



Evidence for interacting cortical control of vestibular function and spatial representation in man

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Abstract

The objective of this research was to determine the possible relation between deficits in spatial representation capability and vestibular function following cortical lesions. We thus investigated vestibulo-ocular behaviour in a group of 14 patients with unilateral cortical damage involving the occipito-temporo-parietal junction. Patients were divided in three sub-groups: (1) Group R+: five patients with right sided cortical lesions associated with a left hemi-neglect, (2) Group R–: four patients with right sided cortical lesions with no hemi-neglect and (3) Group L: five patients with left-sided cortical lesions. The patient groups were compared to a group of eight healthy age-matched subjects. The vestibulo-ocular reflex (VOR) was tested in complete darkness by rotating the subject around the vertical axis by sinusoidal rotation at different frequencies, and by steps of acceleration or deceleration. The nystagmus slow phase velocity was measured and plotted as a function of the head velocity and the VOR parameters including gain, bias, time constant and phase were calculated.

The cortical lesions induced a significant VOR asymmetry in terms of: a directional preponderance of the VOR gain to the contralesion side, only during sinusoidal rotation, and, in contrast, a VOR bias and a directional preponderance of the VOR time constant and of the nystagmus frequency to the side of the cortical lesion. These latter VOR deficits were the most significant in the R+ group, i.e. in right cortical lesions with hemi-neglect syndrome. These results demonstrate in man, the existence of a cortical influence on vestibular function related to the mechanisms of spatial representation.

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1. Introduction

Anatomical and electrophysiological evidence has been provided, in the monkey, for multiple vestibular-related cortical areas distributed from the posterior parietal cortex to the frontal regions (Akbarian, Grusser, & Guldin, 1993, 1994; Fukushima, 1997; Fukushima, Sato, Fukushima, Shinmei, & Kaneko, 2000; Grusser, Pause, & Schreiter, 1990; Kawano & Sasaki, 1984; Kawano, Sasaki, & Yamashita, 1980; Ventre & Faugier-Grimaud, 1988). Neuronal activity of these areas, especially in the parietal and parieto-insular cortices, is characterized by a multimodal convergence, including visual, vestibular, proprioceptive or corollary discharge signals, that reflects a role of these regions in associative high-ordered neural transformations (Andersen, Snyder, Bradley, & Xing, 1997; Brotchie,

Andersen, Snyder, & Goodman, 1995; Duhamel, Colby, & Goldberg, 1992). From a functional perspective, behavioural studies related to the effect of unilateral cortical lesions on vestibular function established the existence of a direct control of the parieto-temporal (PT) cortex upon the symmetry of vestibulo-ocular function in cat and monkey (Ventre, 1985b; Ventre & Faugier-Grimaud, 1986; Ventre, Flandrin, & Jeannerod, 1984). Taken together, these electrophysiological and behavioural observations suggest that the parieto-temporal cortex is involved in complex processes associated with vestibular integration.

In man, while brain imaging studies provide some insight into the functional organization of vestibular cortex, the role of the different vestibular-related cortical regions remains quite obscure. Interestingly, the vestibular cortical network described in the human by cerebral activation studies is quite comparable to that described in the monkey, with several distinct areas distributed in the temporal and parieto-insular regions and in the frontal and premotor

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cortices (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Bottini et al., 1994, 2001; Lobel, Kleine, Le Bihan, Leroy-Willig, & Berthoz, 1998). Recently, a possible functional role for these different regions has been suggested to include self-motion perception, spatial perception and memory, all based on the integration of vestibular-related signals (Brandt, Bartenstein, Janek, & Dieterich, 1998; Doricchi, Siegler, Iaria, & Berthoz, 2002; Israel, Rivaud, Gaymard, Berthoz, & Pierrot-Deseilligny, 1995; Straube & Brandt, 1987). In a vestibular memory contingent task, it has been shown that normal subjects can produce accurate vestibularly guided saccades while labyrinthine defective patients and cortically damaged patients cannot, thus demonstrating the use of vestibular inputs in spatial processing (Bloomberg, Melvill-Jones, Segal, McFarlane, & Soul, 1988; Israel et al., 1995; Nakamura & Bronstein, 1995). This crucial role of vestibular inputs in spatial integration has also been studied in a visual-vestibular memory contingent saccade task derived from Bloomberg's task (Blouin, Gauthier, van Donkelaar, & Vercher, 1995; Blouin, Gauthier, & Vercher, 1997; Israel, Ventre-Dominey, & Denise, 1999). In this task, the subject had to memorize the retinal error of a peripherally located visual target and then, after angular rotation, to update the retinal error using vestibular information to maintain a constancy of the spatial representation during eye-head displacements. These studies suggest a clear interaction between vestibular information and space representation.

The asymmetric misrepresentation of space, described as a neglect syndrome, can occur in man following parietal cortex lesions. This syndrome can be expressed in different perceptual dimensions, including perception of objects in the extrapersonal space or perception of the body schema. To explain the neglect disorder, several hypotheses have been proposed including dysfunction in attentional processing (Gainotti, D'Erme, & Bartolomeo, 1991; Kinsbourne, 1987; Posner, Walker, Friedrich, & Rafal, 1984), horizontal anisometry of space representation (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996), ipsilesional deviation of the egocentric spatial frame (Ventre et al., 1984) or hypokinesia (Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Heilman, Bowers, Valenstein, & Watson, 1987) and finally, more recently, motor programming impairment of leftward movements (Husain, Mattingley, Rorden, Kennard, & Driver, 2000). Moreover, patients with a lesion of the parieto-temporal cortex and/or the visual cortex cannot perceive the usual sensation of self-motion induced by an optokinetic stimulation directed to the contralesional space (displacement of the whole visual field) (Straube & Brandt, 1987). In right-brain damaged patients (Incoccia, Doricchi, Galati, & Pizzamiglio, 1995) and recently, Doricchi et al. (2002) observed a co-occurrence between a left (contralesional) hemi-neglect and right (ipsilesional) deficits of nystagmus slow phase gain and frequency during optokinetic and combined optokinetic-vestibular stimulation. Interestingly, several studies converge to show that visual

or vestibular stimulation can temporarily improve neglect in right-brain damaged patients (Bisiach et al., 1996; Cappa, Sterzi, Vallar, & Bisiach, 1987; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990; Vallar, Bottini, Rusconi, & Sterzi, 1993; Vallar, Papagno, Rusconi, & Bisiach, 1995). Vallar et al. (1995) demonstrated in a rare case of right hemi-neglect with dysphasia due to a left brain damage, that the beneficial effects of vestibular stimulation were limited to the visuo-spatial disorders and consequently could be the result of specific effects related to integration of vestibular inputs rather than a general hemispheric activation.

Based on the literature, we can assess that, even though the underlying mechanisms are still unknown, the neural transformation sub-tending the representation of space in the parieto-temporal cortex includes the integration of vestibular information. In this context, one can ask: (1) whether such a vestibular cortical mechanism is linked only to the perceptual or cognitive aspects of the vestibular function, or to its motor output as well, (2) in this latter perspective, whether the vestibulo-motor deficits will be correlated with the visuo-spatial disorders and finally (3) whether such a possible interaction between cortex and vestibulo-motor function follows the same rule of hemispheric lateralization, particularly the right hemispheric dominance observed in visuo-spatial oriented behaviour.

In this study, we addressed these questions by investigating vestibulo-ocular performance of 14 patients presenting with a unilateral brain damage either in the right hemisphere, accompanied or not by a left hemi-neglect, or in the left hemisphere, without neglect. To better understand the cortical mechanism involved in vestibular function, we carefully analysed the different dynamics of vestibulo-ocular responses induced by head rotation in different paradigms. Some of these results have been presented in a preliminary form (Ventre-Dominey, Vighetto, & Denise, 1999).

2. Materials and methods

2.1. Subjects

Vestibulo-ocular function was investigated in a group of 14 right-handed patients (six males and eight females; mean age: 54 years, S.D. ± 14) with unilateral cortical lesions, including the parieto-temporal and occipital cortex due to ischaemic or haemorrhagic stroke, excluding one patient with a metastatic tumour (Table 1). The patients were recruited from the Cerebro-Vascular Clinic of the Lyon Neurology Hospital. All patients were screened for absence of psychiatric, ORL and ophthalmological disorders (except for contralesional visual hemifield defects in six cases) and for absence of neurological disorders other than their current cerebral disease. The patient group was compared to a group of eight healthy age-matched subjects (mean = 46 years; S.D. ± 13 ; four males and four females).

Table 1
Clinical characteristics of the patients with cortical lesions

Cases	Age (years), sex	Disease duration (days)	Visual field deficit	Visuo-spatial neglect	Lesion etiology	Lesion site	Patient group
YB	60, F	120	PH	+	Ischaemic	O-P-T-F	R+
PH	66, F	30		+	Ischaemic	P-T	R+
RPE	57, M	7	H	+	Ischaemic	O-P-T	R+
RPI	72, F	72		+	Ischaemic	Internal capsule	R+
RJ	77, M	10		+	Ischaemic	O-P-T-F	R+
JO	78, M	7	PH		Haemorrhagic	P-T	R–
JB	58, M	22			Haemorrhagic	O-P-T	R–
DC	50, F	15	IQ		Haemorrhagic	O-P-T	R–
JLM	46, M	18			Ischaemic	P-T	R–
LL	52, F	10			Ischaemic	P-T	L
MJk	31, F	150			Ischaemic	O-P-T	L
MC	36, M	30			Arterio-venous malformation	P	L
NF	29, F	7	PH		Tumour	O-P	L
RK	47, F	19	H		Ischaemic	O-P	L

M: male; F: female; H: hemianopia; PH: partial hemianopia; IQ: inferior quadrantanopia; R+: right-brain damage with neglect; R–: right-brain damage without neglect; L: left brain damage; F: frontal lobe; P: inferior parietal lobe; O: occipital lobe; T: temporal lobe.

Before vestibulo-ocular testing, all the subjects gave their informed consent to participate in this research previously approved by the local ethical committee (CCPRB L. Berard, Proposal No. 98/006).

2.2. Anatomical location and characterization of the cortical lesions

In each patient, the cortical lesion site was first identified by CT scan or MRI axial brain images. Each CT or MRI image was scanned and digitized on PC computer using an image processing software (CorelScan). A precise reconstruction of the lesion in the cerebral cortex was then established first by identifying and delineating the focus of the cortical lesions on each CT or MRI slice then by superimposing each CT or MRI slice, including the delimited lesioned areas, onto the corresponding template of the stereotaxic atlas (Talairach & Szikla, 1967). Finally, the same digitized stereotaxic templates were again superimposed upon each other for further identification of a common overlapping site of the cortical damage (Fig. 1). We calculated the surface area of the lesions on the different successive templates using the image processing software ACTIVIS (CNRS-INSERM software, Lyon, France), and then calculated the average over these values. The lesion volume was then estimated by multiplying this average surface area by the anterior–posterior length of the lesion, corresponding to an ellipsoid volume, similar to the method employed by (Heide, Kurzidim, & Kömpf, 1996).

According to the location of the cortical lesion and the accompanying visuo-spatial disorders, the patients were divided into three sub-groups: (1) Group R+: five patients with right cortical lesions associated with a left hemi-neglect, (2) Group R–: four patients with right cortical lesions with no hemi-neglect and (3) Group L: five patients with left cortical lesions. The chronicity of the cortical lesions was not

significantly different between the patient groups (ANOVA: $F(2, 11) = 0.6$, $P > 0.05$).

In all the patients but one (RPI), the lesion involved the parieto-temporo-occipital (PTO) junction, including the superior part of the posterior temporal lobe and the inferior part of the posterior parietal lobe irrigated by the middle cerebral artery. As shown in Fig. 1, the lesioned region always corresponded to the supra-marginalis and the angular gyri, involving part of the Brodmann's areas 39 and 40. The lesion could extend rostrally, in two R+ patients (RJ, YB), into the frontal regions up to the superior frontal sulcus, and caudally, in three R+ patients (RPE, RJ and YB), into the junction of areas 19 and 37 and the underlying white matter thus reaching the optical radiations to the occipital cortex. In one patient (RPI), the lesion involved the internal capsule, partly disconnecting the temporo-parieto-occipital regions from sensory inputs. In the R– and the L groups, none of the patients presented any involvement of the frontal regions. Each group of patients included some cases with cortical damage extending caudally in the occipital lobe. Such occipital extents of the lesion could induce visual deficits (complete or partial hemianopia) in these patients (Table 1).

These extensions of the cortical damage into the frontal and the occipital lobes implies that the sizes of the cortical lesions could differ over the patients. The main disparity in lesion volumes occurred between the patient groups with right lesions and the patient group with left lesions as the mean volume of the lesioned cortex was 29 cm^3 (S.D. = 20) for the R+ group, 21 cm^3 (S.D. = 10) for the R– group as compared to 11 cm^3 (S.D. = 7) for the L group.

2.3. Neuropsychological tests

Before vestibulo-ocular testing, each subject underwent a complete neurological examination and ophthalmological (visual accuracy, visual field completion) and ORL examina-

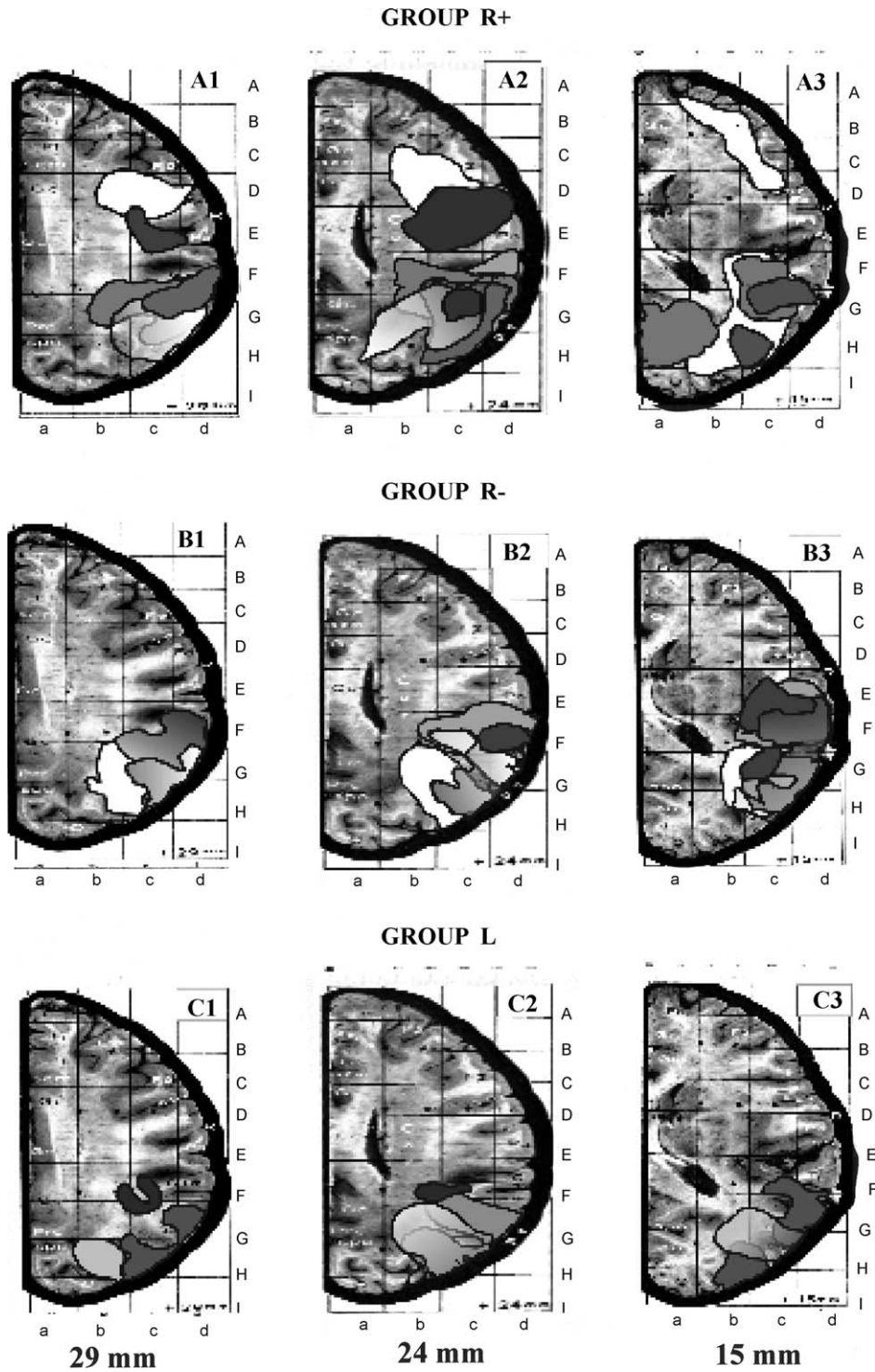


Fig. 1. Stereotaxic horizontal templates (Talairach & Szikla, 1967) with the delineated superimposed lesions within the frontal, parietal, temporal and occipital gyri in the R+ group (A1, A2, A3), in the R- group (B1, B2, B3) and in the L group (C1, C2, C3). Distance from the bicommissural plane is indicated on the bottom of the figure.

tion (caloric test). Visuo-spatial hemi-neglect was assessed by using three different standardized tasks: (1) the line bisection test requiring subjects to mark the midpoint of a line (22 cm long and 1 mm wide) drawn on a paper, (2) the line cancellation test or Albert test (Albert, 1973) requiring subjects to bar all the lines (total of 40) equally distributed on the two halves of a sheet of paper and (3) the reproduction of different sketched objects (clockface, flower) or composite pictures with symmetrical features (houses surrounded by trees) (Gainotti, D'Erme, Monteleone, & 1986). These neuropsychological tests were performed on standard A4 format paper whose midline was aligned with the body axis. The possibility of visual extinction was investigated by simultaneous bilateral visual stimulation, and a neglect dyslexia was assessed by reading a paragraph. These tests were performed both by the controls and the patients. A visuo-spatial hemi-neglect was assessed first at the neurological clinical examination and, when the subject made errors, usually in the left hemispace, in at least two of the tests presented. Controls and patients of the R– and L groups made no mistakes in any of the neuropsychological tests.

All patients included in the R+ group, who had been previously identified with a left neglect syndrome at the clinical examination (1) failed in sketching symmetrical figures by leaving the left features of the drawings unfinished and (2) missed part of the bars (error score: 3/20 to 10/20) located on the left half of the paper at the Albert test. In the line bisection test, three out of five R+ patients shifted the midpoint of the line (from 10 to 20 mm) to the right (Table 2).

2.4. Recording procedure

The subject was seated in a rotating chair in complete darkness, in front of a panel supporting LEDs. Head movements were restricted by maintaining the head fixed to the head rest by a frontal strap. The head rest was tilted forward at a 15° angle to make the vestibular stimulation in the horizontal semi-circular canal plane. Eye movements were

recorded by DC electro-oculography (EOG), using disposable cutaneous electrodes, on the outer canthi for horizontal eye movements and on the upper and lower ridges of the right eye for vertical eye movements. Vertical eye movements were recorded for monitoring of blinks. Horizontal and vertical EOG signals were amplified and filtered with a low-pass analogue filter (40 Hz). By using an interactive data collection software, we could monitor the eye position during data acquisition and correct any EOG offset. These EOG signals were collected on a PC computer (sampling frequency: 100 Hz) and stored to be subsequently analysed with an interactive software (SAMO) (Denise, Darlot, Ignatew Charles, & Toupet, 1996).

2.5. Paradigm

Before the recording session, the subject was dark-adapted for 10 min to prevent changes in EOG gain (Krogh, 1975). Spontaneous eye movements were recorded for 1 min in the dark, before and after the vestibular stimulation session. The vestibulo-ocular reflex (VOR) was induced by rotation of the subject around the vertical axis during a series of sinusoidal rotations and two velocity step trials.

- Sinusoidal rotation: The chair was sinusoidally rotated with a peak angular velocity of 60°/s at different frequencies (0.02, 0.05 and 0.1 Hz). At each frequency, VOR was continuously recorded over five cycles of rotation.
- Velocity step: The chair was immobile and suddenly rotated at constant velocity (acceleration 100°/s²; constant velocity: 60°/s) and after 90 s of rotation, the chair was stopped (deceleration: 100°/s²). The two directions of rotation (clockwise: CW and counterclockwise: CCW) were tested in two successive trials. For each trial, VOR was recorded in response to the chair acceleration as the per-rotatory nystagmus and in response to the deceleration (chair stop) as the post-rotatory nystagmus.

The horizontal EOG signal was calibrated with ocular saccades to visual targets (10, 20 and 30° in the right and left visual hemifields). In case of partial or complete hemianopia (five patients), the visual targets were displayed in the normal parts of the visual fields and the EOG calibration curve was extrapolated into the anopic zone. EOG calibration was performed at the beginning and at the end of the session and twice during the session.

2.6. Data analysis

Eye movement velocity was calculated by an interactive software using the two-point central difference algorithm (50 ms step size). Quick phases were then removed by an algorithm using velocity and acceleration thresholds (Denise et al., 1996). In the few cases where a spontaneous nystagmus was recorded in the dark, the mean slow phase velocity of the spontaneous nystagmus was calculated and then

Table 2
Neuropsychological results of the neglect patients (R+ group)

Patients	Group	Symmetrical drawings	Albert test (error score)	Bisection line (shift in mm)
YB	R+	+	10	20
PH	R+	+	3	10
RPE	R+	+	3	–
RPI	R+	+	3	–
RJ	R+	+	7	14
JO	R–	–	–	–
JB	R–	–	–	2
DC	R–	–	–	3
JLM	R–	–	–	–
LL	L	–	–	1
MJ	L	–	–	–
MC	L	–	–	–
NF	L	–	–	2
RK	L	–	–	–

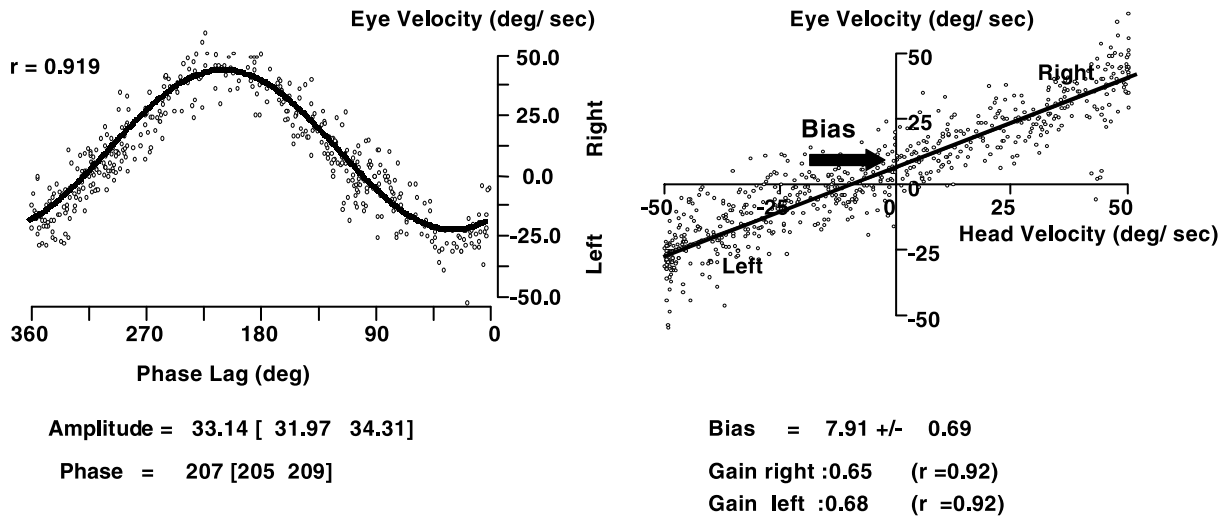


Fig. 2. Example of the data analysis method for a session of sinusoidal rotation at 0.05 Hz in one patient of the R+ group. (A) Plot of slow phase velocities over the phase lag and sinusoidal adjustment on the slow phase velocity curve. (B) Plot of phase-corrected slow phases velocities over the head velocities with linear regression fitting. *r*: correlation coefficients of the sinusoidal fit and of the linear regression. Bias: bias value corresponding to the intercept of the regression line with the ordinate. Right: eye velocity of the slow phases directed to the right (CW direction). Left: eye velocity of the slow phases directed to the left (CCW direction).

automatically subtracted in the further VOR analysis of the corresponding subjects. Different parameters were quantified based on the slow phase velocity (SPV) as following:

2.6.1. For sine responses

1. For the VOR gain and bias calculation, the software provides a two-level data analysis: (a) A sinusoidal fit was performed on the SPV curve according to the formula $SPV(t) = B + A \times \sin(2\pi ft + \phi)$ with *t* being the time, *f* the frequency of rotation, *B* the bias, *A* the amplitude and ϕ the phase (Fig. 2). The VOR phase with respect to the chair position was then removed from the eye velocity response to obtain the phase-corrected SPV. (b) The phase-corrected eye velocity was plotted against the head velocity in order to evaluate the VOR velocity bias. As shown in Fig. 2, the absence of any discontinuity in the eye velocity versus head velocity plot indicates that the bias is the same for both directions. Thus, the VOR bias was calculated as the mean eye velocity for head velocity ranging from $-2^\circ/s$ to $+2^\circ/s$. Finally, in each direction of rotation, we computed a linear regression (on eye and head velocities) with the constraint that the *Y*-axis intercept was equal to this bias value. The VOR gain was then calculated for each direction as the slope of the respective regression lines.
2. For the phase calculation, the software provides the phase values for each direction of rotation by forcing sine-wave fits on half-cycles (Lasker, Hullar, & Minor, 2000).

2.6.2. For per- and post-rotatory responses

VOR gain was calculated as the ratio between maximal slow phase velocity and constant chair velocity. VOR time constant was measured as the time when the area under the

slow phase velocity curve reaches 63% of the total area (Denise et al., 1996). For each parameter, the mean value between the two per- and post-rotatory slow phase responses induced in the same direction was calculated to be used for further statistical analysis. VOR nystagmic slow phase frequency (NF) was analysed by measuring the number of nystagmic movements in 1 s.

As the cortical lesions were lateralized, we expressed the data of the patient groups in terms of the direction of slow phase velocity towards (ipsilateral SPV) and away from (contralateral SPV) the hemispheric lesion.

To quantify the VOR asymmetry in patients, we calculated the relative directional preponderance (DP) for all parameters (except the bias):

$$DP = \frac{(\text{contralateral SPV} - \text{ipsilateral SPV}) \times 100}{\text{contralateral SPV} + \text{ipsilateral SPV}}$$

Positive DP: directional preponderance of SPV away from the lesion, negative DP: directional preponderance of SPV towards the lesion

In the control group, for each dependent variable, DP was calculated as following:

$$DP = \frac{(\text{CCW SPV} - \text{CW SPV}) \times 100}{\text{CCW SPV} + \text{CW SPV}}$$

In this group, for all parameters, DP was not significantly different from 0 (Student's *t*-test: $P > 0.05$).

Before any statistical analysis, each dependent variable was verified for the homogeneity of variances by the non-significance of the Levene's test in each group.

For each parameter, statistical analysis was performed by using repeated measures ANOVA analysis and the Newman-Keuls post hoc comparison. The between sub-

jects factors were the group (control, patient), the hemisphere (right and left), the presence or not of neglect (C, R+, R– and L), the presence or not of visual field defects including hemianopia (H+, H–) and the location of the cortical lesion including or not the occipital cortex. The slow phase direction (CW, CCW or ipsilateral, contralateral) and the sinusoidal rotation frequency (0.02, 0.05 and 0.1 Hz) were analysed as the within subjects factors. The significance level was established at a 95% confidence interval. All statistical analysis were performed using the STATISTICA software package (Statsoft Inc., Tulsa, OK, USA).

3. Results

A spontaneous nystagmus was found in the dark in only two patients of R+ group (HP; RPE) while VOR performance was asymmetrical in all the patient groups as detailed below. During vestibular stimulation, we never observed any systematic gaze deviation in the patient groups (as shown in one patient in Fig. 5).

3.1. VOR gain

During sinusoidal rotation, VOR gain was asymmetrical in the patients with right lesion (hemisphere \times direction interaction: $F(2, 19) = 3.7, P < 0.05$). The gain of nystagmic slow phase movements directed towards the lesion was significantly decreased during sinusoidal rotation in the patient group with right lesion (post hoc comparison: $P < 0.01$) as compared to the control group (Table 3). As shown in Fig. 3, the gain asymmetry, as measured by the DP, was significantly more pronounced in the patient group with hemi-neglect (R+) (main Neglect effect: $F(3, 17) = 3.8, P < 0.05$), as compared to the control group (post hoc comparison: $P < 0.05$). This VOR deficit was independent of the stimulus

frequency (neglect \times frequency interaction: $F(6, 34) = 1.6, P > 0.05$). Interestingly, the DP of VOR gain was dependent on the occipital extent of the lesion (main Lesion effect: $F(2, 19) = 4.4, P < 0.05$) and was significant only in patients with occipital involvement (post hoc comparison: $P < 0.05$). This DP effect for VOR gain was not related to the presence of visual field deficits (main Hemianopia effect: $F(1, 12) = 0.46, P > 0.05$).

At the level of individuals, the DP of the VOR gain was abnormal in four R+ and two R– patients and in three L patients with occipital lobe involvement (Table 4). In the R+ group, the only patient (PH) without a VOR gain deficit presented a cortical lesion limited to the parieto-temporal cortex with almost no extent in the occipital lobe. With velocity step stimulation, even if VOR gain was higher (Table 3) and asymmetric (Fig. 3), the level of significance was not reached in any group of patients with or without neglect (neglect \times direction interaction: $F(3, 18) = 0.59, P > 0.05$).

3.2. VOR phase

In the patients with right lesions (Table 3), there was a VOR phase lag predominantly for the SPV directed toward the side of the lesion (hemisphere \times direction interaction: $F(2, 16) = 8, P < 0.01$) independently of the stimulus frequency (hemisphere \times direction \times frequency interaction: $F(4, 32) = 0.8, P > 0.05$). This phase lag asymmetry was dependent on neglect (neglect \times direction interaction: $F(3, 15) = 5, P = 0.01$). Significant VOR phase abnormalities were found in three patients of R+ group (YB, RJ, RPE) and in one of R– group (JLM) (Table 4).

3.3. VOR bias

VOR was significantly biased toward the lesion side in patient groups as compared to the control group (main

Table 3

Values of the gain, phase and time constant in each direction of the VOR slow phases in the different control (C) and patients (R+, R– and L) groups

		Sinusoidal rotation				Velocity step			
		Gain		Phase		Gain		Time constant	
		CW	CCW	CW	CCW	CW	CCW	CW	CCW
C	Mean \pm S.D.	0.68 \pm 0.2	0.64 \pm 0.2	12 \pm 5.4	11 \pm 5.4	0.77 \pm 0.2	0.73 \pm 0.2	16 \pm 3.6	15 \pm 2.8
		Ipsi	Contra	Ipsi	Contra	Ipsi	Contra	Ipsi	Contra
R+	Mean	0.57	0.66	24	22	0.95	0.99	17	8
	S.D.	0.2	0.1	7.9	7.8	0.3	0.1	4.8	2.9
R–	Mean	0.57	0.58	15	11	0.92	0.82	13	8
	S.D.	0.2	0.1	4.3	5.3	0.3	0.3	5.7	3
L	Mean	0.79	0.75	10	10	0.85	0.79	15	12
	S.D.	0.06	0.1	3.9	4.9	0.2	0.2	5.3	5.4

CW: clockwise; CCW: counterclockwise; Ipsi: ipsilateral to the lesion; Contra: contralateral to the lesion; S.D.: standard deviation. As the VOR gain for sinusoidal rotation was significantly independent of the stimulus frequencies, mean gain values are computed over the three frequencies.

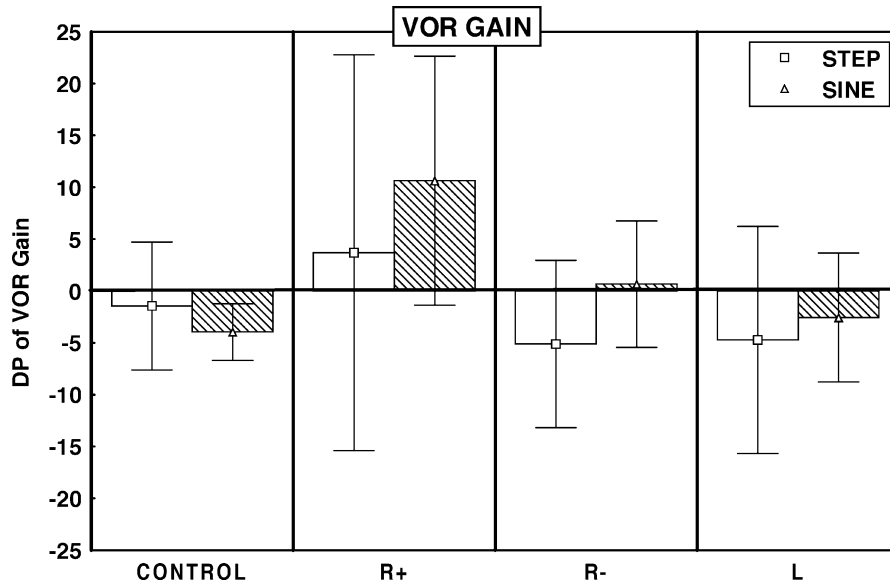


Fig. 3. Bar graph of the mean directional preponderance (DP) of VOR gain in each group of patients in the two conditions of stimulation: rotation by step of velocity (STEP) and sinusoidal rotation (SINE). Standard deviations are indicated. Note the significant positive value indicative of a VOR gain preponderance to the contralesional direction in the R+ group only during sinusoidal rotation.

Group effect: $F(2, 17) = 7, P < 0.01$): in the right lesion groups at $P = 0.003$ and in the left lesion group at $P = 0.004$. As shown in Fig. 4, this VOR bias was more pronounced in R+ group (main Neglect effect: $F(3, 16) = 7, P = 0.002$). By using post hoc comparison, the VOR bias was significant in R+ group as compared to the control ($P < 0.01$), R- ($P < 0.05$) and L groups ($P < 0.01$). This VOR bias was independent of the stimulus frequency (neglect \times frequency interaction: $F(6, 32) = 1.2, P > 0.05$) and also of the occipital involvement (main Lesion effect: $F(2, 17) = 0.15, P > 0.05$). The individual subjects' data showed a consistent VOR bias in 12 out of 14 patients (Table 4).

3.4. VOR time constant

The VOR time constant was reduced for the slow phases directed towards the side opposite to the lesion in the patient groups with right lesions (main Hemisphere effect: $F(2, 19) = 4, P = 0.03$; hemisphere \times direction interaction: $F(2, 19) = 3, P = 0.06$) as compared to the control ($P < 0.05$) and L ($P < 0.05$) groups (Table 3). This deficit was dependent on the presence of neglect in the patient groups (neglect \times direction interaction: $F(3, 18) = 3.3, P < 0.05$). The asymmetry of the VOR time constant is seen in Fig. 5 depicting an example of post-rotatory nystagmus obtained in one R+ patient (PH). As shown in Fig. 6, the DP of the

Table 4

Synoptic table of the main VOR deficits, evaluated on the DP, in the patient groups with cortical lesion, including (+) or not (-) the occipital lobe

Cases	SN ($^{\circ}$ /s)	Gain (sinusoidal)	Phase	Bias	Time constant	Nystagmus frequency	Occipital involvement
YB, R+		++++	+	++++	++	++	+
HP, R+	5			++++	++++	++++	-
RPE, R+	5	++		++++	++++	++++	+
RPI, R+		+++	+	+	++	+	+
RJ, R+		++++	+	+	++		+
JO, R-		+			+	+	-
JB, R-		+		+			+
DC, R-				++++			+
JLM, R-			+	+++	++		-
LL, L				++	+	+	-
MJ, L		+		++++		+	+
MC, L				+			-
NF, L		+		++++	++	++	+
RK, L		++					+

R+: right brain damage with neglect; R-: right brain damage without neglect; L: left brain damage; SN: spontaneous nystagmus; 2 S.D. $< + < 3$ S.D., 3 S.D. $< ++ < 4$ S.D., 4 S.D. $< +++ < 5$ S.D., $++++ > 5$ S.D. with S.D.: standard deviation of the normal group.

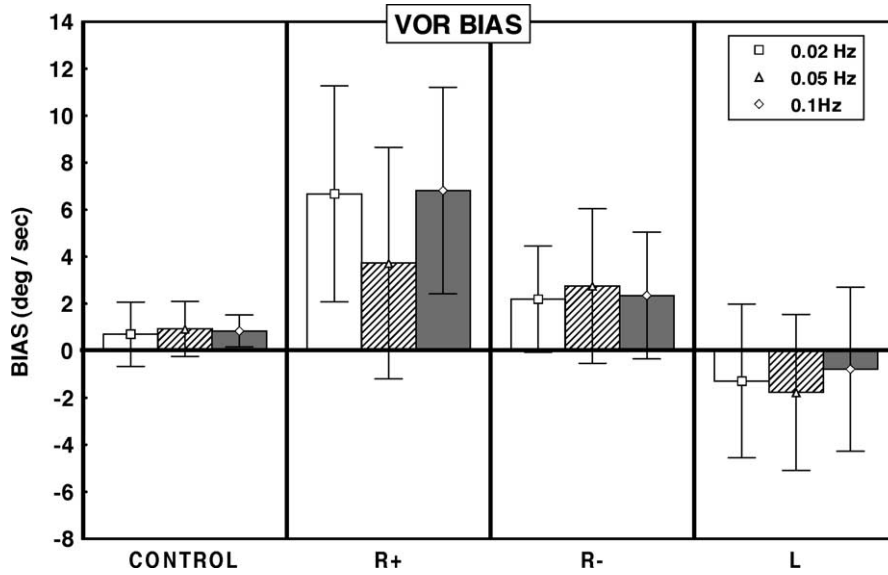


Fig. 4. Bar graph of the mean VOR bias in each group of patients at the three frequencies of sinusoidal rotation (0.02, 0.05, 0.1 Hz). Standard deviations are indicated.

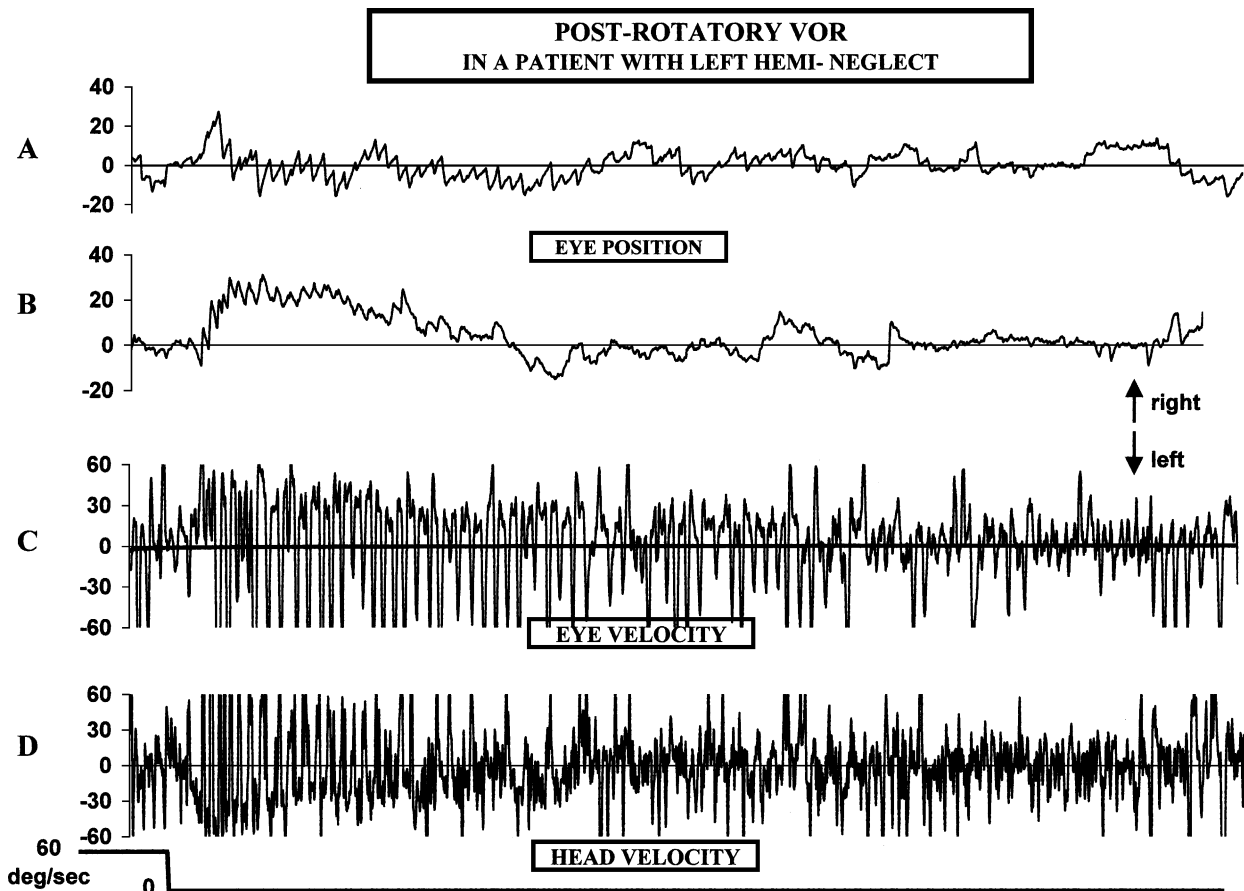


Fig. 5. Example of post-rotatory nystagmic eye movements in one patient with a left hemi-neglect (group R+). Upper recordings: horizontal post-rotatory nystagmus in the two clockwise (CW) and counterclockwise (CCW) directions. Lower recordings: velocity of post-rotatory nystagmus. Note the shortened duration of post-rotatory VOR for the contralesional (CCW) slow phases of the nystagmus.

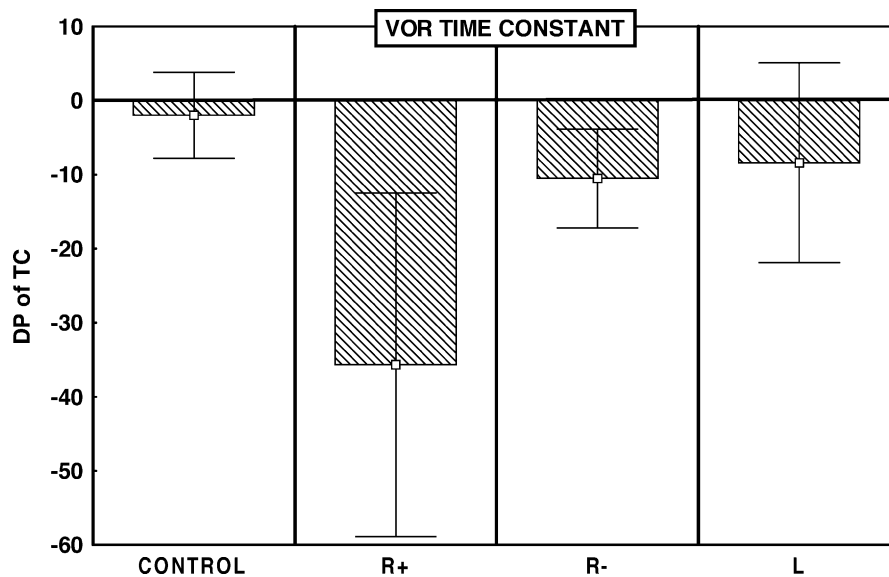


Fig. 6. Bar graph of the mean directional preponderance (DP) of VOR time constant in each group of patients. Note the negative values in patients groups indicative of a VOR time constant preponderance to the ipsilesional direction. Standard deviations are indicated.

VOR time constant was significant to the lesioned side in the R+ group with respect to the control ($P < 0.01$), the R- ($P < 0.01$) and the L ($P < 0.05$) groups (main Neglect effect: $F(3, 18) = 6.7$, $P = 0.002$). The VOR time constant was independent of the occipital involvement (main Lesion effect: $F(2, 19) = 1.5$, $P > 0.05$; lesion \times direction interaction: $F(2, 19) = 1.8$, $P > 0.05$). All the R+ patients and two R- (JO, JLM) and two L patients (LL, NF) presented a significant time constant deficit as compared to the control group (Table 4).

3.5. Nystagmus frequency (NF)

The mean NF, calculated on the per- and post-rotatory VOR, was significantly increased towards the lesion side in the patient group with right lesion (hemisphere \times direction interaction: $F(2, 18) = 3.2$, $P < 0.05$). Indeed, the DP of nystagmus frequency was significantly shifted towards the lesion side in patient groups (main Group effect: $F(2, 19) = 4$, $P = 0.03$) and mainly in the R+ group (DP = -28%) as compared to the control group (DP = -0.8%) (main Neglect effect: $F(2, 19) = 7$; $P < 0.01$). This NF deficit was independent of an occipital involvement (main Lesion effect: $F(2, 19) = 2.8$, $P > 0.05$).

4. Discussion

In this study, we demonstrated a clear interaction between the cerebral cortex and the vestibulo-ocular reflex function in human patients. Unilateral lesion of the cerebral cortex, including the parieto-temporo-occipital junction, induced a significant VOR asymmetry as revealed by a direc-

tional preponderance of the gain to the contralesional side and in contrast, a VOR bias and a directional preponderance of the time constant to the ipsilesional side. Interestingly, these latter vestibular deficits are more pronounced in cortical lesions localized in the right hemisphere accompanied by hemi-neglect syndrome.

4.1. Anatomical organization of the vestibular-related cortex

Cerebral imaging techniques (Bense et al., 2001; Bottini et al., 1994; Bottini et al., 2001; Brandt and Dieterich, 1999; Lobel et al., 1998) demonstrate in man a large network of vestibularly activated cortical areas distributed between the posterior cortex (the parieto-temporo-occipital region), the insula (possibly the homologue of the parieto-insular vestibular cortex or PIVC), the superior parietal lobe (possibly the homologue of area 2v), the central sulcus (possibly the homologue of area 3a) and the frontal premotor cortex. This network is represented on a lateral view of the brain in Fig. 7. In our study, the common cortical region involved in vestibulo-motor function in our three groups of patients corresponded to the PTO junction (Fig. 7), including the Brodman's areas 40 in the supra-marginalis gyrus and 39 in the angular gyrus. This common cortical focus excluded the vestibular insular area and also the junction of areas 19 and 37, the possible homologue of the MST area involved in motion perception and ocular smooth pursuit (Barton, Sharpe, & Raymond, 1996; Heide et al., 1996). However, in view of the variability of the lesion size, spreading to the frontal lobes in some cases, one can ask about the functional specificity of the posterior cerebral cortex in the vestibulo-ocular disorders described in our current study. For example in the

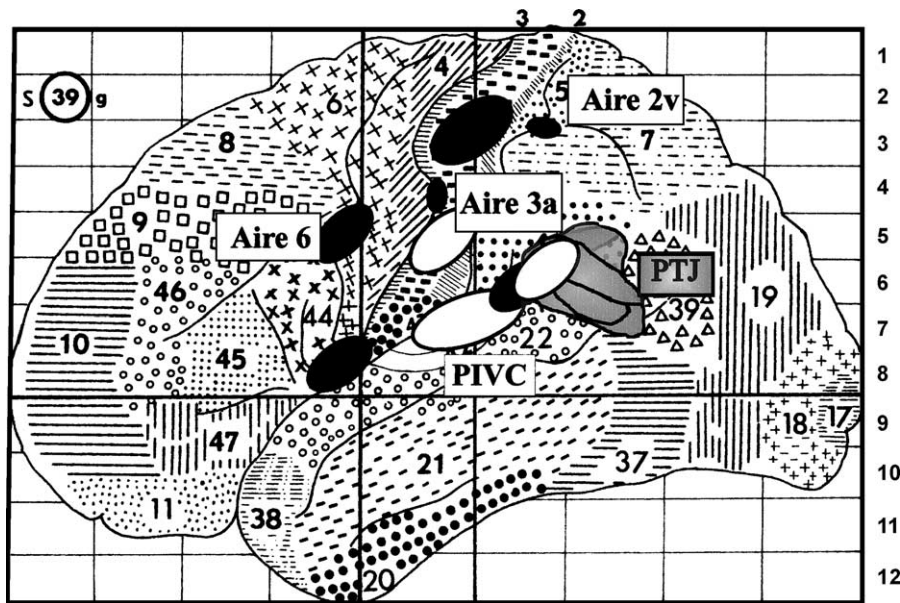


Fig. 7. Representation on a lateral view of a human brain of the vestibularly driven cortical areas identified by previous neuro-imaging studies and the common cortical area identified in the parieto-temporal junction in our current study. The cortical areas correspond to Brodman's areas. White areas: vestibular cortical areas activated by caloric vestibular stimulation and visualized by PET (Bottini et al., 1994, 2001). Black areas: vestibular cortical areas activated by galvanic vestibular stimulation and visualized by fMRI (Lobel et al., 1998). Grey areas: vestibular cortical areas lesioned in our patients groups. These vestibular cortical areas have been reconstructed by intrapolating the lesion boundaries between the stereotaxic slices. PTJ: parieto-temporal junction. PIVC: parieto-insular vestibular cortex.

R+ group, some patients had large cortical damage involving both posterior and frontal cortex while others had a limited posterior cortex damage. As similar VOR deficits were found in all patients of the R+ group with or without frontal involvement, a frontal origin of these VOR deficits could be excluded. Consequently, even if the lesion size may interact with the quantitative aspects of the deficits, we suggest that the vestibular deficits observed in this study are likely to result from a functional specificity of the posterior cerebral cortex, rather than from a lesion size effect alone. By analysing the effects of the lesion extent at the level of both groups and individuals, we could distinguish two functional regions within the posterior cortex: (a) one in the occipital lobe, likely including the junction of areas 19 and 37, whose lesion induced disturbances in VOR gain and (b) another related to a VOR time constant modulation usually associated with damage in the right parieto-temporal cortex accompanied with a neglect. This latter observation suggests that the cortical control of the VOR time constant might be lateralized to the right hemisphere in man.

4.2. The posterior cerebral cortex as a vestibulo-motor related cortex

In this study, we have found major vestibulo-ocular deficits in gain and time constant after lesion of posterior cerebral cortex as previously described in animal studies. Accordingly, by lesion and single unit recording studies, the parietal cortex, particularly the lateral part of area 7,

has been identified as participating in visuo-vestibular functions, especially in VOR and optokinetic nystagmus (OKN) gain control (Kawano & Sasaki, 1984; Kawano et al., 1980; Ventre, 1985a,b; Ventre et al., 1984). Interestingly, an asymmetry in the VOR time constant was observed in the monkey after unilateral lesion of area 7a (Ventre-Dominey, unpublished observation). To firmly establish the functional link between the parietal cortex and vestibular function, anatomical studies in monkey demonstrated the existence of direct projections from the parietal area 7a, previously investigated in lesion studies, onto the vestibular complex of the brainstem (Faugier-Grimaud & Ventre, 1989; Ventre and Faugier-Grimaud, 1988). In a recent study, Doricchi et al. (2002) described changes in VOR frequency in neglect patients similar to those found in the current study, and changes in VOR gain only during combined VOR-OKN stimulation. In contrast with our findings, in their right-brain damaged patients either with or without neglect, they could find no gain deficits for VOR induced in the dark. To resolve such a discrepancy, several explanations are available including different lesion locations (as we observed a trend to an occipital control of VOR gain) and/or the different methods used in the two studies to calculate VOR gain values. From the current work and these previous observations, evidence is thus provided that the posterior cerebral cortex is closely involved in vestibulo-motor processing in human and non-human primates. Interestingly, in recent case reports, a vestibular syndrome was described after cortical stroke in the insular region (Brandt, Bötzel, Yousry,

Dieterich, & Schulze, 1995) and in the parieto-temporal cortex (Fukutake & Hattori, 2000; Ventre-Dominey et al., 1999). After a PT cortex stroke, the patients could exhibit a significant vestibulo-ocular asymmetry (Ventre-Dominey et al., 1999) or a motion sickness syndrome (Fukutake & Hattori, 2000). In view of the same functional (vestibular) implication and of the anatomical vicinity (insular and PT cortex), one can ask: “Are these two vestibularly driven cortical regions (retro-insular cortex and PT cortex) part of the same functional network involved in vestibulo-motor output or are they implicated in different cortical mechanisms of vestibular integration?” To date, no available studies on the role of cortex in vestibular processing can resolve this issue in the understanding of vestibular cortical function. However, to our knowledge, the current work constitutes one of the rare studies to demonstrate that at least the posterior cerebral cortex in man is involved in the modulation of some aspects of the vestibulo-ocular output.

4.3. Possible dissociated cortical mechanisms involved in vestibular function

As previously mentioned, posterior cortical lesions could induce contrasting directional VOR deficits such as *contralateral* preponderance in VOR gain and *ipsilateral* preponderance of VOR time constant and bias. Moreover, VOR gain disturbance was significantly associated with a cortical involvement including the occipital region independent of the hemisphere. In contrast VOR time constant and bias deficits were often linked to damage of the right PT cortex independent of an occipital involvement. As these VOR deficits are opposite in direction and not correlated to identical cortical lesions, they cannot originate from a common and unique dynamical mechanism but rather from two distinct cortical mechanisms disrupted by cortical damage. Likewise, anatomo-functional observations in the brainstem and cerebellum previously suggested distinct neural mechanisms involved in VOR: (a) one related to VOR gain and its modifications during visual-vestibular interaction, involving the flocculus and more recently the MST cortical pathway and (b) the other related to the VOR time constant which relies on the so-called velocity storage mechanism operating at low frequencies and involving the cerebellar nodulus (Cheron, Gillis, & Godaux, 1986; Katz, Vianney de Jong, Buettner-Ennever, & Cohen, 1991; Raphan & Cohen, 1985; Tabata, Yamamoto, & Kawato, 2002; Walker & Zee, 1999). In the following section, we will attempt to develop a theoretical basis for the possible cortical mechanisms responsible for such findings.

After posterior cortical damage in either hemisphere, we found ipsilesional VOR (slow phase) gain defects significantly correlated to a temporo-occipital involvement, including the junction of areas 19 and 37, the putative homologue of area MT-MST (Heide et al., 1996; Morrow & Sharpe, 1990). As temporo-occipital lesions often induce impairments in the contralesional visual field that we compen-

sated for by an extrapolation method for eye movement calibration, one can argue for a pure methodological origin for our VOR ipsilesional gain deficits. However, as visual and VOR gain defects were not significantly co-occurring and indeed, were opposite in direction, we can exclude a purely methodological bias and/or an incidence of the abnormal vision in our VOR gain disorders. Interestingly, single unit recording in temporo-occipital cortex in monkey demonstrated neuronal modulation during visual tracking, combined visual and vestibular stimulations (VOR enhancement or cancellation) and also during sinusoidal vestibular stimulation in the dark (Bremmer, Kubischik, Pekel, Lappe, & Hoffmann, 1999; Ilg, 1997; Kawano and Sasaki, 1984; Kawano, Sasaki, & Yamashita, 1984; Komatsu & Wurtz, 1988; Thier & Erickson, 1992). Likewise, lesions studies of posterior cerebral cortex in human and non-human primate have shown ipsilesional deficits in visual tracking and OKN (Barton et al., 1996; Dursteler & Wurtz, 1988; Lekwuwa & Barnes, 1996; Morrow & Sharpe, 1990) and in VOR gain in the dark (Ventre & Faugier-Grimaud, 1986). In accordance with these findings, we demonstrated that in the patients whose cortical lesion extended caudally into the temporo-occipital cortex (possibly involving the MT-MST region), the VOR (slow phase) gain was decreased toward the lesion side. In agreement with our current observation, in a case of a right localized temporo-parietal lesion with no occipital involvement, we found no VOR gain defects while the VOR time constant was clearly affected towards the contralesional side (Ventre-Dominey et al., 1999). Based on the literature and our own observations, we argue that the vestibulo-ocular gain might be controlled by a multimodal cortical processing of combined signals from smooth pursuit, optokinetic and vestibular systems. Such an interactive cortical process might be implicated in the production of ipsilateral slow eye movements in response to retinal slip during head displacements.

In contrast, another reliable result observed in all of our patients with right brain damage, concerns the inertial aspects of VOR, including the time constant and the dynamic VOR bias. Indeed, only in patients with left neglect due to a right posterior cortical damage (the possible common lesioned region), the VOR time constant was significantly affected towards the side of the neglect syndrome. Such a co-occurrence and co-lateralization between defects in the inertial VOR components and neglect suggest a functional relation between inertial vestibular mechanism and visuo-spatial representation. As we mentioned above, the inertial components of VOR, especially the time constant, result from a “velocity storage” network in the brainstem that during visuo-vestibular stimulation, stores the velocity information in order to return this information after stimulation as an after stimulus response (Cheron et al., 1986; Katz et al., 1991; Raphan & Cohen, 1985; Raphan & Sturm, 1991). Accordingly, this mechanism is responsible for the low-frequency induced VOR and the persisting nystagmic responses observed during the per- and post-rotatory VOR

as well as during the optokinetic after nystagmus (OKAN). Recently, following cross-coupling experiments in monkey (Raphan & Cohen, 1988; Raphan & Sturm, 1991; Wearne, Raphan, & Cohen, 1997), the role of this velocity storage mechanism has been reconsidered as not only a velocity storing mechanism but as a spatially oriented multimodal integrator involved in a reconstruction and storage of spatial coordinates. This new concept based on strong experimental arguments fits well with our observations demonstrating a correlation between visuo-spatial function and a modulation of the VOR inertial components by the posterior cerebral cortex. In keeping with our previous assumptions (Ventre et al., 1984; Ventre-Dominey et al., 1999), we suggest that the parieto-temporal cortex might participate in a network forming a high-order multimodal integrator distributed over cortical and sub-cortical structures and sub-serving an internal spatial representation function.

Thereby, the occipito-temporal cortical areas might integrate both visual and vestibular motion signals (velocity signals) to calculate the animal's motion through space and eventually to produce rapid eye-head displacements. In contrast, more anterior cortical areas such as the temporo-parietal cortex, would realize a slower integrative processing extracting the inertial canal signals to establish a head centered frame. However, while our study is suggestive of such distinct, fast versus inertial, cortical vestibular mechanisms, further studies are necessary to confirm the existence of such a functional dissociation in the parieto-temporo-occipital cortex.

5. Conclusions

This study demonstrates in man that posterior cortical damage induces an impairment of vestibulo-ocular function occurring mainly as an asymmetry in VOR gain and time constant and an ipsilesional VOR bias. The cortex commonly damaged between all the patients was localized in the parieto-temporal cortical region responsible for visuo-spatial neglect in man. The co-occurrence of VOR time constant deficits and visuo-spatial disorders suggest a functional link between the representation of space and the integration of inertial vestibular information in cortex. We thus postulate that the posterior cerebral cortex might participate in a multimodal integrative network distributed between cortical and sub-cortical structures and sub-serving visuo-spatial representation.

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