described in primates, a region identified by other investigators as an analog of the parietoinsular vestibular cortex.

INTRODUCTION

The vestibular, visual, and somatosensory systems jointly perceive the spatial orientation of the human body and coordinate the processes that play a role in bringing about this orientation. Egocentric coordination and exocentric coordination are distinguished on the basis of whether the individual or the surrounding world is referred to (Bottini et al. 2001; Brandt 1999; Brandt and Dieterich 1999; Brandt et al. 2002). It is generally accepted that the above function can be ascribed to a complex network of cortical and subcortical regions that continuously process afferent impulses, with one or another element of the network possibly predominating in this process (Guldin and Grüsser 1998).

A number of animal experiments have been performed to identify the elements of the network. As a result, areas with vestibular afferentation have been found in the parietal and temporal regions of primates. These areas comprise area 2v, located at the ventral tip of the intraparietal sulcus, area 3a, situated along the central sulcus, the parietoinsular vestibular cortex (PIVC), at the posterior pole of the insula, and area 7, in the inferior parietal lobe (Faugier-Grimaud and Ventre 1989; Grüsser and Guldin 1995; Ödkvist et al. 1974; Pandya and Sanides 1973; Schwarz and Fredrickson 1971).

Parts of the network responsible for spatial orientation have been identified in patients with lesions of one cerebral hemisphere and suffering from the contralateral spatial neglect syndrome. Elements have been located in the inferior parietal lobe, the area of the temporoparietal junction, the lateral region of the premotor cortex, and certain subcortical regions such as the thalamus and basal ganglia (Husain and Kennard 1996; Vallar and Perani 1986; Vallar et al. 1993).

The most widely used examination techniques in which stimulation is applied involve optokinetic, galvanic, and caloric vestibular stimulation (CVS) and the neck vibration (NV) test (Bense et al. 2001; Bottini et al. 1994 2001; Bucher et al. 1998; Kisely et al. 2001; Lobel et al. 1998 1999; Paulesu et al. 1997). The various authors agree that any technique of stimulation will affect more than one modality. Accordingly, the cerebral activation patterns obtained by using different techniques may be discordant. An attempt has been made to circumvent this problem (Bottini et al. 2001) by measuring the brain activation in healthy volunteers on the use of CVS and mechanical vibration stimulation of the cervical muscles and by identifying the anatomical structures responsible for the representation of egocentric space as the overlap between the activation patterns obtained with the two techniques. Bottini et al. (2001) suggested that the vestibularly driven human cortical system comprises four areas, in contrast with the findings in primate

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experiments, which supported a core region hypothesis in the vestibular cortical system.

In an attempt to supplement the capabilities of single-unit recording experiments and tracer studies, in the present investigation we applied a different approach. In addition to including healthy volunteers in the brain activation studies, we also examined patients following the removal of tumors from the right cerebello pontine angle (CPA). All of these patients had suffered a complete loss of peripheral vestibular input on that side. Accordingly comparison of the CVS-induced regional cerebral blood flow (rCBF) changes in populations with or without this input seemed a promising way to delineate the cortical area most sensitive to pure vestibular signaling. The cerebral area responsible for vestibular signal processing was identified by statistical comparison of the perfusion changes detected in the two populations.

METHODS

Study populations

Six healthy volunteers (3 males and 3 females, aged 35.5 ± 9 yr) and six patients (4 males and 2 females, aged 49.2 ± 16 yr), all of them right-handed, were examined. Each of the patients had undergone tumor removal from the right CPA. Histologically, the tumors were schwannomas in five cases and meningeoma in one case. PET investigations were performed 6–18 mo postoperatively. This period of time was sufficient for complete central vestibular compensation to develop. Chronic otitis media, previous ear surgery, disorders of the inner ear, and neurological diseases involving other than the cerebello pontine process were exclusion criteria in the operated patients.

Postoperative anacusis and complete lesion of the right-sided facial nerve developed in all of the patients in addition to a complete loss of the vestibular function. Pure-tone audiometric tests confirmed that the contralateral hearing was intact and appropriate for age. No complaint of dizziness was mentioned at the time of the examinations. Thorough electronystagmographic vestibular investigations (examination of spontaneous signs, calorimetric excitation with cold and warm water, and the rotational stimulus response) demonstrated a complete peripheral vestibular lesion on the operated side in all of the patients and normal responses to the stimuli on the intact side. Moreover the vestibular clinical signs in patients with left-sided CVS were very similar to those observed in the healthy volunteers. Identical investigations did not reveal any deviation from physiological conditions in the healthy volunteers, who were selected as the best responders to CVS on the basis of the frequency and amplitude of nystagmus.

The individuals taking part in the investigations were all provided with fully detailed information concerning the procedure and the possible complications. Perfusion measurements were carried out only after the permission of the Ethical Committee of the University of Debrecen and the written consent of the individuals involved in the tests had been obtained.

Caloric stimulation

CVS was performed by the injection of 30 ml of water (0°C) in 60 s into the external acoustic meatus (Bottini et al. 1994, 2001; Kisely et al. 2001). To ensure standard conditions, the injection was always performed with a Braun perfusion pump. Nystagmus was observed during each PET scan with CVS (except in patients with right-sided CVS), proving the efficacy of the stimulation, but it was not recorded by electronystagmograph.

PET investigations

Perfusion investigations were performed with a GE 4096 Plus PET camera. Special attention was paid to the sensory deprivation to ensure the correspondence of the activation pattern to the specific stimulation applied. To achieve this, complete silence and near-complete darkness were provided in the examination room. The individuals were asked to relax completely and regular checks were made that they were awake between stimulations. During the screening session of the patients and volunteers, three conditions, i.e., rest (A), left-sided CVS (B), and right-sided CVS (C), were repeated alternately three times (sequence: ABCABCABC).

The reconstructed images contained 15 tomographic slices within the 10.5-cm field of view of the camera. The sections were made in planes parallel to that determined by the temporal canthus of the eye and the tragus on both sides. To decrease errors caused by motion, the head of each individual was kept in the same position by a fixation method, using a plastic mesh. The correction for tissue attenuation was based on the data of 25-min transmission measurements, performed with a ^{68}Ge source of 8 mCi activity. [^{15}O]-butanol (45 mCi) was injected 55 s after the start of vestibular stimulation in a 5-s iv bolus. Dynamic data acquisition (36 × 5 s) was started simultaneously with the administration of the tracer. Prior to reconstruction, sinograms were summed up for 90 s data collection, starting from the moment when the butanol reached the brain tissue. This happened with a 10- to 20-s delay relative to the start of the bolus injection. Thus the data used for the image reconstruction were acquired 5 s following the end of the CVS or later. The PET images of the individual measurements were reconstructed by applying a 4.2-mm Hanning filter (image matrix size: 128 × 128 × 15; image voxel size: 2 × 2 × 6.5 mm) after completion of the necessary corrections for random coincidence, scattering, dead time, and tissue attenuation.

A T1-weighted, 3D MPRAGE sagittal plane MR investigation (Siemens MAGNETOM Harmony 1.0 T Whole Body MR, slice thickness 1.5 mm, repetition time (TR) = 11.1 ms, echo delay time (TE) = 4.3 ms) was carried out in each case. MR images were transformed into Talairach's system of coordinates (Collins et al. 1995; Evans et al. 1994; Talairach and Tournoux 1988). The PET images were realigned into the same anatomical position as the relevant MR images (Woods et al. 1993) and stereotaxially normalized perfusion images were prepared by applying transformations determined during the spatial standardization of the MR images. Gaussian-weighted, isotropic spatial smoothing with a half-width of 16 mm was applied to these spatially normalized perfusion images to improve the signal-to-noise ratio and to decrease perfusion differences arising from individual variations in gyral anatomy. Because of the limitation of the axial field of view of the scanner, the searching volume of the statistical analysis after the spatial normalization was limited from below by the $z = -28$ mm plane, with the highest values of the z coordinate being 34 mm (occipitally) and 58 mm (frontally).

Statistical analysis

Statistical analysis was performed on a voxel by voxel basis, using SPM99 software. Global differences in CBF were covaried out for all voxels. Comparisons of the means across CVS and control tasks in the populations, and comparisons of the responses of the populations, were made by using t statistics with appropriate linear contrasts (Friston et al. 1995, 1996). The statistical parametric maps (SPMs) of both populations were generated first with standard subtraction contrasts (B − A and C − A). The distribution of the differences between the responses of the populations (i.e., the activations in the controls exceeding those in the patients) during the given stimulation was examined by fixed-effect analysis. The appropriate SPMs were evaluated via the contrasts $[B - A]_c - [B - A]_p$ and $[C - A]_c - [C - A]_p$ (with subscripts c and p referring to the control and patient populations, respectively). A probability threshold of $P < 0.05$ corrected for multiple comparisons (corresponding to $Z > 4.36$) and an activation cluster-size minimum ($k > 20$) were chosen to highlight the differences in the SPMs (Poline et al. 1997).

The activation foci were superimposed on the averaged, T1-

TABLE 1. *Ipsilateral and contralateral activations of the healthy volunteers induced by left-sided CVS*

	Ipsilateral				Contralateral			
	x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Precentral gyrus	−48	−12	10	4.07	46	−8	10	5.54
Precentral gyrus	−50	−14	16	4.45	50	−14	16	5.44
Precentral gyrus	−60	−4	26	4.16	—	—	—	—
Postcentral gyrus	−58	−24	22	4.31	60	−28	20	4.27
Subcallosal gyrus	—	—	—	—	38	6	−18	3.82
Insula	−36	0	4	3.79	40	0	4	5.01
Insula	−34	2	6	3.59	34	6	6	4.44
Insula	—	—	—	—	40	4	−4	5.00
Insula posterior	−36	−20	4	3.71	38	−20	4	4.78
Area SII	−44	−12	14	3.67	46	−12	14	5.50
Ri cortex	−48	−28	16	5.08	40	−30	16	5.78
Putamen	−26	4	6	3.28	30	6	−4	4.20
Cingulate gyrus	0	−4	46	3.16	0	−4	46	3.15

The stereotactic coordinates refer to the location of maximal statistical magnitude (*Z* score) in the particular anatomical structure. Distances are relative to the intercommissural line in the horizontal (*x*), anterioposterior (*y*), and vertical (*z*) directions. CVS, caloric vestibular stimulation.

weighted MR images of the populations (Evans et al. 1994), which allowed a precise anatomical description.

RESULTS

Left-sided and right-sided CVS were applied for both the healthy volunteers and the patient population. All the subjects complained of earache, lasting on average for 30 s, and a sensation of cold following stimulation. Nevertheless, dizziness and vegetative symptoms (sweating and nausea) predominated both in the healthy control group and in the patients during left-sided CVS. There was no difference between the nystagmus evoked in the patients and that in the healthy subjects during left-sided CVS, whereas stimulation on the right side elicited no eye movements in the former group, but a strong response in the latter group.

The results of the group analyses are reported in Tables 1–4 ($[B - A]_{c,}$ $[B - A]_{p,}$ $[C - A]_{c,}$ and $[C - A]_{p}$, respectively). Large activations induced by left-sided CVS were seen bilaterally in the SPMs of both populations. Activations were observed in the precentral and postcentral gyrus, the insula, the area SII, and the retroinsular (Ri) cortex (Tables 1 and 2). Nevertheless, the statistical magnitudes of activations of the right hemisphere were higher (contralateral dominance) in both SPMs. Activations with limited spatial extent and low magnitude were observed in the cingulate cortex of both populations, the putamen of healthy volunteers, and the thalamus of the patient group.

Large activations induced by right-sided CVS were seen bilaterally in the SPM of healthy volunteers as well. Activations were observed in the precentral and postcentral gyrus, the insula, the area SII, and the Ri cortex and activations with limited spatial extent were observed only in the cingulate cortex of this populations (Table 3). The statistical magnitudes of activations of the left hemisphere were higher (contralateral dominance) in this SPM.

Activations induced by right-sided CVS were seen only ipsilaterally in the SPM of the patient group (precentral gyrus, postcentral gyrus, and insula), while activations with limited spatial extent and low magnitude were observed in the left hemisphere (precentral and postcentral gyrus). The statistical magnitudes of the activations induced by right-sided CVS in the left insula of the patient group were less than the $P_{\text{uncorrected}} < 0.001$ (corresponding to $Z > 3.09$) statistical threshold (Table 4).

Statistical analysis of the group comparison did not reveal

TABLE 2. *Ipsilateral and contralateral activations of the patient population induced by left-sided CVS*

	Ipsilateral				Contralateral			
	x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Precentral gyrus	−50	0	8	3.96	50	−10	10	5.68
Precentral gyrus	−46	−14	10	3.81	48	−16	12	5.95
Precentral gyrus	−60	−2	14	4.05	62	2	10	4.14
Temporal gyrus	−56	−34	20	3.91	60	−32	16	5.32
Insula	−38	−4	0	3.38	42	−4	−4	4.98
Insula	−42	0	4	3.18	42	0	4	4.73
Insula	—	—	—	—	38	2	8	3.91
Insula posterior	−40	−14	4	3.11	40	−12	−4	4.94
Insula posterior	−40	−10	8	3.38	40	−20	10	5.57
Area SII	−50	−18	12	3.79	50	−18	12	5.95
Ri cortex	−50	−28	16	4.14	50	−28	16	5.88
Thalamus	−4	−10	−6	3.96	—	—	—	—
Cingulate gyrus	0	20	36	3.58	0	20	36	3.58

The stereotactic coordinates refer to the location of maximal statistical magnitude (*Z* score) in the particular anatomical structure. Distances are relative to the intercommissural line in the horizontal (*x*), anterioposterior (*y*), and vertical (*z*) directions.

TABLE 3. *Ipsilateral and contralateral activations of the healthy volunteers induced by right-sided CVS*

	Ipsilateral				Contralateral			
	x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Precentral gyrus	46	−6	6	5.53	−48	−2	6	4.10
Precentral gyrus	46	−6	14	4.77	−52	−6	14	4.96
Precentral gyrus	60	0	20	3.27	−60	−6	26	4.29
Postcentral gyrus	60	−26	22	4.48	−54	−22	20	5.24
Insula	42	2	−4	4.44	—	—	—	—
Insula	34	8	12	3.53	−32	4	12	3.89
Insula	38	−12	16	4.72	−38	−12	16	4.34
Insula posterior	38	−18	12	5.01	−38	−18	12	5.09
Area SII	46	−14	14	5.18	−44	−14	14	5.00
Ri cortex	40	−28	18	4.58	−46	−24	22	7.27
Cingulate gyrus	0	4	46	3.13	0	4	46	3.14

The stereotactic coordinates refer to the location of maximal statistical magnitude (*Z* score) in the particular anatomical structure. Distances are relative to the intercommissural line in the horizontal (*x*), anterioposterior (*y*), and vertical (*z*) directions.

any cerebral region for which there was a significant difference in the CVS-induced response with the data obtained following left-sided CVS (the contrast $[B - A]_c - [B - A]_p$ was used) when the statistical criteria were $P_{corrected} < 0.05$ and $k > 20$. In the case of right-sided CVS with the same statistical thresholds, however, a large cluster was found within which CVS induced a significantly higher rCBF increase ($[C - A]_c - [C - A]_p$) in the control group than in the patient group (coordinates of the cluster maximum: $x = -40$, $y = -28$ mm, $z = 24$ mm, maximum Z score = 4.89; $P_{corrected} < 0.006$, size of the cluster = 1,360 mm^3). Repeated analysis with a lower statistical threshold, $P_{uncorrected} < 0.001$ (corresponding to $Z > 3.09$), resulted in a larger (8,880 mm^3) single cluster covering the contralateral inferior parietal lobe, the transverse and superior temporal gyri, and the area of the temporoparietal junction, corresponding to the posterior region of the insula (Figs. 1 and 2; Table 5). A lower statistical threshold ($P_{uncorrected} < 0.01$) resulted an extra cluster with small spatial extent and low statistical magnitude in the insula (Fig. 2; Table 5).

The statistical comparison of the right-sided CVS response of the individuals in the two groups, which differed from each other exclusively as concerns the presence or absence of the peripheral vestibular (and acoustic) input, demarcated a cortical area corresponding to part of the particular cortical region observed by Bottini et al. (2001) that can be activated by both CVS and NV stimulation. This part is anatomically identical to the sum of somatosensory area SII and the region identified in primates as the Ri cortex. The displayed data (Table 5) show that, in contrast with that of Bottini and coworkers, our experimental approach did not demonstrate a significant rCBF difference between the healthy volunteers and the operated patients within the insula. At the same time, the CVS-induced activation patterns of the two populations included a rCBF increase in these areas relative to the rest state, though the statistical comparison of these activations did not indicate a significant difference between the groups. In a similar way, we were able to demonstrate right-sided CVS-induced activation in both populations in the splenium of the corpus callosum and the ipsilateral superior temporal gyrus, but again statistical comparison of the population responses did not reveal any significant difference between the activation patterns.

DISCUSSION

The introduction of functional imaging into research relating to the processing of signals of the vestibular system proved to be a breakthrough (Bense et al. 2001; Bottini et al. 1994 1995, 2001; Brandt et al. 1998, 2002; Brandt 1999; Brandt and Dieterich 1999; Kisely et al. 2001; Lobel et al. 1998 1999; Ödkvist et al. 1974; Paulesu et al. 1997; Penfield 1957; Takeda et al. 1996). These techniques are suitable for studies of the regional blood flow in the CNS, which are effective in the localization of different cerebral functions. As an increased rCBF ensures the extra glucose required by the increased neuronal cerebral activity, the rCBF and the neuronal activity undergo change in close correlation with each other (Ganong 1999). With the ^{133}Xe inhalation technique, a significant activation due to vestibular stimulation was demonstrated in regions behind the primary auditory cortex (Friberg et al. 1985; Penfield 1957). The data obtained in consequence of the de-

TABLE 4. *Ipsilateral and contralateral activations of the patient population induced by right-sided CVS*

	Ipsilateral				Contralateral			
	x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Precentral gyrus	63	0	8	4.35	−56	0	8	4.13
Precentral gyrus	62	−4	20	3.66	−60	−3	20	3.61
Postcentral gyrus	56	−22	18	4.80	−52	−28	18	3.62
Postcentral gyrus	56	−14	16	5.19	−54	−14	16	3.15
Insula	44	−10	2	3.85	−44	−10	2	2.91
Insula	42	−6	−4	3.13	−42	−4	−6	2.60
Cingulate gyrus	6	12	48	3.38	—	—	—	—

The stereotactic coordinates refer to the location of maximal statistical magnitude (*Z* score) in the particular anatomical structure. Distances are relative to the intercommissural line in the horizontal (*x*), anterioposterior (*y*), and vertical (*z*) directions.

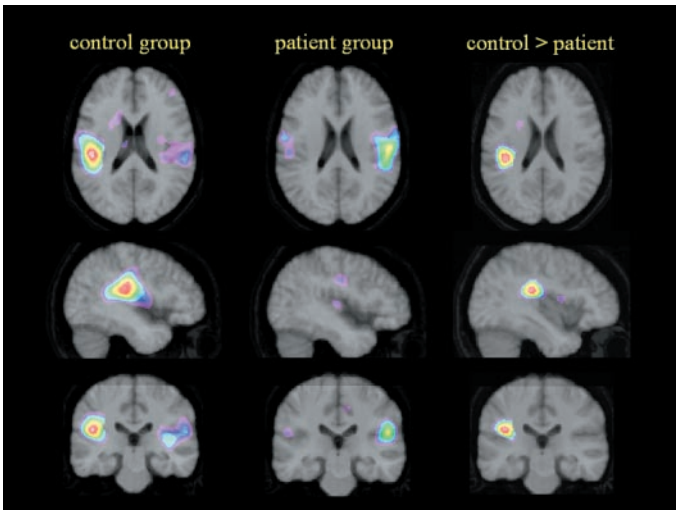

FIG. 1. Activated clusters indicated by the right-sided caloric vestibular stimulation (*left* and *middle*) and the activation pattern revealed by the response difference approach (*right*), superimposed on the spatially standardized, averaged T1-weighted MR data of the populations.

veloping technologies, the ever-increasing sensitivity, and the improved resolution have documented that, together with the insular and retroinsular regions, the inferior parietal lobe, certain temporal areas, and other regions also take part in the processing of vestibular signals received from the periphery. These areas are situated in both hemispheres, with a contralateral predominance over the stimulated side. Additionally, increased activity has been registered in the postcentral gyrus, claustrum, putamen, precentral gyrus, and gyrus cinguli (Bottini et al. 1994, 1995, 2001; Brandt 1999).

The considerable discordance of the published data may be explained by the differences in the experimental conditions. The effects of several modalities are usually involved in brain activation studies of the cerebral projection of the egocentric coordination. The optokinetic technique stimulates both the visual cortex and the oculomotor system. Changes resulting from galvanic stimulation have been described in the activities of the nociceptive and auditory parts of the cortex (Bense et al. 2001; Bucher et al. 1998). The rCBF increase induced by galvanic stimulation was corrected for the rCBF increase resulting from the pain caused by the stimulus, but the activation caused by pain still could not be completely excluded from the response (Bense et al. 2001). In the stimulation of subjects by NV, an attempt was made to prevent acoustic stimulation from the vibrator by keeping the turned-on device near the patients (without skin contact) even in investigations at rest, but exclusion of the tactile component was unsuccessful (Bottini et al. 2001). Which nonvestibular elements contribute to those changes in rCBF caused by CVS must be clarified.

CVS cannot ensure pure vestibular stimulation either. Scientists relying on this technique have made efforts to guarantee experimental conditions under which the tactile, nociceptive, and possibly auditory components of CVS do not influence the results of the measurements, i.e., waiting for 10 s after the injection of cold water prior to the start of PET data acquisition (Bottini et al. 1994, 2001) or delaying the start of PET investigations by an average of 145 and 25 s following stimulation with cold water or warm air, respectively, in an effort ensure that the effect of fast-quenching activation due to mechanical and CVS is decreased (Wenzel et al. 1996). In earlier experiments (Kisely et al. 2001), we applied the technique of stimulation with icy water and found that this resulted in an expressed and prolonged sensation of cold and pain, which persisted during data acquisition. These observations immediately led to the question as to which of the components of the changes in rCBF induced by CVS stimulation could be attributed to the processing of vestibular signals and which were related to the pain or cold sensation.

To separate the vestibular and nonvestibular components in our brain activation studies with CVS, PET investigations were performed on two populations. All of the patients included in the present study had suffered a complete loss of right-sided hearing and a right-sided peripheral lesion of the facial nerve. Consequently, the activation obtained through the CVS of the operated side was certainly free of vestibular and acoustic components. Joint evaluation of the perfusion results obtained using right-sided CVS in the healthy and the operated patient populations made it possible to distinguish the effects of the stimuli on the rCBF via the trigeminal, glossopharyngeal, and vagus nerves, as it may be assumed that the vestibular component is the only difference between the activation in the healthy subjects and that in the operated patients. This assumption is supported by the fact that the acoustic stimulation-induced effects faded out completely during the 5-s or more delay of the acquisition of the data used for the image reconstruction relative to the end of CVS.

Our statistical comparison of the CVS-related responses by these two populations of subjects, who differed only in the existence of the vestibular input, resulted in a single contralateral area with vestibular activation. This cortical area corresponds to part of the cortical region described by Bottini et al. (2001), which can be activated by both CVS and NV. This subregion appears to be anatomically identical to the aggregate of the somatosensory area SII and the Ri cortex identified in primates. Other investigators have identified this region as an analog of the PIVC described in primates (Brandt and Dieterich 1999). Bottini et al. (1994, 1995, 2001) reported on six

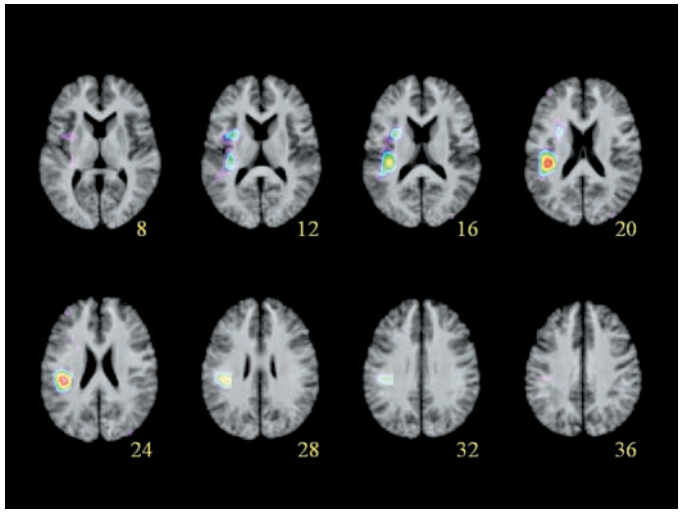

FIG. 2. Statistical parametric map of response difference (thresholded by $P_{\text{uncorrected}} < 0.01$) superimposed on the spatially standardized, averaged T1-weighted MR data of the populations. The numbers indicate the stereotactic coordinates of slices relative to the intercommissural line in vertical (*z*) direction.

TABLE 5. *Contralateral activation shared by CVS and NV compared with the response differences observed in the present study*

	Activation Shared by CVS and NV*				Response Differences			
	x	*y*	*z*	*Z* score	*x*	*y*	*z*	*Z* score
Insula	32	4	−8	5.02	−32	4	−4	0.92
Insula	34	−4	4	7.68	−32	−2	6	2.01
Insula	n/a	n/a	n/a	n/a	−28	6	16	3.02
SII	40	−16	16	5.83	−40	−20	16	4.03
Putative Ri cortex	38	−24	20	4.59	−40	−26	18	4.82
Putative Ri cortex	n/a	n/a	n/a	n/a	−40	−28	24	4.89
Superior temporal gyrus	−54	−12	12	3.94	50	−12	12	0.61
Splenium of callosum	−4	−26	16	4.47	2	−24	14	0.57

The stereotactic coordinates refer to the location of maximal statistical magnitude (*Z* score) in the particular anatomical structure. Distances are relative to the intercommissural line in the horizontal (*x*), anterioposterior (*y*), and vertical (*z*) directions. NV, neck vibration. n/a, not available. * Data from Bottini et al. (2001).

(four contralateral and two ipsilateral) maxima in the CVS–NV shared activation pattern. We made a detailed study of the Gaussianized *t* (*Z*) values in our SPMs, at the locations corresponding to the maxima in the activation pattern reported by Bottini et al. (2001), within the overlap of the areas relating to CVS and NV (Table 5). The evaluated results for the three insular maxima indicate a small difference of subthreshold significance between the CVS-induced rCBF responses of the control and the operated subjects. The extents of the activation in the healthy and operated groups were similar. Accordingly, within these regions we did not succeed in proving a systematic difference by means of the statistical comparison (Table 5). As a probable explanation of the difference between our results and those of Bottini et al., we suggest that the activation within these insular areas is related to the stimulation modalities, which differ from the vestibular component and which are also present during NV stimulation. It should be noted, however, that the small number of subjects in our study may also contribute to the different results observed by ourselves and by Bottini et al. (2001) and an increase in the number of scans might result in the appearance of additional areas in our SPMs.

In a very similar way, use of our protocol led to the detection of a significantly elevated rCBF ipsilaterally in the area of the superior temporal gyrus in both the healthy volunteers and the patient population. However, differential statistical analysis did not indicate a difference in this localization between the perfusion changes detected in the two groups. Here again, it can be presumed that these activations were brought about by the nonvestibular components of the applied stimulation. Our measurements further disclosed low *Z* scores within the area of the splenium of the corpus callosum. This is explained by the similarly low-level perfusion increase of this area as a result of CVS in both the voluntary group and the operated subjects.

In almost all of the previous studies, the resting state served as the reference state in the stimulation protocols and paradigms applied to explore the cortical structures participating in the adjustment and control of the spatial orientation. Consequently, the investigated state was characterized by multimodality signal processing, resulting in a complex multicomponent activation pattern whose interpretation was rather difficult. Bottini and coworkers followed a more efficient strategy, applying two different paradigms, both stimulating the vestibular system. Thus the overlap of the two activation maps definitely contained all regions participating in the processing of the signals from the vestibular periphery. Moreover, the effects of nonvestibular stimulation present in only one of the two paradigms will not appear in the common part of the involved activation patterns. It is theoretically possible, however, that regions excited by nonvestibular modalities, but otherwise present in both stimulation protocols, will also appear in the overlap of the two individual activation patterns. In our experimental approach, the cortical area representing the projection of the vestibular signaling is defined as the difference of two activation patterns relating to two different groups of subjects but obtained through use of exactly the same experimental protocol. Consequently, all activations resulting from the same modality of the applied paradigm will be canceled unless special excitation appears in the activation pattern of one of the populations, due to some special feature in that group. We consider that this experimental protocol (if it can be applied) may be more instrumental in certain cases, as it allows exclusion of the effects of unwanted stimulations.

Our differential method resulted in a single continuous area being activated by the vestibular input signals. For the reasons detailed above, it is quite unlikely that this area embodies subregions excited by nonvestibular components of the CVS applied. The population of healthy volunteers and that of operated patients differed only in the peripheral and acoustic vestibular input, which had been lost completely due to the surgical intervention in the patient group who received right-sided CVS. The specifically tailored stimulation protocol (the data acquisition started with a 5-s delay relative to the end of the injection of cold water) excluded the disturbing effect of any auditory response. Thus the complete lesion of the acoustic nerve did not disturb the analysis of the population differences. This was supported by the fact that no activation of the primary auditory cortex was observed in either of the populations. This condition resulted in an advantageous arrangement, with only a single modality differing in the brain activation of the two experimental populations: the signals from the semicircular canals of the inner ear.

The significant difference in regional response of the two populations to CVS, localized in the Ri/SII areas, can be unequivocally ascribed to the cortical representation of the sensory input provided by the vestibular nerve. Thus our result provides further evidence via functional imaging concerning the hypothesis that this region is the human analog of the PIVC ascribed in primates (Bottini et al. 2001; Guldin and Grüsser 1998). Earlier results achieved with electrophysiological, histological, and functional imaging techniques suggested that specific areas of the CNS participating in the adjustment of the spatial orientation of the body comprise the elements of a

network with a multimodal sensorium (cortical vestibular system). It seems quite feasible that the area with the most significant perfusional change induced by pure vestibular stimulation, and whose perfusion increases significantly in response to either CVS or NV excitation, can be regarded as the "core region" (Guldin and Grüsser 1998), i.e., the common constituent of all neural systems contributing to the spatial recognition. This accords well with the finding of Brandt and Dieterich (1999) and Brandt et al. (2002) that the PIVC is the dominant cortical vestibular area.

Although we have also found activations related to right-sided CVS in brain regions different from the PIVC, these areas were present in both populations. Statistical comparison revealed population differences, but these were below the set significance threshold. The difference between the groups was statistically acceptable only in the PIVC region; the other cortical and subcortical differences could be regarded as mere chance, related to the small number of subjects in each group. These regions include two insular gray matter fields and one in the left frontal lobe, as well as subcortical regions in the left putamen and thalamus. All the clusters of elevated rCBF demarcated by group comparison statistics possibly belong in the vestibular cortical system described by Guldin and Grüsser (1998). The elements of this system are connected to the vestibular nuclei through the thalamus and also to each other (Akbarian et al. 1993 1994; Guldin et al. 1993; Guldin and Grüsser 1998). Single-unit recording studies (Guldin and Grüsser 1998, Grüsser et al. 1990a,b) documented that they differ from each other in the fraction of neurons responding mainly to vestibular, somatosensory, or visual stimuli. Moreover, simultaneous activation and inhibition to specific modalities can be demonstrated in these areas. Thus it is not surprising that the activation pattern in the healthy volunteers was dominated by the highly significant rCBF increase in the Ri/SII (PIVC) region, since more than 50% of the neurons in this area are primarily responsive to the vestibular stimulus. On the other hand, it is reasonable that some of the elements of this network with a smaller fraction of vestibularly driven units (e.g., the vestibular cingulate area) were not found in our study, given the small number of subjects. Activations of this kind in clusters of the vestibular cortical system could be attributed in part to the vestibular input, but the contribution of proprioceptive and visual stimuli due to involuntary muscle responses to cold and pain cannot be excluded. In view of the missing vestibular nerve, it seems quite obvious that the clusters activated in the patient group with right-sided CVS represent areas responsive to nonvestibular modality of the stimulation scenario. The relatively subtle dissimilarity of the activation patterns of the groups with respect to the clusters distinct from the PIVC may be related to the multimodal feature of these areas. At the same time, it is quite feasible that the inherent properties of the imaging method used are responsible for the enhancement of the PIVC region on comparison of the activation patterns of the populations. With the pure vestibular input as the major difference between the groups, the integrated effect of the stimulation on the rCBF is manifested in a dramatic perfusion change if this input reaches the specific cortical areas. Since this integrated response in the PIVC region is so much more pronounced and different from those observed at other sites of the cortical vestibular system, the role of this area in the processing of vestibular input seems in a way to be unique. This finding is in full agreement with the observation that the PIVC is the only vestibular cortex in the squirrel monkey model that is connected with all other areas suggested to belong to the vestibular cortical system. In consequence, this area of the human brain may be regarded as the core region of this system, though further investigations of larger populations are needed to provide stronger support of this.

This study was supported in part by the Hungarian Health Science Committee (ETT 11/526 and ETT 591/2000) and a Mecenatura Grant of the University of Debrecen, Health Science Center (no. 14/99).

REFERENCES

Akbarian S, Grüsser OJ, and Guldin WO. 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 OJ, and Guldin WO. Corticofugal connections between the cerebral cortex and brainstem vestibular nuclei in the macaque monkey. *J Comp Neurol* 339: 421–437, 1994.

Bense S, Stephan T, Yoursy TA, Brandt T, and Dieterich M. Multisensory cortical signal increases during vestibular galvanic stimulation (fMRI). *J Neurophysiol* 85: 886–899, 2001.

Bottini G, Karnath HO, Vallar G, Sterzi R, Frith CD, Frackowiak RSJ, and Paulesu E. Cerebral representations for egocentric space. Functional-anatomical evidence from caloric vestibular stimulation and neck vibration. *Brain* 124: 1182–1196, 2001.

Bottini G, Paulesu E, Sterzi R, Warburton E, Wise RJS, Vallar G, Frackowiak RSJ, and Frith CD. Modulation of conscious experience by peripheral sensory stimuli. *Nature* 376: 778–781, 1995.

Bottini G, Sterzi R, Paulesu E, Vallar G, Cappa FS, Erminio F, Passingham RE, Frith CD, and Frackowiak RSJ. Identification of the central vestibular projections in man: a positron emission tomography activation study. *Exp Brain Res* 99: 164–169, 1994.

Brandt T. *Vertigo: Its Multisensory Syndromes.* London : Springer, 1999.

Brandt T, Bartenstein P, Janek A, and Dieterich M. Reciprocal inhibitory visual-vestibular interaction: visual motion stimulation deactivates the parieto-insular vestibular cortex. *Brain* 121: 1749–1758, 1998.

Brandt T and Dieterich M. The vestibular cortex: its locations, functions and disorders. *Ann NY Acad Sci* 871: 293–312, 1999.

Brandt T, Glasauer S, Stephan T, Bense S, Yousyy AT, Deutschlander A, and Dieterich M. Visual-vestibular and visuovisual cortical interaction: new insight from fMRI and PET. *Ann NY Acad Sci* 956: 230–241, 2002.

Bucher SF, Dieterich M, Wiesmann M, Weiss A, Zink R, Yoursy TA, and Brandt T. Cerebral functional magnetic resonance imaging of vestibular, auditory, and nociceptive areas during galvanic stimulation. *Ann Neurol* 44: 120–125, 1998.

Collins DL, Neelin P, Peteres TM, and Evans AC. Automatic 3-D intersubject registration of MR volumetric data in standarized Talairach space. *J Comput Assisted Tomogr* 18: 192–205, 1995.

Evans AC, Collins DL, Neelin P, MacDonald D, Kamber M, and Marrett TS. Three-dimensional correlative imaging: applications in human brain mapping. In: *Functional Neuroimaging, Technical Foundations.* San Diego, CA: Academic Press, 1994, p. 145–162.

Faugier-Grimaud S and Ventre J. Anatomic connections of inferior parietal cortex (area 7) with subcortical structures related to vestibulo-ocular function in monkey (*Macaca fascicularis*). *J Comp Neurol* 280: 1–14, 1989.

Friberg L, Olse TE, Roland PE, Paulson OP, and Lassen NA. Focal increase of blood flow in the cerebral cortex of man following vestibular stimulation. *Brain* 108: 609–623, 1985.

Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, and Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapping* 2: 189–210, 1995.

Friston KJ, Poline JB, Holmes AP, Frith CD, and Frackowiak RSJ. A multivariate analysis of PET activation studies. *Hum Brain Mapping* 4: 140–151, 1996.

Ganong WF. *Review of Medical Physiology,* 19th ed. Stanford, CT: Appleton and Lange, 1999.

Grüsser OJ and Guldin WO. *Multisensory Control of Posture.* New York: Plenum Press, 1995, p. 51–62.

Grüsser OJ, Pause M, and Schreiter U. Vestibular neurones in the parieto-insular cortex of monkeys (*Macaca fascicularis*): visual and neck receptor responses. *J Physiol* 430: 559–83, 1990a.

Grüsser OJ, Pause M, and Schreiter U. Localization and responses of neurones in the parieto-insular vestibular cortex of awake monkeys (*Macaca fascicularis*). *J Physiol* 430: 537–57, 1990b.

Guldin WO and Grüsser OJ. Is there a vestibular cortex? *Trends Neurosci* 21: 254–259, 1998.

Guldin WO, Mirring S, and Grusser OJ. Connections from the neocortex to the vestibular brain stem nuclei in the common marmoset. *Neuroreport* 5: 113–116, 1993.

Husain M and Kennard C. Visual neglect associated with frontal lobe infarction. *J Neurol* 243: 652–657, 1996.

Kisely M, Tóth Á, Emri M, Lengyel ZS, Kálvin B, Horváth G, Trón L, Bogner P, and Sziklai I. Verarbeitung vestibulärer Impulse im Zentralnerversystem. *HNO* 49: 347–354, 2001.

Lobel E, Kleine JF, Bihan D, Leroy-Willig A, and Berthoz A. Functional MRI of galvanic vestibular stimulation. *J Neurophysiol* 80: 2699–2709, 1998.

Lobel E, Kleine JF, Leroy-Willig A, Moortele P, Bihan D, Grüsser O, and Berthoz A. Cortical areas activated by bilateral galvanic vestibular stimulation. *Ann NY Acad Sci* 871: 313–323, 1999.

Ödkvist LM, Schwarz DWF, Fredrickson JM, and Hassler L. Projection of the vestibular nerve to the area 3a arm field in the squirrel monkey (*Saimuri sciureus*). *Exp Brain Res* 21: 97–105, 1974.

Pandya DN and Sanides F. Architectonic parcellation of the temporal operculum in rhesus monkey and its projection pattern. *Z Anat Entwicklungsgesch* 139: 127–161, 1973.

Paulesu E, Frackoviak RSJ, and Bottini G. *Human Brain Function.* San Diego, CA: Academic Press, 1997, p. 183–243.

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

Poline JB, Worsley KJ, Evans AC, and Friston KJ. Combining spatial extent and peak intensity to test for activations in functional imaging. *Neuroimage* 5:83–96, 1997.

Schwarz DWF and Fredrickson JM. Rhesus monkey vestibular cortex: a bimodal primary projection field. *Science* 172: 280–281, 1971.

Takeda N, Hashikawa K, Moriwaki H, Oku N, Koizuka T, Taya N, Kobo T, and Nishimura T. Effect of caloric vestibular stimulation on parietal and temporal blood flow in human brain: a consecutive technetium-99m-HMPAO SPECT study. *J Vestib Res* 6: 127–134, 1996.

Talairach J and Tournoux P. *Co-planar Stereotaxic Atlas of the Human Brain.* Stuttgart, Germany: Thieme, 1988.

Vallar G, Bottini G, Rusconi ML, and Sterzi R. Exploring somatosensory hemineglect by vestibular stimulation. *Brain* 116: 71–86, 1993.

Vallar G and Perani D. The anatomy of unilateral neglect after right hemisphere stroke lesions: a clinical CT correlation study in man. *Neurophysiologia* 24: 609–622, 1986.

Wenzel R, Bartenstein P, Dieterich M, Danek A, Weindl A, Minoshima S, Ziegler S, Schwaiger M, and Brandt T. Deactivation of human visual cortex during involuntary ocular oscillations: a PET activation study. *Brain* 119: 101–110, 1996.

Woods RP, Mazziotta JC, and Cherry SR. MRI-PET registration with automated algorithm. *J Comput Assisted Tomogr* 17: 536–546, 1993.