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Vestibulo-ocular and optokinetic impairments in left unilateral neglect

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Abstract

Right brain damaged patients affected by left unilateral neglect (N+) typically fail to explore the contralesional space. For the first time, this study investigates the dynamic and spatial features of the horizontal vestibular–ocular response (VOR), the optokinetic response (OKR) and the VOR–OKR interaction in six N+ and in five right brain damaged patients without neglect (N−). No lateral asymmetry of the gain (i.e. eye velocity to head velocity ratio) of VOR slow phases was found in either group. In the VOR, N+ had higher frequency of slow-rightward/fast-leftward phases and higher contralesional shift of the beating field (i.e. orbital position of fast phases). In the VOR–OKR, there was an increase of gain in both lateral directions and in both groups even though in N−, there was a lower phase shift between eye and head velocity. In contrast to the VOR, in the VOR–OKR, N+ had higher frequency of slow-leftward/fast-rightward phases. The VOR–OKR interaction also introduced an ipsilesional shift of the beating field in both N+ and N−. In the OKR, N+ showed a drop in the velocity, amplitude and frequency of slow-rightward/fast-leftward phases. These findings potentially suggest that each hemisphere modulates VOR with contralaterally directed slow phases and OKR with ipsilaterally directed slow phases. This organisation could facilitate maintenance or fast recovery of combined VOR + OKR after unilateral brain damage. The same findings suggest that by inducing slow-leftward phases, vestibular and optokinetic stimulation improve left side neglect through the activation of different hemispheric pathways. No ipsilesional deviation of the subjective "straight ahead" was found in N+. These results show that chronic unilateral neglect can be dissociated both from deficits of ipsilesionally directed VOR and from ipsilesional deviation of the subjective midsagittal plane of the body.

Keywords: Neglect; Vestibular; Optokinetic; Nystagmus; Space

1. Introduction

Anatomical, electrophysiological and brain imaging studies have established that discrete regions of the cerebral cortex receive vestibular input. In monkeys, these regions include the parieto insular vestibular cortex (PIVC) to which other areas of the central sulcus (area 3a) and the prefrontal and frontal cortex are connected to form a "vestibular cortical system" [25,33]. In humans, cold water irrigation of the left ear determines nystagmus with slow phases in the direction of the stimulated ear and predominant activation of the temporal–parietal junction, the insula, the putamen and the anterior cingulate in the hemisphere contralateral to the side of stimulation [10,11,26]. Galvanic-vestibular stimulation (exciting both semicircular canals and otolith efferents [31]) determines activations in the temporal parietal junction, central and intraparietal sulci and in the premotor regions of the frontal lobe [46]. The interaction between the cortical–subcortical and the brainstem mechanisms controlling the vestibular–ocular response (VOR) not only takes place bottom–up but also top–down. Lesion studies in the monkey [65] showed that unilateral surgical ablations of the convexity of the inferior parietal lobule (area 7a) reduce the gain of the slow phases of the VOR directed ipsilesionally. Bilateral efferent connections from each hemisphere to vestibular nuclei were documented both by retrograde [2,25] and anterograde tracing [24]. In the monkey, cortical projections from the parietal and temporal cortex to the vestibular nuclei are predominantly ipsilateral whereas projections from the frontal (area 6) and somatosensory area (3a) are predominantly contralateral ([2]; for review see [27,33]).

Clinical reports documented VOR dysfunction in humans following unilateral brain damage [16]. In hemispherectomised patients, the gain of horizontal slow phases directed ipsilesionally is reduced and the suppression of slow phases directed contralesionally is impaired [22,57]. Patients with temporal or parietal lesions [4,16] can also suffer from

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this latter deficit. Interestingly, an opposite pattern of VOR impairments was recently documented by Ventre-Dominey et al. [66] in a patient with a right temporal–parietal damage showing higher frequency and gain of slow phases directed ipsilesionally.

In natural settings, the VOR is functionally and synergistically coupled with the optokinetic response (OKR). This interaction favours gaze stabilisation on visual targets during head–body rotation. The OKR is also subjected to the influence of higher cortical and subcortical structures. In humans, unilateral lesions of the temporal–parietal–occipital junction typically reduce the gain and frequency of the slow phases of the OKR directed toward the damaged side [4,39,59]. These clinical observations were confirmed by fMRI studies showing larger activations of V5 [18,29], of the intraparietal sulcus and the putamen [29] in the hemisphere ipsilateral to the direction of horizontal optokinetic stimulation.

No evidence is currently available on the VOR of unilateral brain damaged patients affected by contralesional attentional neglect. These patients are characterised by defective exploration and representation of the contralesional space. This is most frequently caused by a right brain damage involving the inferior parietal lobe [62] or the frontal lobe and basal ganglia [37]. Failure to remember already explored locations can contribute to reiterating the inspection of the ipsilesional space [38]. Neglect is doubly dissociated from primary sensory or motor impairments and can be temporarily ameliorated by unilateral proprioceptive stimulation [60,62] or vestibular and optokinetic stimulation inducing slow phases toward the neglected hemispace ([15,54,56], for review see [60,62]). This stimulation is supposed to orient attention toward the neglected space [28] and re-centre the pathological ipsilesional deviation of an egocentric spatial reference frame based on the multimodal integration of visual, proprioceptive and vestibular inputs. In the intact organism, this frame of reference is aligned to the sagittal body midline and is used to code the left and right horizontal hemispace [3,62,63]. Ventre et al. [64] found reduced gain and frequency of ipsilesionally directed horizontal VOR and spontaneous contralesional nystagmus in monkeys and cats with neglect due to unilateral parietal or collicular ablations. According to Ventre et al. [64], these modifications of the VOR should not be considered as primary symptoms but, rather, as secondary effects of unilateral disruption of the neural system providing a balanced multimodal representation of the space lying on the two sides of the body midsagittal plane.

We previously reported [39] that right brain damaged patients with left unilateral neglect may show a drop in the frequency, amplitude and speed of slow and fast phases evoked by optokinetic stimulation moving ipsilesionally. Whether a similar (or complementary) deficit of the VOR and the VOR–OKR interaction is associated with neglect still remains to be investigated. The study of lateral horizontal VOR and OKR deficits consequent to unilateral brain damage should provide cues about the way the synergistic VOR–OKR interaction is functionally distributed within and between the cerebral hemispheres. Most importantly, defining the lateral VOR and OKR impairments suffered by neglect patients should clarify whether vestibular or optokinetic stimulation inducing slow phases toward the contralesional side improves neglect through re-activation of damaged or spared central VOR and OKR mechanisms.

It is well known that the pauci-synaptic vestibulo-ocular reflex (the “true” VOR) can only be tested by imposing rapid head-on-trunk rotations (i.e. impulse test) according to the method defined by Halmagyi et al. [34]. Submitting subjects to angular whole-body rotations tests the pauci-synaptic brainstem reflex plus other higher-order components of the vestibular response including the cortical component brought by projections from the cortex to the vestibular nuclei [7,17]. In the present study, we shall consider VOR the combination of both lower and higher order components of the vestibular response.

1.1. Method

1.1.1. Patients

The patients were six unilateral right brain damaged patients with signs of left unilateral neglect (N+) and five right unilateral brain damaged patients with no signs of neglect (N−). None of the patients showed clinical vestibular symptoms. The presence of neglect was evaluated with the following tests.

(a) *Line cancellation* [1]: The score is the number of lines cancelled (total score range: 0–21; 0–11 on the left, 0–10 on the right).
(b) *Letter cancellation* [19]: The score is the number of target-letters cancelled (total score range: 0–104; 0–53 on the left, 0–51 on the right).
(c) *Wundt-Jastrow area illusion test* [48,53]: The score is the frequency of perception of the optical illusion when the two fans are oriented toward the contralesional or the ipsilesional side of space (score range: 0–20).
(d) *Sentence reading test* [53]: The score is the number of sentences read without omissions (score range: 0–6).
(e) *Line bisection task*: In this task, patients were required to mark the subjective centre of a horizontal line (20 cm; six trials) presented on a sheet of A3 paper with its objective centre aligned to the midsagittal plane of the patient’s trunk. Ipsilesional deviations of the subjective midline were coded as positive values (in cm) and contralesional deviations as negative ones.

In order to disclose the possible presence of ipsilesional deviation of the subjective sagittal head–body midline, all patients were also administered a “straight ahead” position task. In this task, which was carried out in complete darkness, the experimenter slowly moved a dimly lighted red led on a horizontal bar located 60 cm away from the patient. The bar was parallel to the coronal plane of the patient’s trunk and its centre was aligned to the midsagittal plane of the

patient's trunk. At the beginning of each trial, the led was positioned 20° to the left or to the right of the bar centre. In six trials, the led was moved from the left to the right and in six trials from the right to the left. These trials were randomly intermixed. The patient verbally guided the displacement of the led and adjusted its position until it was judged to be straight in front of him. In one session, the task was performed with the head free to move and in a second session with the midsagittal plane of the head restrained and aligned to the trunk midsagittal plane. Ipsilesional deviations from the objective "straight ahead" were coded as positive values (in cm) and contralesional deviations as negative ones.

Individual clinical data, results of tests evaluating neglect and of the line bisection and "straight ahead" position tasks are reported in Table 1. Concomitant visual field defects were evaluated with Goldman perimetric testing. The site and size of the lesion was evaluated through MRI or CT scans. The individual scans are reported in Fig. 1 (for case 10, only the report of MRI scans was available).

1.1.2. Evaluation of VOR and OKR

The dc horizontal and vertical EOG were recorded with electrodes placed at the outer canthi and above and below the right eye. EOG calibration was performed with subjects fixating leds positioned 20° to the right and to the left of a central led aligned to the head–body midsagittal plane. A calibration was performed before each trial. EOG signals were amplified, filtered, digitalized (sampling rate 200 Hz) and stored on a PC for off-line processing.

In separate sessions, patients were tested in three different conditions on a computer controlled rotating chair (model "Rotomac", Megaris s.a.s.). The software controlling the movements of the chair also allowed the recording and storing of chair position with a resolution of 0.072° of arc. An optokinetic drum surrounded the chair. The drum was striped with vertical black and white stripes (each subtending 6° of the visual angle). The diameter of the drum was 116 cm and its central vertical axis was centred on the patient's head. The following testing conditions were organised.

(a) *VOR*: The chair was sinusoidally rotated (frequency 0.05 Hz) in the dark at two different peak velocities: 30 and 60°/s.
(b) *VOR + OKR* (visual–vestibular interaction): The chair was sinusoidally rotated (frequency 0.05 Hz) within the illuminated static optokinetic drum at two different peak velocities: 30 and 60°/s.
(c) *OKR*: The illuminated optokinetic drum was rotated around the static chair at two different constant velocities: 15 and 30°/s.

In the VOR and VOR + OKR modes of stimulation, the direction of the first movement (ipsilesional/ contralesional) was balanced among trials. Each trial consisted of two cycles of rotation, and two trials were performed for each peak velocity. The 0.05 Hz frequency was chosen to allow comparison with the single case study of Ventre-Dominey et al. [66] (where similar asymmetries of the VOR were found at 0.02, 0.05 and 0.1 Hz) and with studies in monkeys with unilateral parietal ablations [65] (where comparable asymmetries of the VOR were found within the range of 0.02–0.07 Hz together with a peak asymmetry at 0.05 Hz). In order not to strain patients with a large number of trials, no other frequency was used.

The OKR was recorded during drum rotations lasting 60 s (one ipsilesional and one contralesional). In all conditions, the patient was seated in the rotating chair with head, arms and legs restrained by appropriate rests and straps. A security belt further stabilised the patient's body.

At the beginning of each VOR trial, patients fixated a dim blue led fixed to the chair and centred on the head midsagittal plane for 3 s. When the blue led was switched off, a red ground-fixed led (aligned to the blue one) was switched on and patients had to fixate it for 3 s. When the red led was switched off the rotation started. At the end of the trial, the blue led was switched on again for 3 s and patients were asked to fixate it again. At the beginning of VOR + OKR and OKR trials, a led was presented aligned to the head midsagittal plane. The led was removed by the examiner before the chair rotation started and it was presented again at the end of the rotation. This procedure ensured control of any dc drift of the EOG during trials. Rare trials in which drift was present were discarded. At the beginning of each trial, patients were simply asked to keep their eyes open.

The local ethical committee approved the experimental protocol of the present study.

1.2. Data analysis

For each mode of stimulation, nystagmic eye movements were analysed thanks to a specially designed Matlab program. The beginning and end of each slow and relative fast phase were first selected by visual inspection of eye movement recordings.

1.2.1. VOR and VOR + OKR

For each slow and fast phase, a regression polynomial of degree 3 was fitted to the recorded data of eye movements, as well as to the corresponding chair (i.e. head in space) movement. The number of phases was calculated in each trial. For each patient, the mean frequency of fast/slow phases was calculated for each mode, direction (ipsilesional/contralesional) and peak velocity (30°/s or 60°/s) of rotation.

1.2.2. Slow phases

Three main intrinsic parameters were calculated from regression polynomials: phase amplitude, mean velocity of the eye and mean gain of the response during the phase (i.e. the ratio of eye velocity to chair velocity). For each patient, these values were then averaged across trials to obtain a mean value for each mode, direction (ipsilesional/contralesional) and peak velocity (30°/s or 60°/s) of rotation. This first method of evaluating VOR and VOR + OKR gain is the

Table 1
Clinical data and scores on tests for evaluating neglect

Case	Group	Age	Stroke onset (weeks)	Contralesional visual field	Line cancellation		Letter cancellation		Wundt-Jastrow illusion		Sentence reading	Line bisection (positive = ipsilesional deviation in cm)	Straight ahead (head free) (positive = ipsilesional deviation in cm)	Straight ahead (head fixed) (positive = ipsilesional deviation in cm)
					Left	Right	Left	Right	Left	Right				
1	N+	76	24	Hemianopia	3/11	10/10	0/53	25/51	0/20	20/20	0/6	3.9	0.5	1.3
2	N+	71	52	Inferior quad	11/11	10/10	25/53	43/51	2/20	11/20	2/6	2	−0.1	−4.8
3	N+	69	34	Hemianopia	1/11	10/10	0/53	7/51	7/20	20/20	0/6	2.3	–	0.7
4	N+	68	32	Full	10/11	10/10	6/53	40/51	0/20	15/20	3/6	0.3	−0.8	0.5
5	N+	47	10	Full	10/11	10/10	23/53	34/51	0/20	18/20	2/6	–	−0.4	−0.34
6	N+	73	12	Full	11/11	10/10	51/53	50/51	0/20	17/20	6/6	1.64	−0.63	−0.47
7	N−	65	10	Full	11/11	10/10	52/53	50/51	20/20	20/20	6/6	–	–	–
8	N−	65	24	Full	11/11	10/10	53/53	51/51	20/20	20/20	6/6	0.5	1.1	1.3
9	N−	74	14	Full	11/11	10/10	53/53	50/51	20/20	20/20	6/6	0.1	−4.2	−3.4
10	N−	68	6	Full	11/11	10/10	52/53	51/51	20/20	20/20	6/6	−0.16	−1.1	−0.8
11	N−	57	8	Full	11/11	10/10	53/53	50/51	20/20	20/20	6/6	0.3	−0.86	0.58

Cases 1–6: patients with neglect (N+). Cases 7–11: patients without neglect (N−).

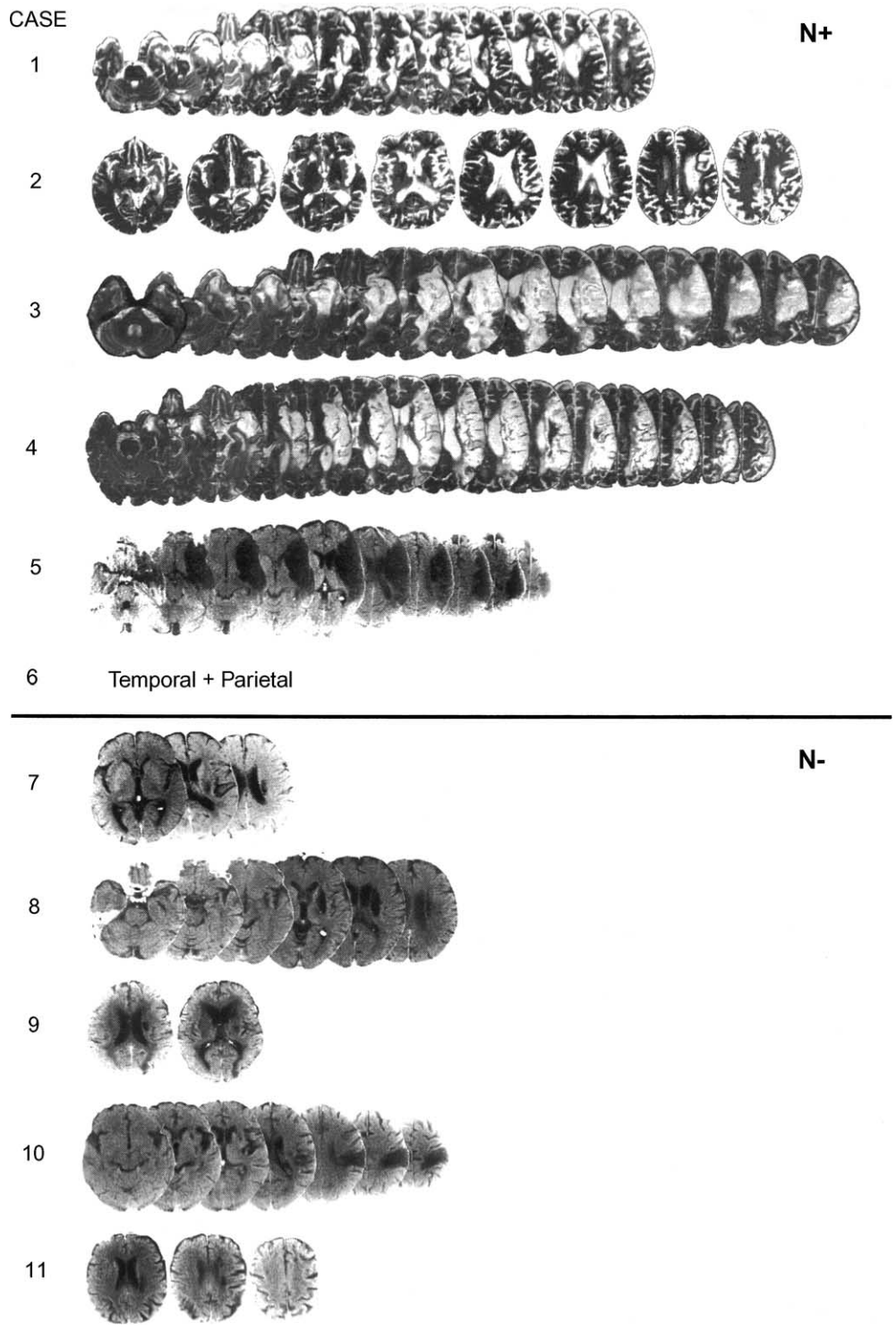

Fig. 1. Individual lesion scans. Cases 1–6: patients with neglect (N+). Case 1 shows damage of basal ganglia and frontal lobe. Case 2 shows involvement of caudate and parietal lobe. Cases 3–5 show extended damage in the territory of the middle cerebral artery. Case 6 had damage involving the temporal–parietal area. Cases 7–11: patients without neglect (N−).

most intuitive one, but it is based on the assumption that eye velocity is directly proportional to head velocity with no phase shift between them. Some asymmetric bias may be present in the VOR response of animals or humans with unilateral cerebral lesions. When an asymmetric bias is present or expected, the eye/head proportionality assumption is not valid. The dynamics of slow phases should also be evaluated with more accurate methods [4,41,52]. Therefore, we calculated linear regressions of slow phase eye velocity as a function of chair (i.e. head in space) velocity for each rotation

direction. The slope of each regression gave the second estimation of gain. We also analysed the value of the intercept of the regression (corresponding to eye velocity when head velocity is null). A non-zero intercept of the regression line indicates the presence of a phase shift in the dynamics of the ocular response compared to the dynamics of the head–body rotation.

1.2.3. Fast phases

Individual averaged amplitude and eye position in the orbit at the midpoint of each phase (i.e. shift of the beating field) were calculated. The shift of the beating field was taken as positive when it was in the direction of fast phases (i.e. in the direction of chair motion) and negative when it was in the direction of slow phases (i.e. opposite to the direction of chair motion).

1.3. OKR

1.3.1. Slow phases

Mean amplitude and velocity were calculated for each experimental condition (i.e. direction x velocity of drum rotation).

1.3.2. Fast phases

Mean frequency and amplitude were measured for each experimental condition.

2. Results

2.1. Clinical data and measures of neglect

N+ and N− did not differ for age (N+ = 67.3 years, N− = 65.8 years; $F < 1$). Patients from both groups were studied in the chronic phase of their stroke. The stroke onset of N− tended to be, but was not, significantly more recent than that of N+ (N+ = 27.3 weeks, N− = 12.4 weeks; $F(1, 9) = 3.8$, $P = 0.08$). N+ performed worse than N− in the letter cancellation task ($F(1, 9) = 12.3$, $P = 0.006$; left side: N+ = 17.5, N− = 52.6 cancelled items; right side: N+ = 33.1, N− = 50.4 cancelled items), sentence reading task ($F(1, 9) = 14.5$, $P = 0.004$; N+ = 2.1, N− = 6), Wundt-Jastrow illusion task ($F(1, 9) = 96$, $P < 0.001$; left side: N+ = 1.5, N− = 20; right side: N+ = 16.8, N− = 20) and in the line bisection test ($F(1, 7) = 7.5$, $P = 0.02$; N+ = +2.02 cm, N− = +0.18 cm). Compared with N−, in the line cancellation task, N+ cancelled less items on the left side of the sheet but not on the right side (group effect: $F(1, 9) = 2.7$, $P = 0.13$; left side: N+ = 7.6, N− = 11 items, planned comparison $P = 0.04$; right side: N+ = 10, N− = 10).

A group (N+, N−) × starting position (left, right) ANOVA showed that in the head free condition N+ had ipsilesional deviation of the “straight ahead” in left to right trials (4.1 cm) and contralesional deviation in right to left trials (−4.9 cm; group × starting position interaction: $F(1, 7) = 10.16$; $P = 0.01$). N− had comparable deviation in both types of trials (left to right: −1.1 cm; right to left: −1.4 cm). In the head restrained condition, no significant effect or interaction was found (N+: left to right = 1.8 cm, right to left = −2.9 cm; N−: left to right = −0.65 cm, right to left = −0.67). When the same ANOVAs were repeated disregarding the starting position, no significant ipsilesional deviation of the subjective “straight ahead” as found in N+. (Head free: N+ = −0.28 cm, N− = −1.2 cm, $F(1, 7) < 1$; head restrained: N+ = −0.51 cm, N− = −0.58 cm; $F(1, 8) < 1$; see individual data in Table 1).

2.2. VOR and VOR + OKR

2.2.1. Gain

Individual mean gain values were submitted to a group (N+, N−) × mode of stimulation (VOR, VOR + OKR) × peak velocity (30, 60°/s) × direction of rotation (ipsilesional, contralesional) ANOVA. The ANOVA showed that VOR + OKR gain (1.06) was higher than VOR gain (0.82; $F(1, 9) = 13$; $P = 0.005$). Gain was higher for higher peak velocities of rotation in both stimulation conditions ($F(1, 9) = 34, 9$; $P = 0.0002$). The ANOVA disclosed a significant group × mode × direction interaction ($F(1, 9) = 8.6$; $P = 0.01$). Planned comparisons (see also Fig. 2) revealed that in N+ the gain of ipsilesionally directed VOR+OKR slow phases was significantly lower than that of phases directed contralesionally (ipsilesional 0.97; contralesional 1.12; $P = 0.003$). No lateral difference was present in the VOR mode (ipsilesional 0.85; contralesional 0.81). N− showed no significant lateral difference of gain either in the VOR (ipsilesional 0.78; contralesional 0.85) or the VOR + OKR mode (ipsilesional 1.05; contralesional 1.08).

2.2.2. Slope and intercept

In order to better define the dynamics of the VOR and VOR + OKR, we analysed the slope and intercept of the individual linear regression of eye velocity on chair velocity through group (N+, N−) × mode (VOR, VOR + OKR) × direction of rotation (ipsilesional, contralesional) ANOVAs.

The value of the slope was higher in N− (0.74) than in N+ (0.61; $F(1, 9) = 4.7$, $P = 0.05$) and tended to be higher in the VOR + OKR mode in both groups (*VOR* = 0.56, VOR+OKR = 0.79; $F(1, 9) = 2.9$, $P = 0.12$). This seems related to the general gain increase found in the VOR+OKR with respect to the VOR mode. The group × mode × direction interaction was close to significance ($F(1, 9) = 3.6$, $P = 0.08$). Compared to the VOR mode, in N+, the increase in the slope of ipsilesional rightward phases in the VOR + OKR mode just reached significance (VOR + OKR = 0.71, VOR = 0.57; planned comparison, $P = 0.053$; see Fig. 3) whereas in N−, the same increase was marked (VOR + OKR = 0.94, VOR = 0.59; $P = 0.0007$). In the VOR + OKR mode, both groups showed a significant increase in the slope of contralesionally directed leftward phases (N+:

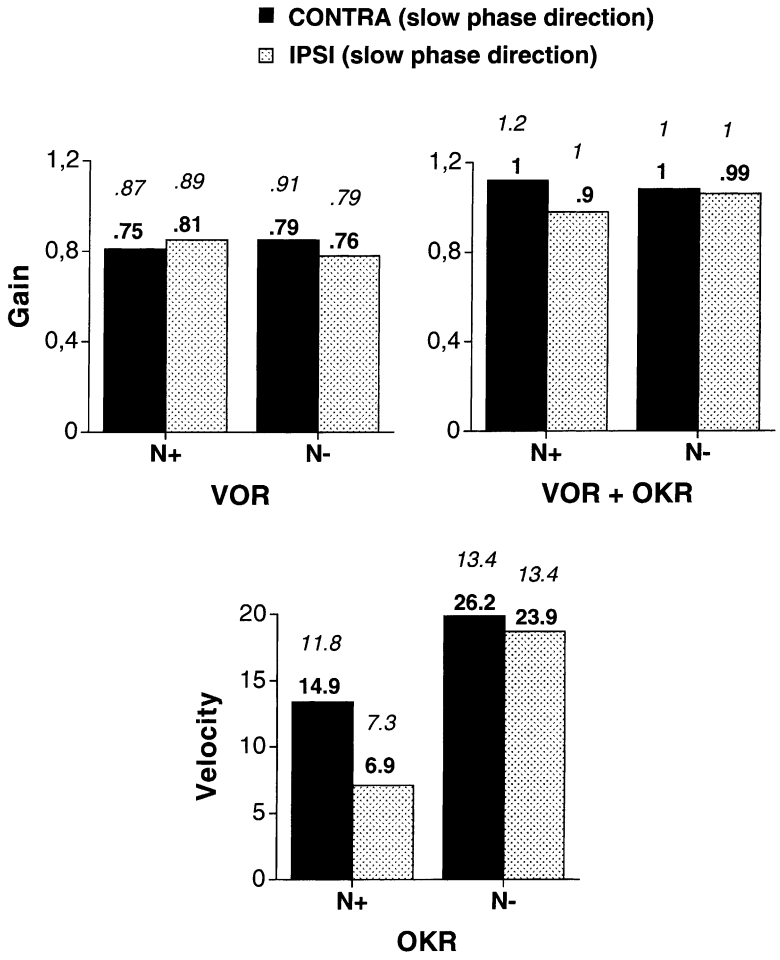

Fig. 2. Gain of VOR and VOR–OKR slow phases and velocity of OKR slow phases. Columns represent gain average between the two experimental velocities. Gain of the VOR and VOR + OKR (peak velocity = 30°/s) and eye velocity of the OKR (velocity = 15°/s) are reported in italics at the bottom of the columns. Gain of the VOR and VOR + OKR (peak velocity = 60°/s) and eye velocity of the OKR (velocity = 30°/s) are reported in bold.

VOR = 0.46, VOR + OKR = 0.70, $P = 0.004$; N−: VOR = 0.63, VOR + OKR = 0.82; $P = 0.02$).

A significant group × mode × direction interaction was found when the intercept was analysed ($F(1, 9) = 13$, $P = 0.005$). Compared with N−, in N+, the intercept was generally and significantly higher ($P \leq 0.001$ in all comparisons) with the exception of leftward phases in the VOR + OKR mode ($P = 0.17$). Importantly, in N−, the intercept of leftward phases did not significantly differ in the two modes of stimulation (VOR = 7.3, VOR + OKR = 8.2; $P = 0.38$), whereas, the intercept of rightward phases dropped in the VOR + OKR mode (VOR = 5.5, VOR + OKR = 1.4; $P < 0.001$; see Fig. 3).

2.2.3. Frequency of fast/slow phases

We submitted the averaged individual frequencies of fast/slow phases (i.e. each fast phase together with its preceding slow phase) to a group (N+, N−) × mode of stimulation (VOR, VOR + OKR) × peak velocity (30, 60°/s) × direction of rotation (ipsilesional, contralesional) ANOVA. Fast phases were more frequently triggered in the VOR + OKR mode (31.6; VOR mode = 19.9; $F(1, 9) = 25, 4$; $P = 0.0006$) and by higher peak velocity (30° = 22.6, 60° = 28.9; $F(1.9) = 14.3$; $P = 0.004$). A significant group × mode × direction of rotation interaction was found ($F(1, 9) = 21.3$; $P = 0.001$). Planned comparisons (see Fig. 4) showed that in the VOR N+ patients had fewer ipsilesionally directed fast-rightward phases (ipsilesional = 14.5 (42%); contralesional = 20.2 (58%); $P = 0.007$) whereas in the VOR + OKR, the lateral difference was reversed and ipsilesionally directed fast-rightward phases were more frequent (ipsilesional = 31.8 (55%); contralesional = 25.9 (45%); $P = 0.006$). In N−, no significant lateral asymmetry was found in either mode condition (VOR: ipsilesional = 22.8 (51%); contralesional = 21.9 (49%); VOR + OKR: ipsilesional = 32.6 (48%); contralesional = 36.3 (52%)).

2.2.4. Amplitude of slow and fast phases

The mean amplitudes of slow and fast phases were submitted to group (N+, N−) × mode of stimulation (VOR, VOR + OKR) × peak velocity (30, 60°/s) × direction of rotation (ipsilesional, contralesional) ANOVAs. The

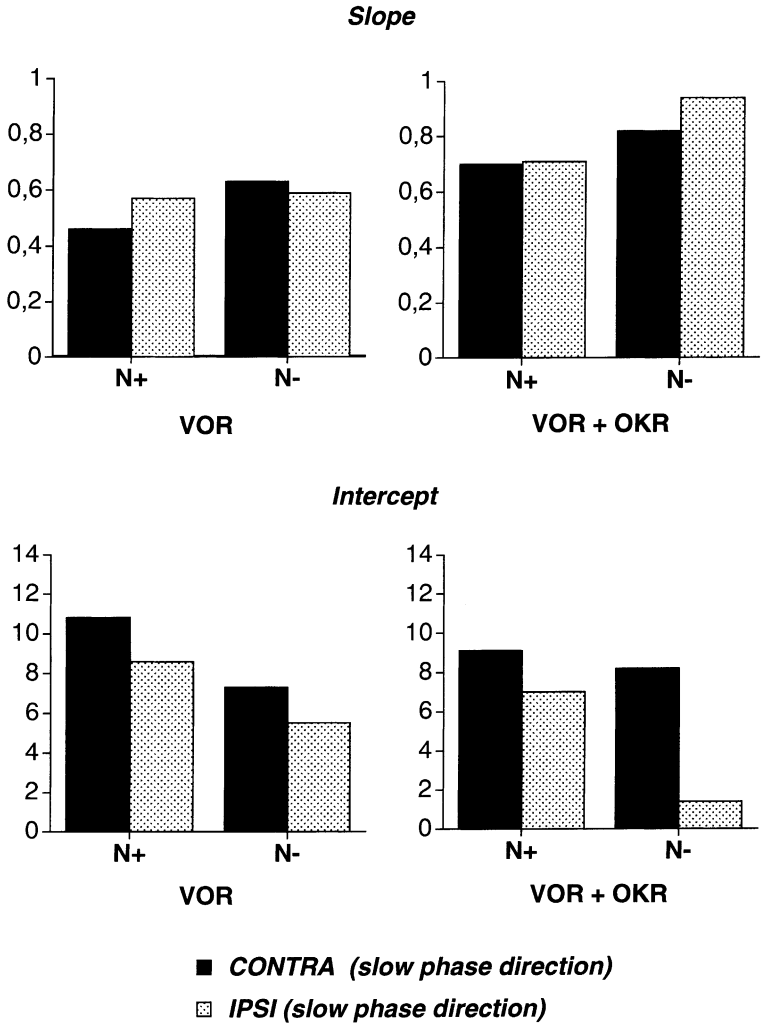

Fig. 3. Averaged slope and intercept values.

amplitude of slow phases was comparable in the groups of patients independently of eye movement direction (N+: leftward = 7.6°, rightward 7.3°; N−: leftward = 7.7°, rightward 8°). Regarding the fast phases, only the group × direction interaction tended toward significance ($F(1, 9) = 2.6$; $P = 0.13$). In N+, rightward ipsilesional phases tended to be smaller (7.8°) than leftward ones (8.5°; the values of P are not significant). The reverse tendency was present in N− (rightward = 9.6°; leftward = 8.5°).

2.2.5. Shift of the beating field

Mean individual values were submitted to a group (N+, N−) × mode of stimulation (VOR, VOR + OKR) × peak velocity (30, 60°/s) × direction of rotation (ipsilesional, contralesional) ANOVA. The group × mode × direction interaction approached but did not reach statistical significance ($F(1, 9) = 2$; $P = 0.1$). We further investigated the behaviour of the two groups of patients in the VOR and VOR + OKR conditions separately. In the VOR, there was a significant group × direction interaction ($F(1, 9) = 5.1$; $P = 0.04$). Planned comparisons (see Fig. 5) showed that N+ had a significantly higher shift of the beating field during contralesional leftward chair rotations (contralesional shift: +10.4°) than during ipsilesional rightward rotations, where the beating field remained slightly and paradoxically shifted in the contralesional direction (−1.4°; planned comparison $P = 0.04$). In N−, the shift during ipsilesional rotations (+6.7°) was not significantly different from that induced by contralesional rotations (+1.8°; $P > 0.3$).

In the VOR + OKR condition, both N+ and N− had higher shifts during rightward ipsilesional rotations ($F(1, 9) = 8.2$; $P = 0.01$; N+: ipsilesional = +14.5°, contralesional = +5.2°; N−: ipsilesional = +19.4°, contralesional = +8.9°).

2.3. OKR

2.3.1. Velocity of slow phases

Mean individual values were analysed through a group (N+, N−) × drum velocity (15, 30°/s) × direction of drum

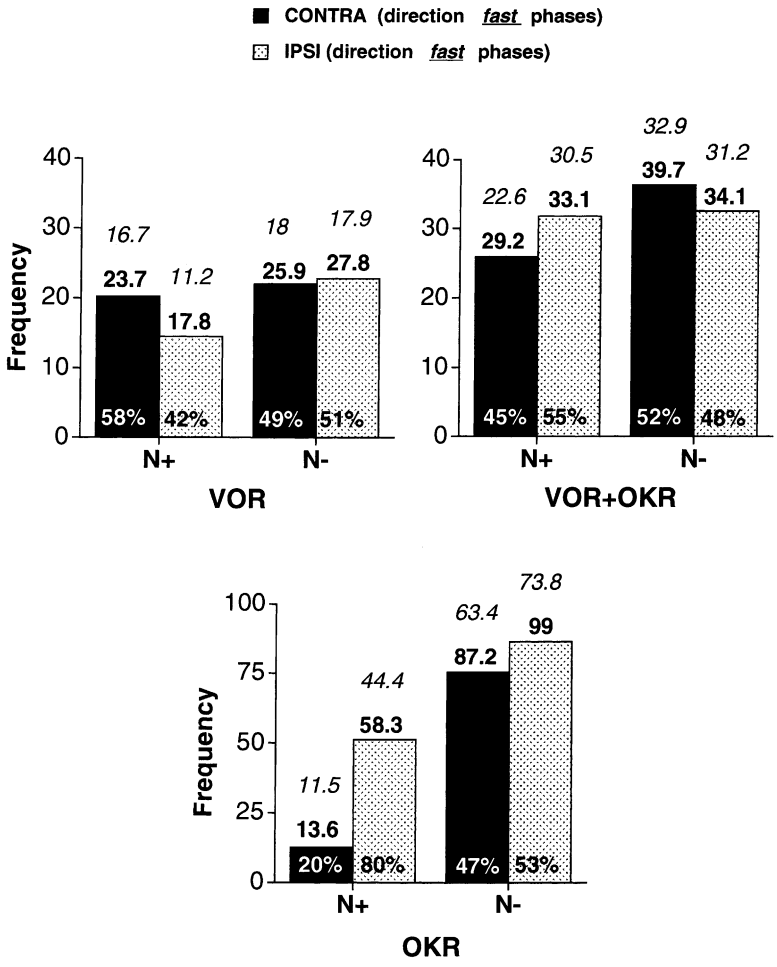

Fig. 4. Averaged frequencies of slow/fast phases in the VOR, VOR + OKR and OKR. Frequencies of the VOR and VOR + OKR (peak velocity = 30°/s) and the OKR (velocity = 15°/s) are reported in italics at the bottom of the columns. Frequencies of the VOR and VOR + OKR (peak velocity = 60°/s) and the OKR (velocity = 30°/s) are reported in bold. Corresponding percentage values are reported inside columns, irrespective of velocity of stimulation.

rotation (ipsilesional, contralesional) ANOVA. There was a main effect of group, with N+ having slower phases than N− ($F(1, 9) = 10.7$; $P = 0.009$), drum velocity ($F(1, 9) = 13.7$; $P = 0.004$) and a main effect of direction of rotation indicating that slow-leftward phases were quicker than rightward ones ($F(1, 9) = 21.2$; $P = 0.001$). There was a significant group × direction interaction ($F(1, 9) = 10$; $P = 0.01$). Planned comparisons (see Fig. 3) showed that in N+, the velocity of contralesional slow-leftward phases (13.3°/s) was higher than that of rightward ones (7.1°/s). No lateral difference was found in N− (ipsilesional = 18.7°/s; contralesional = 19.8°/s).

Since in some N+ (cases 3 and 6) rightward ipsilesional slow phases were completely absent, we repeated the analysis after removal of these patients. The group × direction interaction was again significant ($F(1, 7) = 5.3$; $P = 0.05$) and planned comparisons showed that in N+, the velocity of contralesional slow-leftward phases (14.4°/s) was still higher than that of ipsilesional rightward ones (9.4°/s; $P = 0.004$).

2.3.2. Frequency of fast/slow phases

A group (N+, N−) × drum velocity (15, 30°/s) × direction of drum rotation (ipsilesional, contralesional) ANOVA performed on the individual mean frequencies of fast/slow phases showed a significant main effect for group ($F(1, 9) = 14.1$; $P = 0.004$), direction ($F(1, 9) = 14.7$; $P = 0.003$) as well as a close to significant group × direction interaction ($F(1, 9) = 4.5$; $P = 0.06$). Planned comparisons (see Fig. 4) showed that N+ had more frequent ipsilesional (51.1) than contralesional fast phases (12.5; $P = 0.001$). In N−, there was no significant lateral difference (ipsilesional = 86.4, contralesional = 75.3; $P = 0.2$).

2.3.3. Amplitude of slow and fast phases

The mean amplitudes of slow and fast phases were submitted to group (N+, N−) × drum velocity (15, 30°/s) × direction of drum rotation (ipsilesional, contralesional) ANOVAs. N+ patients with no ipsilesional slow or contralesional fast phases (cases 3 and 6) were excluded from the analyses. Regarding the slow phases, there was

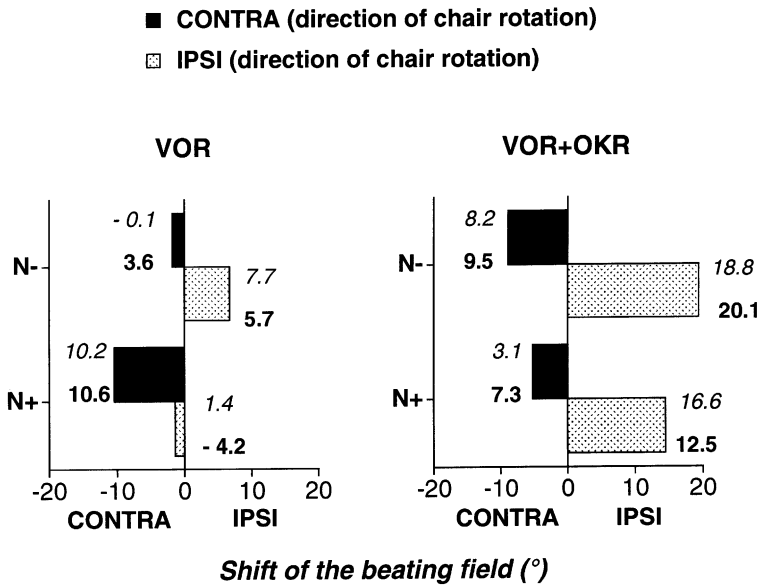

Fig. 5. Averaged shift of the beating field in the VOR and VOR + OKR condition. Shift in the VOR and VOR + OKR (peak velocity = 30°/s) are reported in italics at the endpoint of bars. Shifts in the VOR and VOR + OKR (peak velocity = 60°/s) are reported in bold.

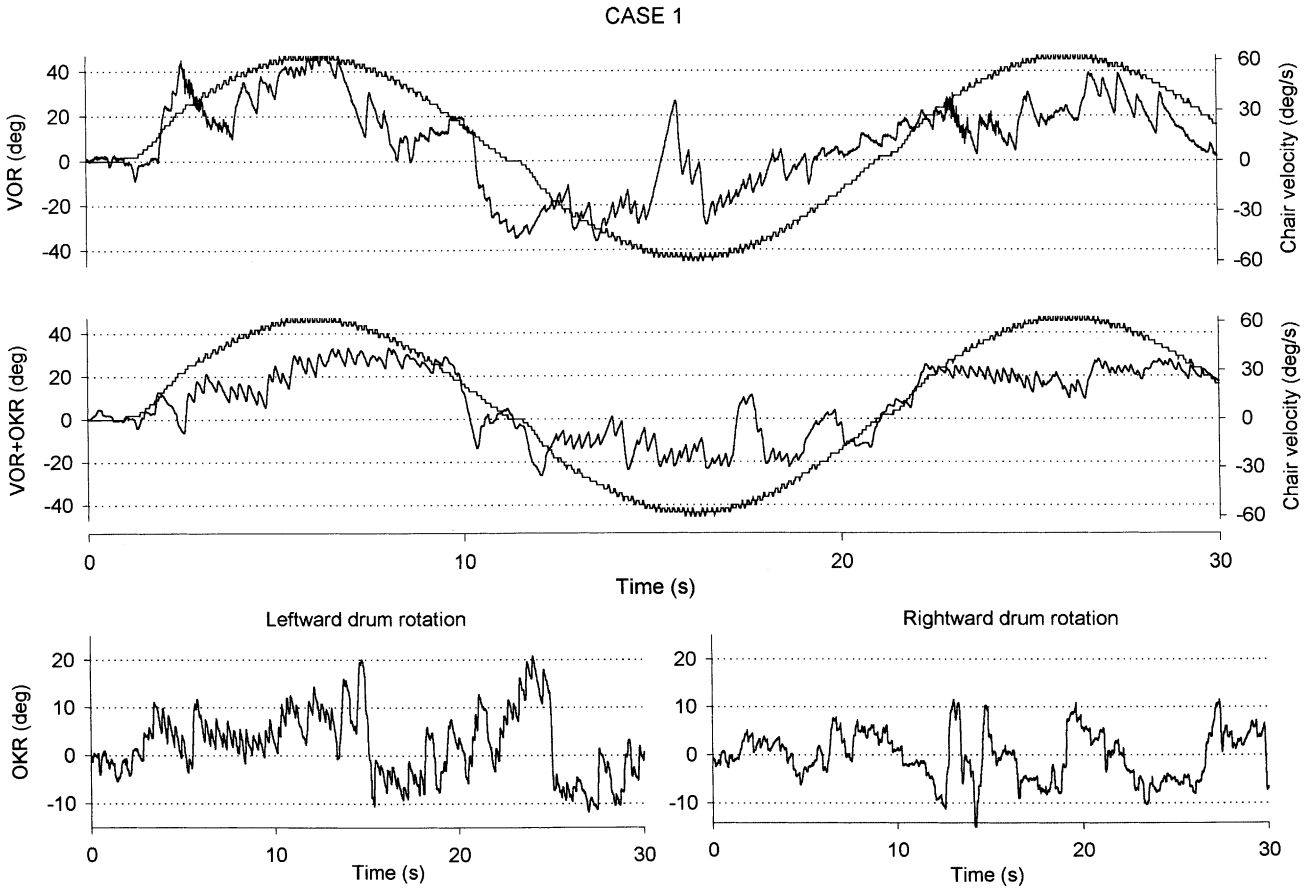

Fig. 6. Case 1: samples of EOG tracings. VOR and VOR + OKR (peak velocity = 60°/s). OKR (velocity 30°/s).

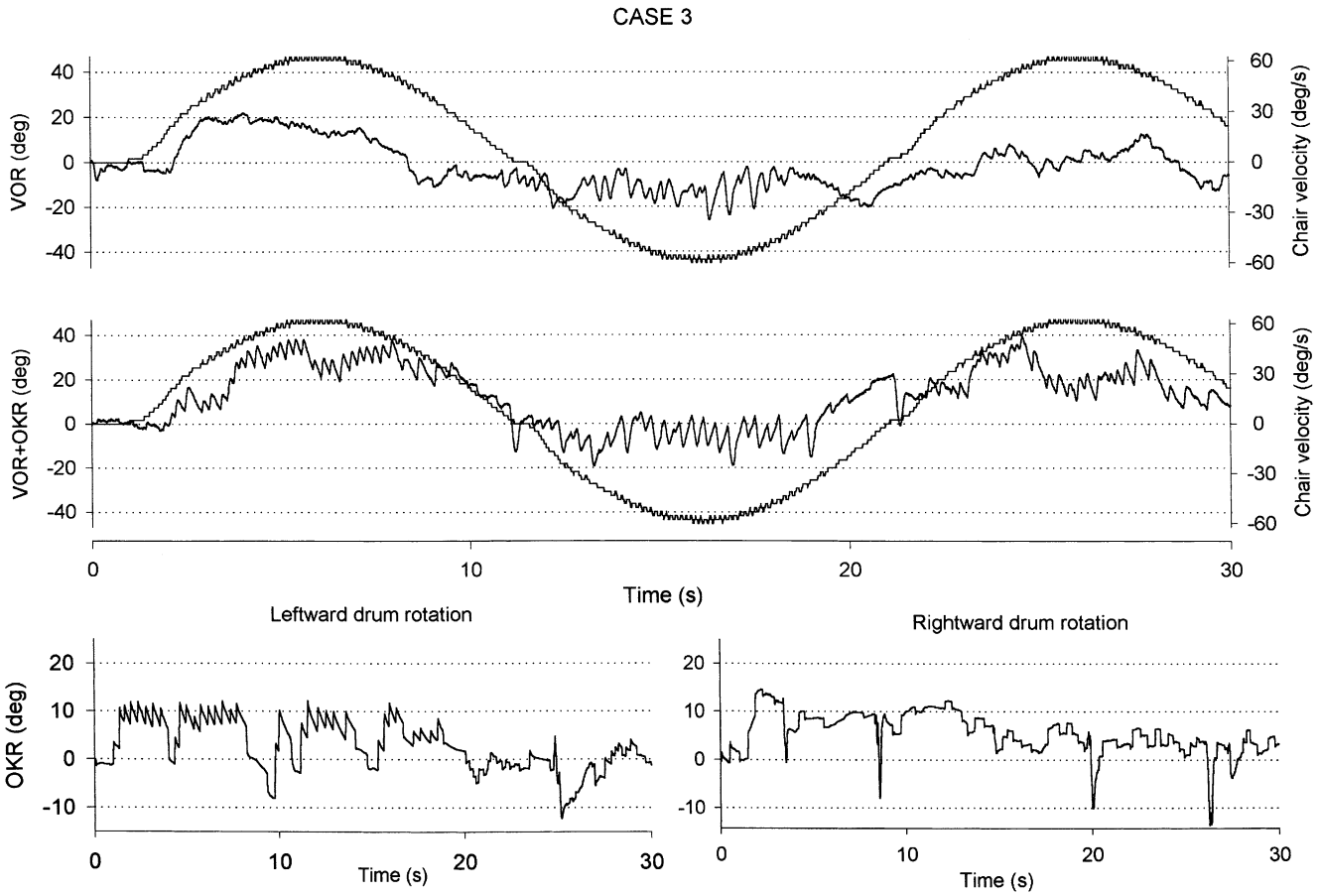

Fig. 7. Case 3: samples of EOG tracings. VOR and VOR + OKR (peak velocity = 60°/s). OKR (velocity = 15°/s).

a significant group × direction interaction ($F(1, 7) = 7.6$; $P = 0.02$). N+ had smaller rightward ipsilesional (2.9°) than leftward phases (5.4°; $P = 0.003$) whereas N− had rightward (5.6°) and leftward (6°) phases of comparable amplitude. Regarding the fast phases, the group × direction interaction was close to statistical significance ($F(1, 7) = 2.6$; $P = 0.1$). Within groups, comparisons showed that in N+ fast-rightward phases were larger (6.5°) than leftward ones (2.6°; $P = 0.03$). No amplitude asymmetry was present in N− (8.9° right versus 8.2° left).

Examples of VOR, VOR + OKR and OKR EOG recordings are reported in Figs. 6–8.

3. Discussion

3.1. Main findings

It has been suggested that higher cortical and subcortical structures receiving vestibular inputs participate in multimodal coding of space and can, in turn, influence the vestibulo-ocular response [25,33,64]. We found that neglect patients suffering from defective coding of the contralesional left hemispace due to damage in the right hemisphere, have higher frequency of ipsilesional-slow/contralesional-fast phases and higher contralesional shift of the beating field of the VOR. When the same vestibular stimulation was delivered in a lighted optokinetic drum (VOR + OKR), these asymmetries reversed toward higher frequency of contralesional-slow/ipsilesional-fast phases and higher ipsilesional shift of the beating field. In the OKR, the frequency and amplitude of ipsilesional-slow/contralesional-fast phases dropped further, confirming previous data reported by our research group [39].[1] These findings suggest that functional hemispheric lateralisation may be in the control of contralaterally directed VOR and confirm previous evidence, gathered from both left and right brain damaged patients [4,39,45,59], on the hemispheric control of the ipsilaterally directed OKR. In our opinion, the advantage of directionally opposite hemispheric control of the VOR and OKR seems clear. Since in a naturally lighted environment VOR and OKR are synergistically coupled,

[1] The higher frequency of contralesional-slow/ipsilesional-fast phases found in the VOR–OKR also demonstrates that the similar asymmetry found in the OKR was not due to the different velocity profile of stimulation used in this latter condition (i.e. constant velocity versus sinusoidal velocity in the VOR and VOR–OKR modes).

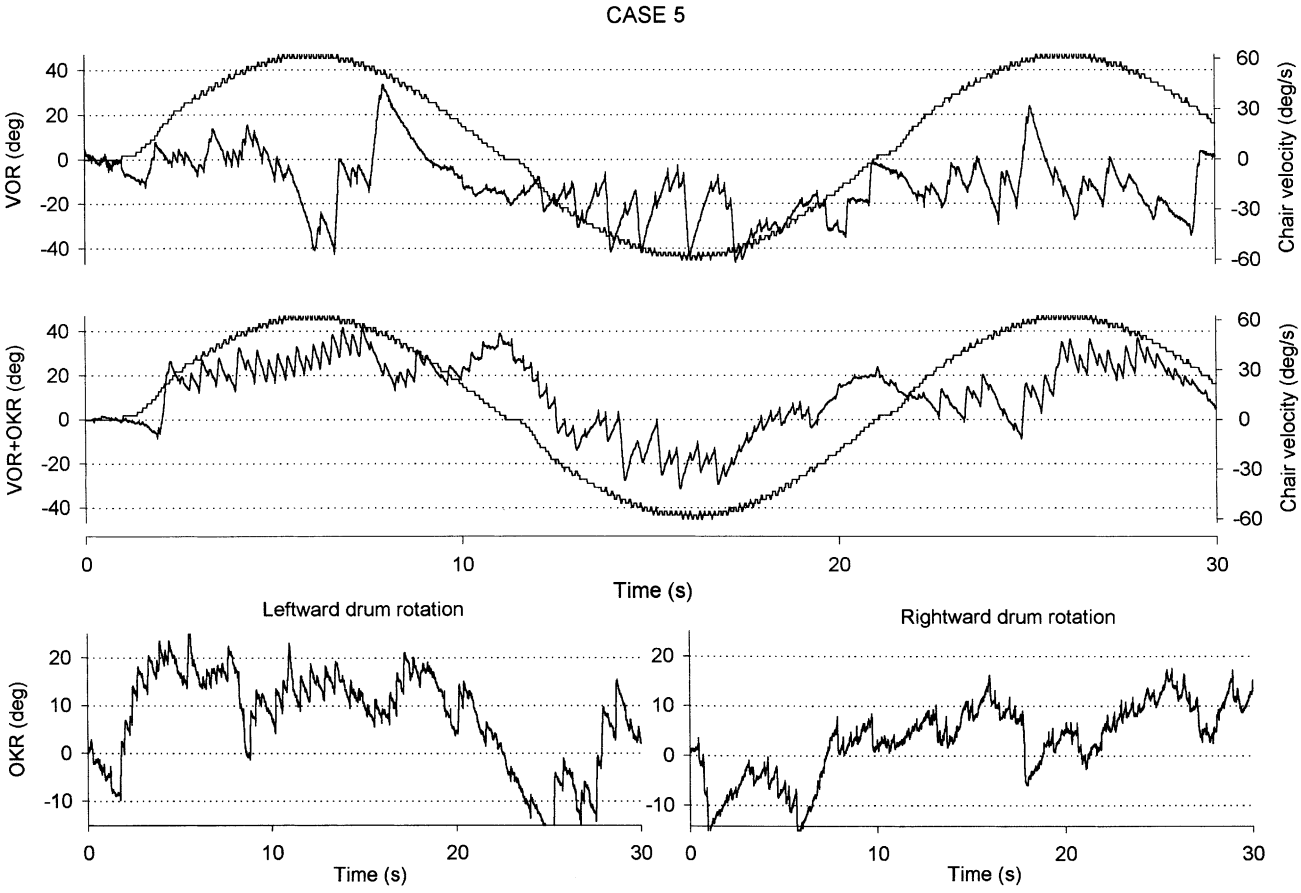

Fig. 8. Case 5: samples of EOG tracings. VOR and VOR + OKR (peak velocity = 60°/s). OKR (velocity = 15°/s).

perturbation of one of the two ocular responses after damage in one hemisphere can be counterbalanced by an intact mechanism mediating the other ocular response in the same horizontal direction in the undamaged hemisphere.

Absence of gain asymmetry in the VOR of N+ suggests that the "vestibular cortical system" [25,33] modulates the triggering of nystagmic responses but has little influence on the neural mechanisms determining the gain of VOR (even though it is well established that specific sensory-motor settings can call into action the cognitive control of the gain [7,51]). The strong cross-midline connections between the two sides of the brainstem [30] could supply VOR plasticity and gain maintenance when a brain damage unilaterally disrupts the influence of hemispheric efferences to vestibular nuclei. The gain of the slow phases was higher in the VOR+OKR than in the VOR both in N+ and N−. To better define the dynamics of eye and head velocities and to evaluate the synchronisation of their phases, we computed the slope and intercept of the linear regression between these two parameters. Both in the VOR and VOR + OKR modes, the slope value was generally higher in N− than in N+, regardless of lateral direction (see Fig. 3), indicating a better proportional relationship between head and eye velocities in N−. Moreover, in the VOR + OKR, N− had a much stronger decrease in the intercept of slow-rightward phases. This suggests that in N+ and N−, the general gain increase in the VOR + OKR was not of the same nature. In N+, ocular compensation of leftward head rotation was not achieved through a reduction of the phase shift between eye and head velocities comparable to that found in N− (as indicated by the significant lower decrease of the intercept value in N+).[2] The pathological reduction of the velocity and frequency of the slow phases of the OKR directed ipsilesionally clearly points out the relevant contribution of higher neural mechanisms in OKR, confirming previous findings in animals and humans [21,39,45,47].

Our results also show that right hemisphere damage disinhibits alternation of slow-rightward/fast-leftward phases of the VOR and inhibits the activity of neural networks modulating the directionally opposite alternation. This could be due to several pathophysiological mechanisms such as the reduction of the inhibitory activity of pause neurons on the

[2] It is to note that any phase advance of the eye to the head velocity can explain gain values >1 (see for example some of the VOR–OKR gain values in Fig. 2). A similar finding was reported by Ventre and Faugier-Grimaud [66] in monkeys with unilateral ablations of area 7, where VOR gain values up to 1.5 were found together with an important phase lead of eye relative to head position.

side of the brainstem ipsilateral to the lesion and consequent reduction of threshold activation of the excitatory–inhibitory burst neurons complex in the contralateral side. Also, the inhibitory interference of brain damage on excitatory projections from right vestibular nuclei to burst driving neurons on the left side of the brainstem could explain reduced triggering of fast phases directed rightward.

Finally, neglect patients had higher ipsilesional than contralesional shift of the beating field in the lighted VOR–OKR condition and (paradoxically) higher contralesional shift in total darkness (i.e. VOR condition). The shift of the beating field was seen as an anticipatory orienting response towards sectors of space and stimuli appearing in the direction of the head–body turn [49,50,58]. Following this interpretation, our findings can be considered in keeping with data emphasising the influence of visual input in worsening the pathological ipsilesional deviation of attention suffered by neglect patients [8,36,40].

3.2. Implications for the treatment of unilateral neglect

The directionally opposed VOR and OKR impairments suffered by neglect patients suggest that improvement of neglect by vestibular or optokinetic stimulation inducing contralesional slow phases is caused by the activation of different hemispheric pathways. Cold water irrigation of the left ear produces slow-leftward phases and predominant activation of perisilvian structures in the right hemisphere [10,11]. Therefore, temporary amelioration of left unilateral neglect following cold caloric stimulation of the left ear seems due to prevalent direct activation of the damaged hemisphere. Optokinetic stimulation directed leftward is perturbed by left hemisphere lesions [5] and in normal subjects causes predominant activation of V5, the intraparietal sulcus and the putamen in the left hemisphere [29]. Thus, amelioration of left unilateral neglect after leftward optokinetic stimulation seems due to prevalent indirect re-activation of the damaged right hemisphere by afferences from the undamaged left hemisphere (this explanation could also apply to the effects of visual background motion toward the neglected side [44]).

Different and not mutually exclusive physiological mechanisms may account for neglect improvement after optokinetic stimulation. Brandt et al. [12] found that leftward optokinetic stimulation produces bilateral activation of the parietal–temporal area and the basal ganglia in right brain damaged patients with contralateral pure hemianopia. These authors initially hypothesised that activation in the damaged hemisphere was conveyed by direct retinal-extrastriate connections bypassing the damaged striate areas or by transcallosal afferents from the spared hemisphere. In a subsequent study on normal subjects, Bucher et al. [13] demonstrated that motion stimulation of one hemifield activates middle and middle-superior temporal areas bilaterally while deactivating optic radiations contralateral to the side of the stimulation. Accordingly, the authors concluded that previous findings in hemianopics were better explained by transcallosal activation. We think that similar transcallosal mechanisms could also underlie the improvement of unilateral neglect produced by optokinetic stimulation directed contralesionally. At the same time, this stimulation could draw attention contralesionally and re-activate, transcallosaly, spared structures in the damaged hemisphere. Conversely, optokinetic stimulation directed ipsilesionally could be ineffective or even worsen neglect (see Vallar et al. [60]), both by drawing attention ipsilesionally and because disruption of mechanisms receptive to ipsilesional optokinetic stimulation in the damaged hemisphere generally prevents boosting of any residual attentional resource in both hemispheres.

This explanation takes into account different hypotheses on the ameliorative effects of optokinetic stimulation on neglect. Gainotti [28] emphasised that contralesionally directed optokinetic stimulation (or vestibular stimulation producing directionally similar oculomotor effects) re-orients covert and overt attention toward the neglected side, contrasting the pathological ipsilesional bias. Vallar et al. [61] stressed that contralesional optokinetic stimulation not only has attentional effects in neglect patients since it improves the proprioceptive-position sense of both arms (i.e. not only of the arm on the side of stimulation direction) whereas stimulation directed ipsilesionally worsens position sense bilaterally. The improvement was interpreted as depending on the re-activation of multimodal mechanisms specialised for the representation of personal body-space in the damaged right hemisphere [61]. This mechanism seems plausible since in healthy humans structures of the right hemisphere related to attentional and oculomotor control (posterior parietal cortex, precentral and posterior medial frontal gyrus) can be activated by optokinetic stimulation regardless of its horizontal or vertical direction of [18].

3.3. Implications for the “egocentric reference” hypothesis

Ventre et al. investigated the VOR in cats with unilateral ablations of the middle suprasylvian gyrus and superior colliculus [64] and in monkeys with unilateral ablation of area 7a [65]. They found decrease of ipsilesional gain, increase of contralesional gain and spontaneous nystagmus with slow phases directed contralesionally. Developing the pioneering observations made by Hecaen and Massonet [35], Ventre et al. [64] interpreted the predominance of slow phases toward the contralesional space as a compensatory response of the vestibular system to counteract the ipsilesional displacement of visuomotor behaviour produced by the unilateral lesion. According to the “egocentric reference” hypothesis (Ventre et al. [64]), the ipsilesional bias of visuomotor behaviour is due to interhemispheric unbalance in the activation of multimodal representations of space usually ensuring symmetry of orienting and the alignment of the subjective sagittal body midline to the objective one. Our results show that patients with extensive unilateral brain damage and chronic contralesional neglect have no contralesional bias

in the gain of the VOR, suffer reduced frequency of contralesionally directed slow phases and show contralesional rather than ipsilesional deviation of the beating field. In the same patients, no ipsilesional deviation of the subjective "straight ahead" was found. This latter finding replicates previous data from several independent authors [6,23,55] and, in the present study, was evident at the individual level and independent from concomitant visual field defects. Taken together, these dissociations do not seem to agree with the "egocentric reference" hypothesis, which assumes that the same pathophysiological mechanism underlies contralesional neglect, ipsilesional deviation of the subjective "straight ahead" and ipsilesional defects of the VOR. However, the original observations by Ventre et al. [64] were made within a few days following surgical ablations. It may be that acute neglect patients show behavioural and vestibular symptoms similar to those described by Ventre et al. in animals.

Our findings are in keeping with a recent case study by Ventre-Dominey et al. [66] documenting decreased gain and reduced frequency of the contralesional VOR in a patient with a right parietal–temporal damage. The deficits found in this patient, when compared with the opposite VOR impairments found in animals with unilateral parietal or collicular lesions [64], were tentatively attributed to adaptive recovery during the subacute phase, to differences in the location of the lesion or to inter-species differences in the cortical distribution of vestibular control. Our data and those from the case study of Ventre-Dominey et al. [66] dovetail both with brain imaging data indicating relative higher activation of the right hemisphere when the slow phases of the VOR are directed leftward [10,11] and with clinical and experimental findings demonstrating hemispheric control of ipsilateral OKR [4,29,39]. This converging evidence does not seem to support the possibility that VOR asymmetries in chronic neglect patients depend on recovery mechanisms causing a shift from ipsilesional to contralesional hemispheric control. The different asymmetries of horizontal VOR impairments found in animals and humans could, therefore, be better explained by inter-species differences in the hemispheric distribution and complexity of mechanisms modulating the VOR. Unicellular recordings in monkeys do not document a clear-cut hemispheric lateralisation in the control of the VOR and VOR–OKR interaction. Grüsser et al. [32] found that in the PIVC area of the monkey, 53% of the neurons respond to contralateral rotation in darkness and 37% to ipsilateral rotation. Büttner and Buettner [14] found no hemispheric specialisation in area 2v (in the lower section of the intraparietal sulcus). Kawano and Sasaki [42] found that in area 7 of the monkey, 60% of the neurons responded to ipsilateral OKR stimulation and the remaining 40% to contralateral stimulation. Half of the neurons responded to synergistic VOR–OKR stimulation (i.e. to vestibular or optokinetic stimulation inducing slow phases toward the same side of space) and the other half to anti-synergistic stimulation [43]. These data might indicate that in lower species, the recovery mechanism after unilateral brain damage is subserved by different populations of VOR and bimodal VOR–OKR neurons which, in each hemisphere, preferentially respond to ipsilateral or contralateral VOR, OKR or combined VOR–OKR stimulation.

3.4. Cautions and conclusions

First, caution should be taken in interpreting our findings because of the possible effects of inactivation (i.e. diaschisis) produced by an extensive unilateral hemispheric lesion on brainstem mechanisms regulating the VOR. In this case, the alteration of the VOR we tentatively attributed to hemispheric lateralisation could be due to dysfunction of more peripheral mechanisms. Although this hypothesis should be taken into consideration, it should be recalled that Ventre-Dominey et al. [66] documented impairments of the VOR similar to those, we found in N+ in a patient with a circumscribed temporal–parietal lesion and no detectable brainstem damage on MRI examination.

Second, our conclusions about the hemispheric lateralisation of the VOR control are currently based on samples of right brain damaged patients and should therefore be substantiated by studying patients with lesions of the left hemisphere.

Third, previous studies in hemispherectomised patients [22,57] disclosed defects of the horizontal VOR that appear directionally opposed to those reported in the present investigation. In many cases, hemispherectomy was performed to bring about relief from seizures with very early onset in the life of patients. Thus, it cannot be excluded that these patients had idiosyncratic patterns of hemispheric vestibular control (and recovery) linked to processes of developmental functional reorganisation due to illness. Nonetheless, the report by different authors of a diametrically opposed deficit of the horizontal VOR after unilateral brain damage requires further clarification.

Fourth, another caution concerns the convergence of our data with imaging data by Bottini et al. [10,11]. In these studies, which were not specifically aimed at identifying oculomotor structures related to the control of the VOR, only cold caloric stimulation of each ear was used. Therefore, brain activations reflected both sensory-nociceptive and oculomotor components. Central brain structures selectively related to VOR control should be specifically investigated considering that they should be equally activated both by cold and warm caloric stimulation inducing VOR toward the same horizontal direction.

In the present study, N+ had larger lesions than N−. It is quite possible that this contributed to the greater VOR and OKR impairments of N+ and also implies that damage to adjacent, independent, brain structures accounts for the association between neglect and VOR/OKR impairments. However, the aim of the present study was to define the pattern of VOR and OKR deficits that can be associated with unilateral neglect rather than to demonstrate their higher

frequency or their exclusive link with the syndrome. The localisation and extent of the lesion has a profound impact on the clinical features of the neglect syndrome [9,20]. Further studies are therefore needed to specifically assess the effect of different lesions producing neglect on the VOR and OKR. Conversely, the effectiveness of vestibular and optokinetic stimulation should be assessed in patients with neglect due to damage of different sectors of the neural network that provide humans with adaptive coding of space.

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