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Original article

Long-term sensorimotor and therapeutical effects of a mild regime of prism adaptation in spatial neglect. A double-blind RCT essay☆

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A B S T R A C T

Spatial neglect (SN) is commonly associated with poor functional outcome. Adaptation to a rightward optical deviation of vision has been shown to benefit to SN rehabilitation. The neurophysiological foundations and the optimal modalities of prism adaptation (PA) therapy however remain to be validated. This study is aimed at exploring the long-term sensory-motor, cognitive and functional effects produced by weekly PA sessions over a period of four weeks. A double-blind, monocentric randomized and controlled trial (RCT) was carried out. Twenty patients with left SN secondary to stroke were included, 10 in the "prism" group and 10 in the "control" group. The sensory-motor effects of PA were evaluated by measurement of manual and visual straight-ahead, and also by precision of pointing without visual feedback before and after each PA session. The functional independence measure (FIM) was evaluated before and at 1, 3 and 6 months after PA, while SN severity was assessed using the Behavioural Inattention Test (BIT) before and 6 months after PA. Before the intervention, only manual straight-ahead pointing constituted a reproducible sensory-motor measurement. During prism exposure, a questionnaire showed that not a single patient were aware of the direct effects of optical deviation on pointing movement performance. The sensory-motor after-effects produced by the PA produced a more rapid reduction of the rightward manual straight-ahead, which was secondarily followed by visual straight-ahead. These sensory-motor effects helped to clarify the action mechanisms of PA on SN. At the conclusion of the 6-month follow-up, the two groups showed similar improvement, indicating that a weekly PA session over 4 weeks was not sufficient to produce long-term functional benefit. This improvement was correlated with the evolution of visual straight-ahead, which can be proposed as a marker for patients outcome.

1. Introduction

Spatial neglect (SN) has been defined as a singular difficulty to detect, respond to or orient one's attention toward stimuli presented or represented on the contralateral side of a brain lesion, particularly in the right hemisphere [1–3]. The syndrome aggravates the severity of the associated motor and sensory deficits and is a predictor of poor functional prognosis [4–8]. Several rehabilitation methods have been proposed to reduce the behavioral bias on the side of the brain injury and the awareness deficit characterizing the contralateral hemi-space of SN; however the level of evidence has been poor (see review: [9,10]). Using a meta-analysis encompassing 23 randomized clinical trials (628 participants), Bowen et al. [11] showed that most studies have assessed the repercussions of rehabilitation programs on the results of standardized tests; while only 15 of them evaluated the impact of these programs on daily activities immediately afterwards. Only 6 measured their impact at a later

☆ The results of this study were the subject of an oral presentation at the 8th World Congress for NeuroRehabilitation and the 19th European Congress of Physical and Rehabilitation Medicine.

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date. The currently available results show a significant effect favoring cognitive rehabilitation procedures, but this is only the case using the standardized tests evaluating SN. Accordingly, efficacy in daily activities has yet to be rigorously demonstrated.

Rehabilitation using prism adaptation (PA) is one of the most widely used methods, and also one of the most effective [12–14]. Its effects involve a wide range of perceptual, cognitive and motor functions that are affected in SN (see reviews: [15–18]): visual neglect [19–21], somatosensory [22] and haptic [23] neglect, tactile extinction [24], auditory extinction [25], representational neglect [26,27], numerical representations [28] and writing [29] or wheelchair movement [30,31]. Beneficial effects on postural imbalance have likewise been observed in patients following clinical SN remission [32].

The effects of PA have been shown to be surprisingly prolonged in time compared to known durations in healthy subjects. Since our initial study, in which we reported on effects lasting at least two hours after a few minutes of visuo-motor exercises using prisms [21], the prolonged effects after a single PA session on visual neglect [33] and clinical manifestations including reading [19], writing [29] and wheelchair driving [30] have been shown to exist. More relevantly for rehabilitation, the effects were shown to be more durable after repeated sessions of adaptation. Several non-randomized [20,34–37] and randomized [38–41] studies have reported long-term effects (exceeding 5 weeks) following intensive rehabilitation involving two daily PA sessions over a 2-week period. In a controlled trial including 38 patients with SN (20 rehabilitated and 18 controls), only in the sub-group of patients with moderate SN was a functional benefit related to PA observed on hospital discharge [39].

To establish a rehabilitation protocol, it is necessary to measure the duration of the effects of a single PA session. The cognitive improvement reported after one session generally fails to exceed 24 hours following PA but can persist for several days, and at times as long as a week (review in: [15]). Given the decline of after-effects magnitude concomitant with the repetition of adaptation sessions, it was decided to space them out. Given the fact that the sensory-motor effects of PA tend to last several days [19,33], it was decided to test a regime consisting in one PA session a week. At the same time, we lengthened the rehabilitation period to one month, whereas in most previous therapeutic trials (e.g. [20,34,36,39]), it lasted two weeks. The main goal of this double-blind randomized controlled trial was to explore the effects of moderately "dosed" PA; we evaluated the effects of weekly PA sessions over 4 weeks on SN and daily life activities in chronic patients. The potential clinical interest of a less intense prism adaptation regime is that it may facilitate therapeutic management in ambulatory care.

The second objective of this study was to explore the development of spatial frames of reference [42] during the recovery of neglect patients and to clarify the relationship between the sensory-motor after-effects of PA [43] and the expansion of these effects in this cognitive sphere [15]. In fact, dissociations between the two levels of action of PA have been reported [33], whereas in other studies a significant correlation between the consecutive proprioceptive effects and SN has been observed [44]. The existence or non-existence of a quantitative relationship between the sensory-motor and the cognitive consequences of PA in cases of SN is of fundamental importance not only for the design and validation of pilot studies in healthy subjects, but also for establishing immediate and objective factors conducive to the therapeutic benefits of PA expected in a given patient. That is why this study includes measurement of the sensory-motor parameters through which it is possible both to monitor the development of the patients'' spatial frames of reference and to quantify PA. These parameters are: manual straight-ahead (MSA), visual straight-ahead (VSA) and open-loop pointing without visual feedback, or open-loop pointing (OLP). Given the fact that some authors tend to confuse visuo-motor adaptation and error reduction during exposure to deviation (thereby leading to the erroneous conclusion that adaptation is deficient in neglect patients [45]), detailed exploration of the above parameters was directed at clarifying the means of measuring true prism adaptation [46]. In addition, issues concerning alteration or facilitation of the adaptation process in neglect have been approached using a questionnaire evaluating patient awareness of prism deviation. The reliability and predictive value of these variables, which have yet to be described in the literature, have also been explored in this study.

2. Methods

2.1. Patients

Nineteen patients admitted to the neurological rehabilitation medicine unit of Hôpital Henry-Gabrielle, Hospices Civils de Lyon and presenting with left SN secondary to a right-hemisphere stroke were included in the study from September 2001 until September 2005 (Fig. 1). All patients were right-handed according to the criteria of the Edinburgh questionnaire [47].

The inclusion criteria were:

- age ranging from 18 to 90 years;
- a single stroke confirmed by a tomodensitometry examination or by brain MRI;
- left SN confirmed by several neuropsychological tests (line bisection test [48], balloon test [49], copy of a drawing, dictation and reading of a text);
- a time lapse of at least one month following the ischemic event.

The exclusion criteria were:

- existence of multiple brain lesions;
- temporo-spatial disorientation;
- psychiatric disorders;
- an associated, non-stabilized pathology.

The characteristics of the patients in the two groups are detailed in Table 1.

2.2. Study description

This was a double-blind monocentric controlled randomized clinical trial involving 2 groups of patients presenting with left SN: a group undergoing PA rehabilitation, and a control group. The primary outcome measure of the study was the functional improvement in daily life activities following rehabilitation as assessed by the Functional Independence Measure (FIM) [50]. This score was previously used in a non-randomized clinical trial evaluating the effectiveness of a trunk orthosis in SN rehabilitation in two groups of patients [51]. The authors demonstrated, at 6 months, a statistically significant difference between the mean scores of the 2 groups (mean difference = 24; $n = 11$). In this study, the FIM end-point had a standard deviation of 10 units. Based on this variability measure, and to have at least a 90% chance of showing a 25-point difference between mean responses in the two treatments with a risk of type 1 error not exceeding 5%, 9 subjects had to be included in each group, ($1-\beta = 0.90$; $\beta = 0.10$; $\alpha = 0.05$ and $\Delta = 25$; $n = \sigma^2 \times M/\Delta^2 = 100 \times 54/625 = 8.6$, i.e. at least 9 subjects).

Block randomization was carried out with the distinction of two levels of deficit severity used according to the initial seriousness of

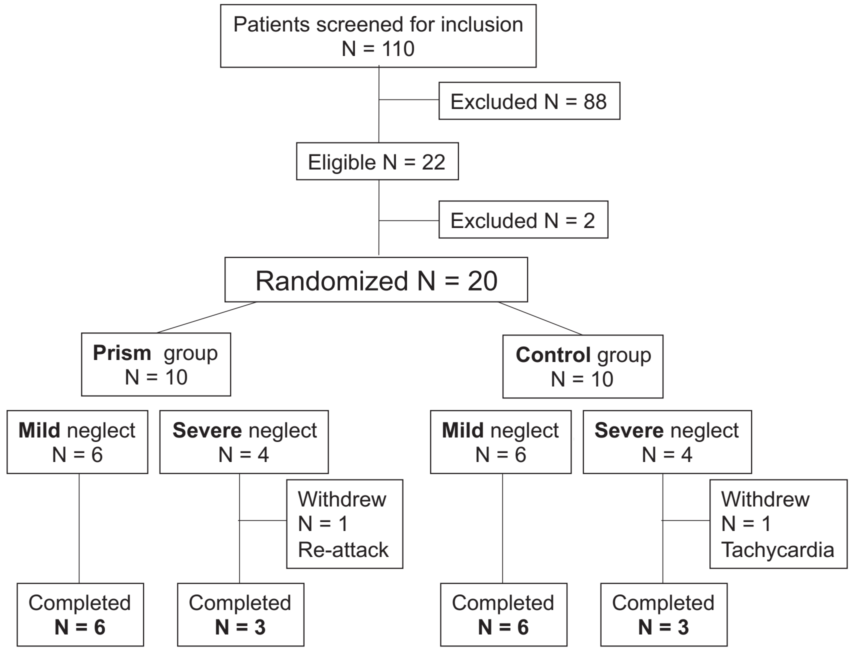

Fig. 1. Study design. Mild neglect: BIT score > 55; Severe neglect: BIT score ≤ 55.

SN as assessed through the inclusion tests. Severe SN: was defined as deficit shown in all the inclusion tests, Schenkenberg score [48] greater than 50° of deviation and BIT score ≤ 55. Moderate SN: was defined as deficit shown in some (from 1 to 4) of the inclusion tests, Schenkenberg score ranging from 11 to 50° of deviation and BIT score > 55.

The study was double-blinded: The examiners carrying out the evaluation (GR, SL, EM), did not know whether a given patient had undergone PA. They were distinct from the examiners performing the task of exposure to prismatic or neutral glasses (YR, SJC, LP). The double-blind procedure was facilitated by the fact that the SN patients were not aware of the disturbance induced by prism deviation and did not present the vegetative reactions expected during the appearance of motor errors when the prisms were worn for the first time (cf. infra and [18]). Consequently, they could be assigned without their knowledge to the "prism" and "control" groups. This also entailed that examiners performing the assessment did not receive information from the patients all of which that might have compromised the double-blind trial.

Table 1
Patient characteristics.

Case	N	Age/sex	LI	MD	SD	LHH	OCD	Delay	Aetiology	Lesion
Prism group										
1	+	40/F	100	3	3	P	1	44	Isch	(Frontal), parietal, occipital, temporal, insula, corona radiata, putamen
7	++	40/F	100	3	3	P	2	47	Isch	Frontal, parietal, temporal, insula, corona radiata, putamen
8	+	47/F	100	3	0	P	1	34	Isch	Frontal white matter, (corona radiata), insula, internal capsule, putamen, caudate nucleus
9	+	69/M	100	3	3	P	0	54	Isch	Temporal, (occipital), corona radiata, internal capsule, putamen
10	++	66/M	16.66	3	3	A	2	60	Isch	Frontal, parietal (temporal), corona radiata, putamen
11	+	59/M	100	2	2	P	1	88	Hem	Parietal, occipital
13	++	49/M	100	3	3	P	1	30	Isch	Frontal (temporal, parietal), putamen
15	+	63/F	100	3	3	P	1	42	Isch	Corona radiata, capsule interne, putamen
16	++	71/M	100	3	3	P	1	60	Isch	Frontal, parietal, corona radiata, putamen
Control group										
2	+	45/M	83.33	3	3	A	1	35	Isch	Frontal white matter, corona radiata, insula, internal capsule, putamen
3	++	45/M	100	3	3	A	1	92	Isch	Frontal white matter, corona radiata, insula, putamen, caudate nucleus
4	++	57/M	100	3	3	P	1	38	Isch	Frontal, temporal, parietal, insula, putamen
5	+	72/M	100	3	3	A	1	60	Hem	Corona radiata, insula, internal capsule, putamen
6	+	62/F	91.66	3	3	P	1	46	Isch	Parietal, occipital
12	+	79/F	100	2	2	P	1	38	Hem	Parietal, occipital
14	++	51/M	100	3	3	P	2	67	Isch	Temporal, parietal, occipital
17	+	75/F	100	1	1	P	1	34	Isch	Occipital, parietal white matter, putamen, caudate nucleus
18	++	69/F	100	3	2	P	2	60	Isch	Frontal, temporal, parietal, corona radiata, putamen, caudate nucleus

N: neglect (+ = mild neglect; ++ = severe neglect); LI: Laterality Index (Edinburgh Test [47]); MD: motor deficit (0 = absent; 1 = monoparesis; 2 = incomplete hemiparesis; 3 = complete); SD: somatosensory deficit (0 = absent; 1 = superficial; 2 = incomplete superficial and deep; 3 = complete); LHH: left homonymous hemianopia (A = absent; P = present); OCD: right ocular and cephalic deviation (0 = no deviation; 1 = spontaneously reducible; 2 = reducible under order; 3 = not reducible); Etiology (Isch = ischemia; Hem = hemorrhage); Lesions: brackets indicate partial involvement of cerebral lobe.

Block randomization and drawing by lots of the patients into the ''prism'' or ''control'' groups was carried out by Denis Pelisson, director of the ImpAct team in the Lyon Neuroscience Research Centre. The randomization was produced at 2 levels, firstly by selection of patients for the ''prism' or ''control'' group; secondly, by selection of patients according to the severity of the initial SN assessed by the BIT score, the objective being that the ratio of patients with severe neglect and patients with moderate neglect is comparable in the two groups.

All patients gave their consent to participate in the study. The experimental procedure was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale Lyon B on 5 June 2001 le (Dossier 2001-040 B). The Hospices Civils de Lyon sponsored this study, which was registered on 2 August 2001 under the number 2001/0294. The study was financed by Inserm, the Hospices Civils de Lyon and the university Claude-Bernard Lyon 1.

2.3. Study parameters

The spatial frames of reference and precision of pointing at a visual target (without visual feedback) were measured from patient inclusion data through six months so as to monitor their evolution while the patients were recovering. Two measurements took place, before and after each exposure session, in view of quantifying the after-effects of prism adaptation.

The primary outcome measure for therapeutic efficacy was the functional score achieved according to the Functional Independence Measure (FIM) [50]. The secondary outcome measure was the total score in the Behavioural Inattention Test (BIT) [52], which constitutes a good indicator of SN severity. Measurement with regard to the primary end-point was carried out 4 times: in pre-tests and in post-tests at 1 (M1), 3 (M3) and 6 (M6) months after the initial PA session. The BIT evaluations were performed twice: in pre-test, and then in post-test at 6 months. No intermediate evaluation took place during monitoring, in order to avoid the confounding effect of learning through repeated testing.

2.4. Prism adaptation and sensory-motor parameters

In the ''prism'' group, PA was carried out by wearing a pair of glasses producing a 10° rightward optical deviation of the visual field (OptiquePeter.com). The prismatic lenses were composed of two superimposed, curved, point-to-point lenses fitted with a ''glacier'' frame containing lateral leather protectors designed to avoid access to non-shifted vision. The prisms covered a total visual field of 105% in which each monocular field represented 75°, while the central visual binocular field represented 45°.

During prism exposure, the patient had to execute 80 rapid pointing movements towards visual targets located 10 degrees to the left or to the right of the middle of her/his body, the targets being made to pseudo-randomly alternate. In spite of repeated instructions to carry out rapid movements, the movements produced in brain-damaged patients generally remain too slow as to allow visual retroaction, and the errors committed by our patients did not necessarily reflect the amplitude of optical deviation or phase of adaptation (Fig. 2). However, their degree of rapidity remained compatible with the development of actual sensory-motor adaptation by reducing the strategic components of compensation [53,54]. The pointing movements were performed with a pause of 30 s after each series of 20, thereby favoring an increased number of errors at the start of the following series. During exposure, the patient did not see the initial position of her/his hand, which entered the visual field only once the movement was approximately 30 to 50% complete [55], in such a way as to favour proprioceptive-visual coding of the movement [56]. All in all, prism exposure lasted from 6 to 10 mins (video tutorial: http://www.chu-lyon.fr/web/4531). While the ''control'' group patients carried out this visuo-motor task under the same conditions, they were wearing a pair of placebo glasses fitted out with neutral lenses of the same weight consisting in two 5° prismatic lenses set-up so as not to produce any optical deviation [21]; (OptiquePeter.com). Each patient carried out the exposure task (with prismatic glasses or neutral lenses) 4 times: at D0 (Expo1), at D + 7 (Expo2), at D + 14 (Expo3) and at D + 21 (Expo4). All of the exposure sessions took place under the same conditions and with the same operators.

The patients' perceptual awareness of the optical deviation and its effects on movement trajectories were systematically studied using a phenomenological questionnaire (cf. Appendix A). This open questionnaire consists in 20 questions divided into 3 main parts and progressing from open-ended formulations to highly specific questions on prism deviation. The first part includes 5 open questions put forward after ten preliminary pointing movements carried out prior to putting on glasses. The questions progress from (Q1: How is the exercise going?) and (Q3: Have you observed anything in particular?) to (Q5: Is it easy to aim toward the target?). The second and main part is administered after 5 movements carried out with glasses on, that is to say during the early exposure period, which usually generates maximal pointing errors [57]. This consisted of 12 questions, the first of which are a reprise of the 5 preceding open questions (Q6 to Q10), while the following queries become increasingly explicit (Q11 to Q17) (Q17: In some patients these glasses can render it difficult to aim with the hand. How about you?). The third and final part of the questionnaire (Q18 to Q20) is given after 20 trials and at the end of active exposure to the prisms.

The after-effects of PA were evaluated by means of repeated MSA measurements in the dark (n = 10), by VSA in the dark (n = 10) and by OLP in the direction of a visual target (n = 10). The VSA and MSA measurements present a double interest in the framework of our study as they are classically used independently to evaluate an egocentric reference [58–60] and by subtraction of the measurements obtained before and after prism exposure (VS = visual shift and PS = proprioceptive shift) in view of quantifying the after-effects of PA [43]. OLP is used to measure through the same subtraction operation (TS = total shift) the total after-effects of PA [43]. The three sensory-motor parameters were evaluated in pre-test and in post-test at 1 (M1), 3 (M3) and 6 (M6) months in order to monitor the development of each patient's frames of reference, and also before and after each prism exposure session (Expo1, Expo2, Expo3 and Expo4) in order to quantify the adaptation. To avoid any contamination of the sensory-motor parameters by cognitive parameters involved in compensation for prism deviation occurring independently of adaptation [43,53,61], we carefully ensured that the pre-test and post-test evaluations were not organized under the same conditions as prism exposure. The target used for OLP and the precision/rapidity instructions given differed from those employed during exposure.

MSA measurement was carried out by asking patients to point with their right hand in darkness in the ''straight-ahead' position in the direction of an imaginary line dividing their body into two equivalent halves. The subject was required to employ her/his arm without any speed or amplitude constraint, and if necessary, was reminded that she/he was not expected to proceed rapidly or stretch out her/his arm to the greatest possible extent. Pointing was measured using a contractor attached to a thimble threaded into the index finger, atop a table covered with isoresistant carbon paper on which two 65 × 1 cm electrodes were applied, thereby delimiting a section at an angle of 50° and a depth of 70 cm centered at the starting position near the torso. A direct 5 V current was generated between the electrodes. When the finger touched the surface of the table, tension between the thimble contact point

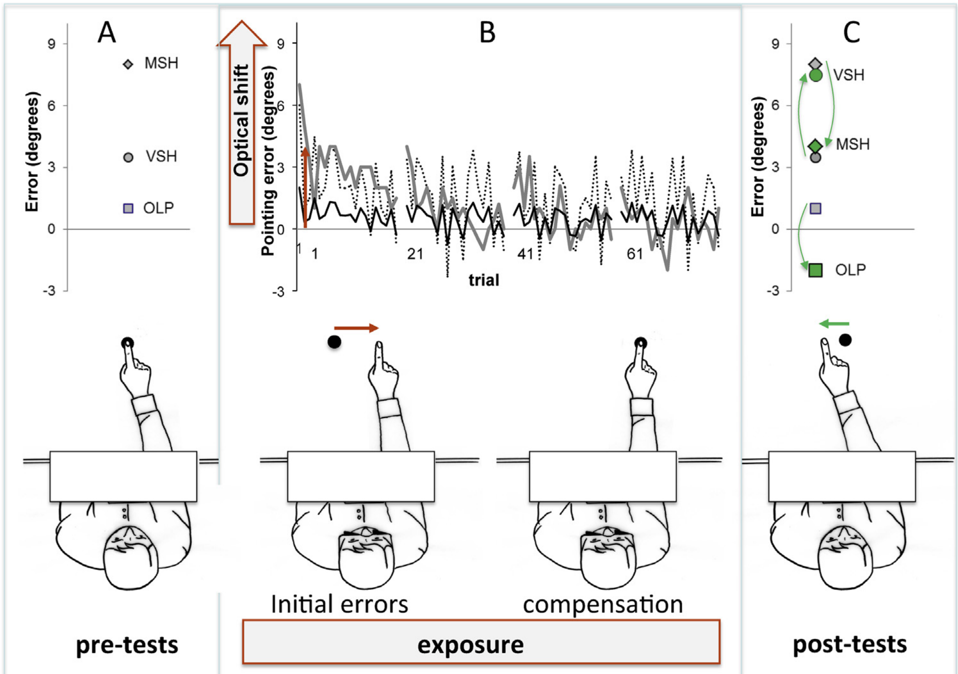

Fig. 2. Prism adaptation phases. A. Pre-test: the subject is comfortably seated in front of a table. A chinrest maintains the trunk in an upright position and prevents the subject from seeing her/his hand as the movement begins; in order to program the movement from proprioceptive to visual coordinates [55,56]. Pre-tests are carried out so as to provide a baseline for later measurement of compensatory after-effects. In the SN patient, OLP remains correct, but straight-ahead pointing (MSA and VSA) is deviated to the right. B. Active exposure: the subject wears a pair of "point-by-point" prismatic glasses deviating vision on the right side by 10 degrees. Rapid pointing movement [53] in the direction of a visual target is shifted to the side of the optical deviation (red arrow) and towards the virtual target. The motor system can then take into account the spatial error consecutive to prism deviation, regardless of whether the subject shows phenomenological awareness of the error [70], and finally compensate for the optical deviation. The three examples of error reduction curves correspond to a patient managing to point rapidly enough to generate initially important errors (gray), a patient pointing slowly enough to produce moderate errors (black), and a patient whose pointing variability is increased (broken line). Progressive correction of pointing deviation is observed, with transient increase following breaks. During active exposure to prism, the subject compensates for the optical deviation of vision, but the actual presence of adaptation can only be evidenced by the presence of after-effects [43,53]. C. After-effects: following removal of the prismatic glasses, when the subject is asked to once again rapidly point towards a target, the movement is shifted in the direction opposed to the optical deviation (leftward: green arrow). This compensatory after-effect is known as total shift, or spatial realignment, and it can be divided into visual and proprioceptive components, both of which are quantified by straight-ahead measurements [43,55,62]. The amplitude of total adaptation is quantified in terms of the difference between OLP measurements in post-tests and pre-tests (OLP_{post}–OLP_{pre}). It reveals a compensatory leftward shift when right-shifting prisms are used. The visual adaptation components (VSA_{post}–VSA_{pre}) illustrate a compensatory shift from the side of the optical deviation, which means rightward. The proprioceptive component (MSA_{post}–MSA_{pre}) shows a leftward compensatory shift. OLP: open-loop pointing (i.e. without visual feedback); MSA: manual straight-ahead; VSA: visual straight-ahead

and the reference electrode was measured as in a potentiometer. Tension measurement enabled us to calculate the angular position in relation to the objective sagittal axis, and this position could then be converted into degrees and conventionally signed (negative on the left, positive on the right) (Fig. 3A). Measurement precision was estimated at ± 0.5 degrees.

VSA measurement was carried out in total darkness. The patient was comfortably seated in front of a table, with her/his head held straight up by a chinrest [21]. A luminescent red diode was moved by the experimenter onto a 2-m horizontal ramp set face to the patient at a distance of 1 m. Speed of traverse ranged from 20 to 30 cm/s. Ten measures were successively carried out by alternating target movement in the left-right and right-left directions. The patient was asked to vocally interrupt ("Stop!") the movement of the target as soon as she/he perceived it to be in a "straight-ahead" position (Fig. 3B). Measurement of the deviation was performed

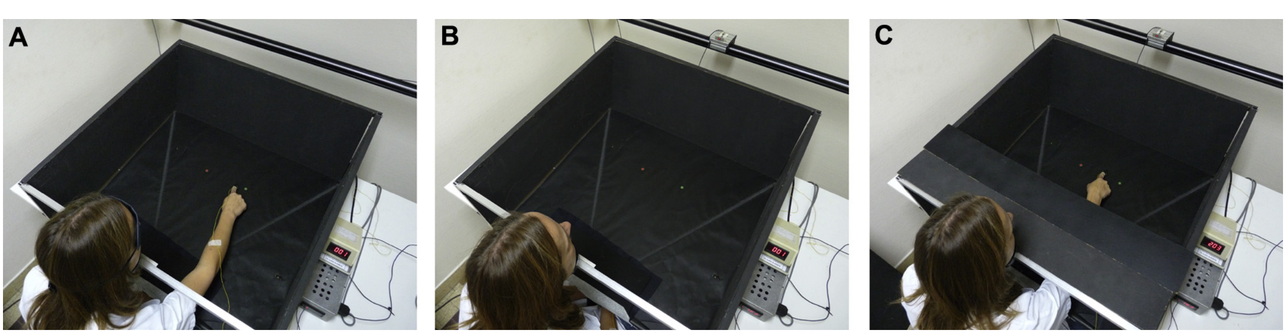

Fig. 3. Quantitative evaluation of prism adaptation. A. Measurement of manual straight-ahead demonstrations: the subject carries out a series of 10 pointing movements in the "straight-ahead" direction with her/his right index finger in darkness. B. Measurement of visual straight-ahead: the subject interrupts the lateral movement of a visual target (10 trials) when the target is perceived in "straight-ahead" position. This measurement is performed in total darkness. C. Measurement of pointing without visual feedback: the subject carries out a series of 10 pointing movements with her/his right hand in the direction of a visual target without seeing her/his hand.

using a calibrated galvanometer and converted into angular deviation with regard to the objective straight-ahead position.

OLP accuracy measurement was carried out under the same conditions of darkness and with the same set of devices (Fig. 3C). The luminous visual target was aligned with the patient's sagittal axis. The instruction given to the patients was to place their right hand at the target drip-line as precisely as possible but without time constraint, the goal being to distance themselves from the pointing conditions employed during exposure in view of obtaining measurements of sensory-motor after-effects that would be less influenced by cognitive factors [43].

During prism exposure, the terminal errors of each movement were captured by means of the thimble and converted into degrees of angular error with regard to the target.

2.5. Statistical analysis

First of all, the pre-test results of the two groups were compared. Initial variance analysis with repeated measurements were compared the two groups according to the parameters of age, FIM, BIT and mean time lapse after stroke. Sensory-motor parameters were compared by means of a repeated measures (RM) Anova including the "Session" factor since two pre-tests were available. Reliability of the sensory-motor measurements was evaluated using correlations.

Evaluation of the sensory-motor effects proceeded using two main steps. The first tests compared the different after-effects measured in terms of post-pre difference using unilateral Student *t*-tests against a theoretical value of zero. A three-factor Anova with repeated measurements then compared the two treatments (group factor, inter-subject: prism and control) with two intra-subject factors: pre-post (measured before and after exposure) and session (Expo 1 to 4). The error reduction curves produced during exposure could not be interpreted, due to highly variable and relatively slow movement speed.

In order to study the long-term impact of the 4 PA sessions on the sensory-motor variables, repeated measures analysis of variance was carried out with the "session" (pre, M1, M3, M6 or pre and M6), and "group" (prism, control) factors for each functional parameter under examination.

To conclude, the results enabled us to explore the predictive value of the sensory-motor parameters on the BIT and FIM scores, along with evolution between the pre-tests and M6.

3. Results

3.1. Pre-tests

Preliminary comparison of the 2 patient groups did not show any significant difference for age (55.2 ± 11.9 for the "prism" group; 61.7 ± 12.9) for the "control" ($t(16) = 1.1$; $P > 0.25$), SN severity (mean BIT score: 76.7 ± 38.2) for the "prism" group; $70{,}2 \pm 37.6$ for the "control" group ($t(16) = -0.36$; $P > 0.7$) and level of disability (mean FIM score: 64 ($\pm$ 24.1)) for the "prism" group and 62.4 ($\pm$ 20.0) for the "control" group ($t(16) = 0.14$; $P > 0.8$) and mean post-stroke time lapse (51 ± 17.4 days for the "prism" group; 52.2 ± 19.3 days) for the "control" ($t(16) = 0.41$; $P > 0.8$).

Initial MSA patient performances were systematically deviated to the right; among the 36 measurements carried out in pre-test in the 18 patients, only two were (moderately: -4.0° and -2.9°) deviated to the left. The other results ranged from 0.3° to 22.3°. The mean score for the "prism" group was 6.0° ($\pm$ 6.47) in the first pre-test and 8.8° ($\pm$ 9.25) in the second. The mean score for the "control" group was 8.1° ($\pm$ 5.5) in the first pre-test and de 8.2° ($\pm$ 8.0) in the second. The differences between the two groups ($F(1.16) = 0.003$; $P > 0.95$) and between the two sessions ($F(1.16) = 3.14$; $P > 0.10$) were not significant, nor was their interaction ($F(1.16) = 0.44$; $P > 0.50$). As regards the 18 patients taken as a whole, average MSA was 7.0° ($\pm$ 5.9) and 8.5° ($\pm$ 8.4) respectively for the two pre-tests. Measurement reliability was excellent; test-re-test correlation between the two measurements was highly significant ($y = 1.32x + 0.06$; $R^2 = 0.73$; $P < 0.00005$).

As regards VSA, task execution was difficult for some patients, and the number of reliable measurements that could be carried out was not sufficient. As a result, the analyses described below only included the data from 13 patients who could complete the task (6 in the "prism" group and 7 in the "control" group). VSA appreciation was weakly lateralized (14 mean scores out of the 26 measurements taken in the two pre-tests were deviated leftward). Mean VSA appreciation value was -3.0° ($\pm$ 6.1) in the first pre-test and 3.5° ($\pm$ 5.0) in the second for the patients in the "prism" group and 1.0° ($\pm$ 4.55) in the first pre-test and 0.4° ($\pm$ 4.4) in the second pre-test for the subjects of the "control" group. For the 18 patients taken as a whole, mean values were -0.85° ($\pm$ 5.55) in the first pre-test and 1.85° in the second pre-test ($\pm$ 4.8), that is to say globally close to zero. The difference between the two groups was not significant ($F(1.11) = 1.22$; $P > 0.70$). Group effect ($F(1.11) = 6.41$; $P < 0.05$) and group $\times$ session interaction ($F(1.11) = 6.16$; $P < 0.03$) were observed, most likely reflecting the sizable variability of this measurement (6 patients out of 13 presented variation between the two pre-tests exceeding 6 degrees). Indeed, the reliability of this measurement with regard to the 13 patients tested two times in pre-test was very poor; correlation between the two sessions was highly mediocre ($y = 0.14x + 2.12$; $R^2 = 0.03$; $P > 0.57$).

Average OLP was precise, with error values of 2.8° ($\pm$ 2.3) for the "prism" group and -2.4° ($\pm$ 5.4) for the "control" group in the first pre-test (mean value of 0.2° ($\pm$ 4.8) for the 18 patients), and error values of 2.6° ($\pm$ 3.6) for the "prism" group and -1.9° ($\pm$ 4.6) for the "control" group in the second pre-test (mean value of 0.3° ($\pm$ 4.6) for the 18 patients). The difference between the two groups was significant ($F(1.16) = 9.14$; $P < 0.01$) but the session factor was not significant, neither alone ($F(1.16) = 0.02$; $P > 0.80$) nor in interaction with the group factor ($F(1.16) = 0.10$; $P > 0.75$). However, reliability of this measurement was mediocre (correlation between the two pre-tests: $y = 0.50x + 0.24$; $R^2 = 0.26$; $P < 0.05$) in spite of a relatively wide spread of individual scores (from -11.0 to 7.0 degrees).

3.2. Direct effects of prism exposure

The reduced speed of the pointing movements carried out by patients often enabled them to correct the optical deviation effects prior to their conclusion through automatic use of visual feedback [53]; that is why many of the pointing series ended without significant error. Fig. 2B presents three representative examples of the error reduction observed in the "prism" group patients. As has already been demonstrated [46,53], error reduction occurred independently of the development of after-effects.

The results of the phenomenological questionnaire were highly instructive. Not a single patient revealed even the slightest sign of detection of the prism effects during the first exposure. The patients' responses to the different questions showed lack of detection of any optical deviation, and the commentaries that were collected showed no implicit awareness or interrogation on any effect on the pointing. Some patients spontaneously commented on the weight of the glasses, or even declared that "they function better than mine". It was remarkable to observe that for the last two questions, which evoked the possibility of visual deviation or movement, the responses were systematically and affirmatively negative. It is worth mentioning, for the sake of comparison, that healthy subjects having tried on the prismatic glasses, including the patients' spouses, all expressed a verbal and emotional reaction

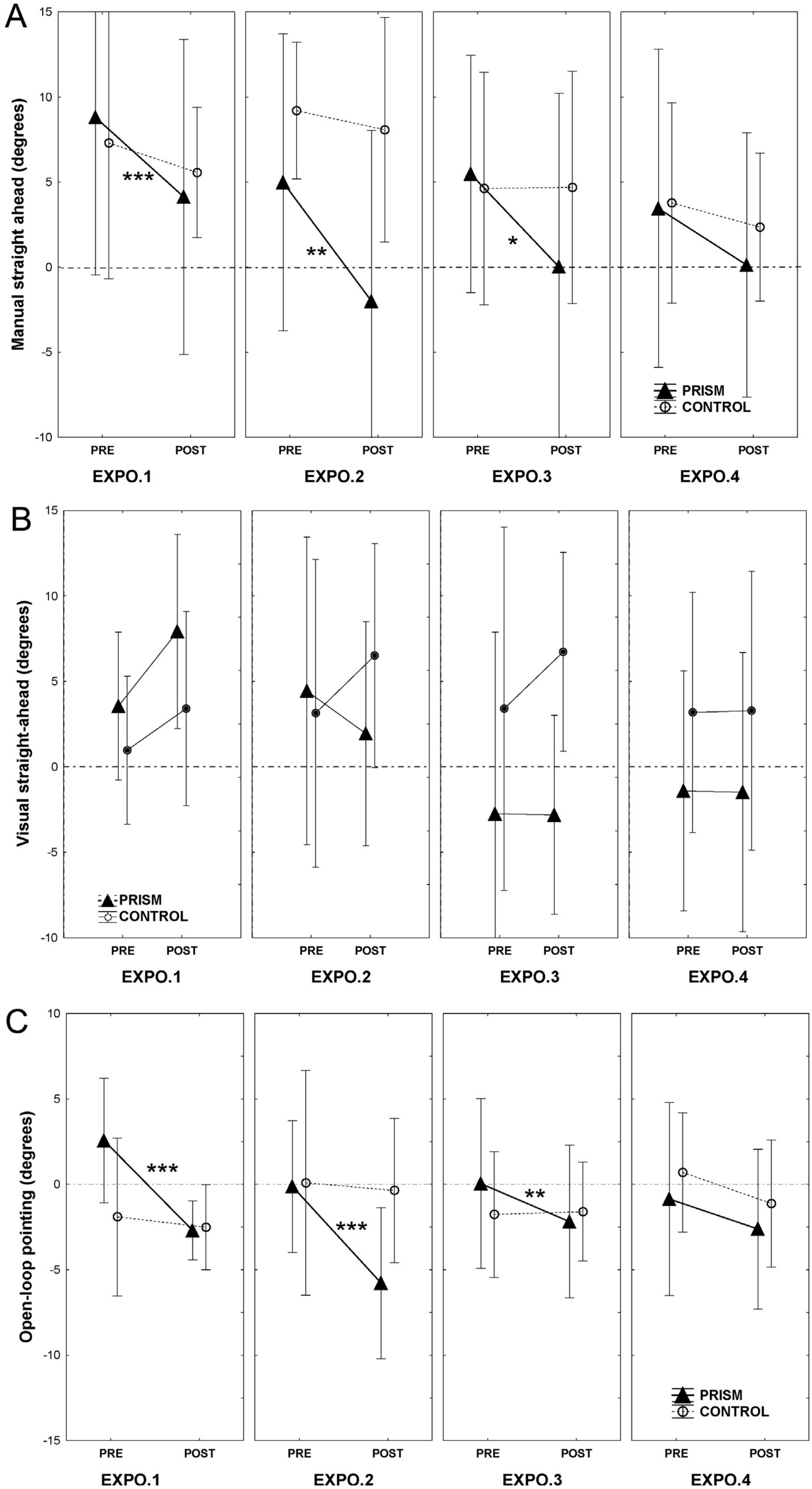

Fig. 4. Quantification of PA by measurement of MSA (4A), VSA (4B) and OLP (4C) after each exposure (Expo1, Expo2, Expo3 and Expo4) for patients in the "prism" (black triangle) and "control" (white circle) groups. A. The MSA measurements carried out before and after each session illustrate ther effects of prism exposure. Each time a leftward shift is observed. Globally, MSA evolves from an initial value strongly anchored to the right toward a more centered value (at the end of treatment). In comparison, the control group remains unaffected by the exposure sessions and follows a less pronounced spontaneous evolution. B. VSA 4B follows a two-phase evolution in the prism group. In the first session, the initial rightward deviation is exaggerated by the adaptation. After that, between as well as during the sessions, it evolves towards paradoxically negative

(surprise, laughter...) as soon as they attempted to engage in pointing with prisms. During the 3 following exposures, the patients' responses essentially remained the same. The single exception to this clear-cut result was observed during a female patient's fourth exposure to real prisms, when she indicated in her response to the final question that "indeed it seemed to her that her hand was deviated rather rightward with the glasses".

3.3. Sensory-motor after-effects of adaptation

3.3.1. Manual straight-ahead

Fig. 4A shows that each exposure session produced the expected modification of MSA in the direction opposed to the prism deviation. Amplitude of adaptation as measured by the post-pre difference was –4.7° (± 3.1) for Expo1 (comparison to zero standard: t(8) = 4.57, P unilateral < 0.001), –7.0° (± 6.47) for Expo2 (comparison to zero: t(8) = 3.23, P unilateral < 0.01, 5.5° (± 8.0)) for Expo3 (comparison to zero: t(8) = 2.04, P unilateral < 0.04) and –3.3° (± 6.8) for Expo4 (comparison to zero: t(8) = 1.46, P unilateral < 0.09) for the "prism" group. Reproducibility of the effects of prism exposure on MSA was illustrated by the fact that 100% of the patients in the "prism" group presented a leftward after-effect for the first three sessions, and 67% for the last. As a comparison, the post-pre difference for the "control" group patients ranged from +0.1° (± 4.7) to –1.7° (± 6.4). As a result, the initial deviation of the egocentric reference was reduced from 8.8° ± 9.25 to 0.1° ± 13.8 between initial and final measurement in the "prism" group, while it declined only from 7.3° ± 8.0 to 2.4° ± 4.35 between initial and final measurement in the "control" group.

Repeated measures analysis of variance (session factors (Expo1, Expo2, Expo3, Expo4)), pre-post (before and after PA) and group (prism, control) showed neither significant pre-post × session × group interaction (F(3.48) = 0.48; $P > 0.70$) nor a main effect due to the group (F(1.16) = 0.81; $P > 0.30$). The main pre-post (F(1.16) = 12.98; $P < 0.005$) and Session (F(3.48) = 3.53; $P < 0.05$) effects can be interpreted in light of the different interactions between two factors. The session × group effect (F(3.48) = 2.92; $P < 0.05$) merely illustrates the fact that for some sessions, the mean for the pre- and post-measurements is lower in the "prism" group. As for the pre-post × group interaction (F(1.16) = 5.62; $P < 0.05$), it illustrates the fact that only the "prism" group produces a significant exposure after-effect (cf. supra tests of comparison to zero standard).

3.3.2. Visual straight-ahead

Fig. 4B shows the development of VSA in the two groups of patients under treatment. On an overall basis, the effect observed in the "prism" group for the first session proceeded in the expected direction, that is to say towards the optical deviation. However, during the month of weekly sessions, a general trend developed in the opposite direction. Inter-individual variability and the spontaneous fluctuation of the "control" group made it difficult to interpret more precisely the variations of this variable. Repeated measures analysis of variance (session factors (Expo1, Expo2, Expo3, Expo4)), pre-post (before and after PA) and group (prism, control) showed no significant effect (only the interaction session × group was marginally significant with F(3.30) = 2.69; $P = 0.064$ and the other $P > 0.30$). No comparison of the post-pre differences significantly differed from zero (Student $t < 1.7$; $P > 0.15$).

3.3.3. Open-loop pointing (without visual feedback)

Fig. 4C shows that in the "prism" group, amplitude of adaptation measured by the post-pre difference was –5.3° (± 2.51) for Expo1, –5.7° (± 3,93) for Expo2, –2.2° (± 1.60) for Expo3 and –1.8° (± 3,65) for Expo4. The Student *t*-tests comparing these values to the zero standard were significant for the first three sessions (t(8) = 6.30; $P = 0.0001$ for Expo1.; t(8) = 4.31; $P = 0.001$ for Expo2.; t(8) = 4.11; $P = 0.002$ for Expo3.; t(8) = 1.44; $P = 0.09$ for Expo4). It is likewise significant to note that 100% of the patients in the "prism" group presented a consequential leftward effect for the first two sessions, 89% of them for the third and 67% for the fourth and last. In comparison, the post-pre difference in the "control" group patients varied haphazardly between +0.2 (2 ± 2.8) and –1.8° (± 0.5), and the Student's *t*-tests comparing these values to the zero standard were marginally significant for the final session only (t(8) = 2.39; $P = 0.05$).

Repeated measures analysis of variance (session factors (Expo1, Expo2, Expo3, Expo4), pre-post (before and after PA) and group (prism, control) revealed significant interaction between the different factors. The main effects (group: F(1.16) = 0.07; $P > 0.8$; session: F(3.48) = 0.17; $P > 0.9$; pre-post: F(1.16) = 27.39; $P < 0.005$) and the simple interactions (session × group: F(3.48) = 3.18; $P < 0.005$; pre-post × group: F(1.16) = 12.97; $P < 0.005$); session × pre-post): F(3.48) = 2.03; ($P > 0.10$) cannot be directly interpreted because of significant group × session × pre-post interaction: F(3.48) = 3.24; ($P < 0.05$). The latter was consequently explored with planned supplementary comparisons through univariate tests, which showed that interaction between pre-post and group (prism, control) was significant for sessions Expo1 (F(1.16) = 10.0; $P < 0.001$), Expo2 (F(1.16) = 9.70; $P < 0.001$), Expo3 (F(1.16) = 5, 30, $P < 0.05$), but not for Expo4 (F(1.16) = 0.002; $P > 0.95$). In conclusion, the analyses confirmed the visual impression given by Fig. 4, according to which the amplitude of after-effects tends to decrease as the prism exposure sessions are repeated.

3.3.4. Alignment of reference frames

In healthy subjects in normal condition, these three sensory-motor measurements are aligned and do not show the significant deviation observed in the SN patient. In fact, quantification of the consequential effects of PA (Post-Pre subtraction) is based on these measurements. What may then generally be observed is the additivity or cumulativeness of PA effects; more precisely, OLP, which measures visuo-proprioceptive alignment, corresponds to the sum of the other two measurements, namely visual straight-ahead and proprioceptive straight-ahead, which are of opposite directions [OLP = MSA + VSA; or Total shift = proprioceptive shift + visual shift] [43,61,62]. It is therefore interesting to determine, using the three measurements, whether or not their coherence is disturbed in neglect patients and in what way it is affected by PA. Two supplementary analyses were carried out explore patients'' visuo-proprioceptive alignment and explore how it was modified by PA.

In addition, repeated measurement of the sensory-motor parameters in this trial enabled us to study the relationships between the visual and proprioceptive frames of reference and precision of pointing. Do the pre-test straight-ahead measurements available for 13 SN patients enable us to predict the results of their pointing without visual feedback? Fig. 5 represents the three sensory-motor measurements and additivity-based predictions (MSA + VSA). It clearly and congruently appears that the sum

values. In comparison, the control group does not undergo a significant trend. C. OLP remains centered during the pre-tests of the two groups. Each prism exposure session produces the expected effect of a leftward shift, but no overall evolution is observed in the two groups; the patients probably realign their sensory-motor systems between each session via feedback gained during their daily actions. The stars indicate the results of the *t*-tests against zero carried out with post-pre difference in the prism group (* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$).

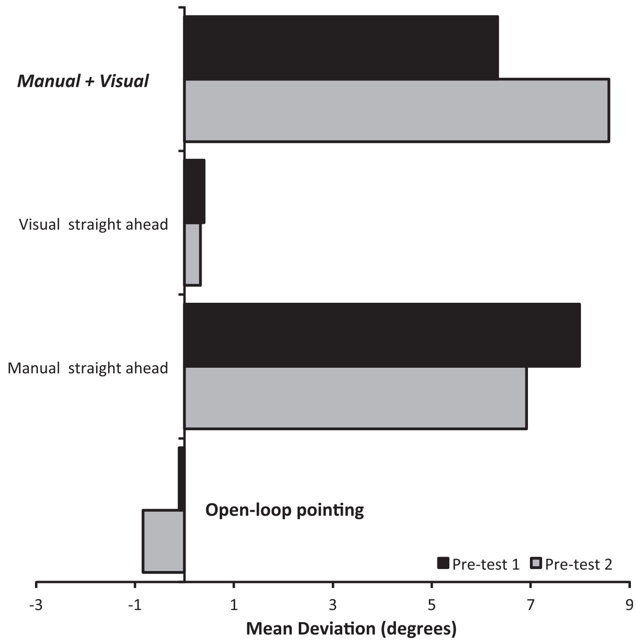

Fig. 5. The sensory-motor parameters measured in the pre-tests. The two pre-tests lead to similar observations: while MSA is deviated rightward, VSA and OLP are on the average close to zero. As a result, the visuo-proprioceptive alignment predicted by the two straight-ahead gestures (MSA and VSA) is pronouncedly deviated rightward and significantly differs from the observed pointing value (OLP); this does not fit with the additivity-based hypothesis (OLP = MSA + VSA). This shift may explain the adaptability of the patients to the right prisms and, reciprocally their resistance to leftward adaptation [71]. (Note: the values presented in this figure are different from those of the previous figures, as data from only 13 patients have been included).

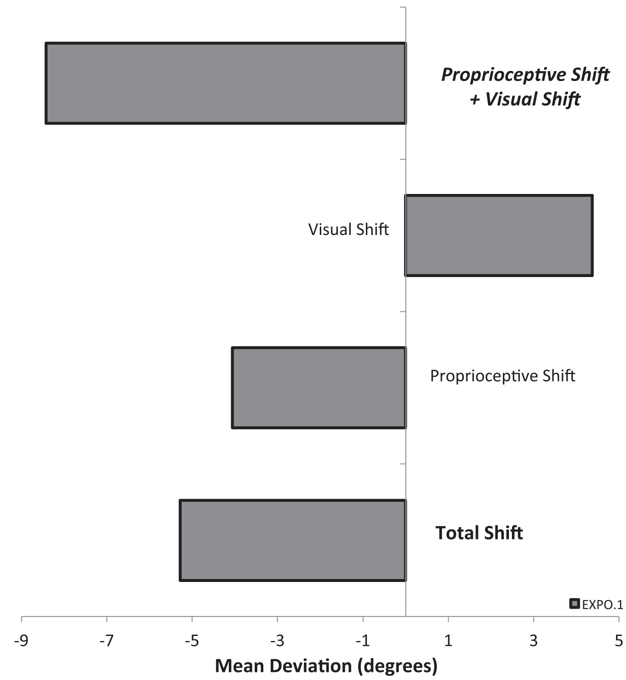

Fig. 6. Additivity of prism adaptation after-effects. During the first exposure session (Expo1), patients exhibited the expected after-effects: visuo-proprioceptive realignment, or the total shift measured by OLP underwent compensatory leftward deviation. The proprioceptive after-effects measured by MSA were deviated leftward, while the visual after-effects measured by VSA were deviated rightward [43,62]. On the other hand, the realignment value predicted by the additivity hypothesis involving the visual and proprioceptive components exceeded the value actually observed. (Note: the values presented here differ from those shown in the previous figures; data from only 6 patients have been included.).

of the visual and proprioceptive measurements (VSA + MSA = 8.6° (± 6.8) for pre-test 1 and 6.3°(± 8.3) for pre-test 2) is markedly different from the measurements for pointing gestures without visual feedback (–0.8° (± 5.2) for pre-test 1 and –0.1° (± 5.1) for pre-test 2). While the predicted alignment is highly rightward-deviated, the visuo-proprioceptive alignment reflected by the OLP of patients is, on the average, very slightly deviated. A paired *1* Student's *t*-test confirms a highly significant difference between the two variables ($t(12) = 4.81$; $P < 0.0005$), which in turn confirms a major difference with the result expected in healthy subjects.

Finally, did the measurement of total adaptation, as evaluated by OLP, correspond to the sum of the visual (VSA) and the proprioceptive (MSA) measurements? Fig. 6 represents a test of the hypothesized additivity of the visual and proprioceptive after-effects, the sum of which would constitute the total after-effect, as measured by OLP [43,61–63]. The results showed that visual and proprioceptive after-effects in fact come from opposite directions, and the visuo-proprioceptive shift measured by OLP was deviated from the same side as the predicted shift. Notwithstanding the imperfectness of the additivity-based prediction, the paired Student's *t*-test did not reveal a significant difference between the two variables ($t(12) = 0.74$; $P = 0.49$).

3.4. Long-term sensory-motor effects of PA

MSA, a marker of both PA and SN that is initially significantly deviated rightward in the two groups, progressively reached values near zero. The advantage the treatment had induced in the "prism" group fades progressively out (at M1: "prism" group = 2.4 ± 7.4 and "control" group = 6.2 ± 3.3; at M3: "prism" group = 0.2 ± 7.7 and "control" group = 1.8 ± 7.9; at M6: "prism" group = 1.9 ± 4.4 and "control" group = –0.15 ± 3.0). The Anova studying the "Month" effect (pre, M1, M3, M6) and the "group" effect failed to record significant interaction ($F(3.48) = 0.19$; $P > 0.9$). While the 'month' effect is significant ($F(3.48) = 5.14$; $P < 0.005$) the "group" effect remains non-significant ($F(1.16) = 1.5$; $P > 0.2$).

Initially (but non-significantly) deviated leftward, VSA evolved in a globally stable manner. The difference between the two groups induced by PA was gradually cancelled after the treatment has been concluded. Anova revealed neither a significant effect nor substantial interaction between the "Group" and "Month" factors ($Fs < 1.25$).

As for OLP, which initially differed in the two groups for no apparent reason, it subsequently stabilized close to optimally precise zero in the "prism" group following treatment (–0.5 ± 3.0 at M1; –0.3 ± 4.3 at M3; 0.3 ± 4.5 at M6). It was still deviated leftward at M1 (–3.0 ± 9.3) in the "control" group, but pointing was as precise as in the "prism" group at M6 (–0.15 ± 3.0). Once again, Anova revealed neither a significant effect nor substantial interaction between the "Group" and "Month" factors ($Fs < 2.60$).

3.5. Long-term functional and cognitive effects of PA

3.5.1. FIM score

Fig. 7 shows that the two groups improved while they were being monitored. Repeated measures analysis of variance (Anova) 'session' factors (pre, M1, M3, M6), 'group' factors (prism, control) does not show interaction between the session and group factors ($F(3.48) = 0.03$; $P > 0.05$) with regard to the primary outcome measure. There nonetheless exists a significant time-related effect, which underlines enhanced autonomy in the two groups ($F(3.48) = 34.1$; $P < 0.0001$).

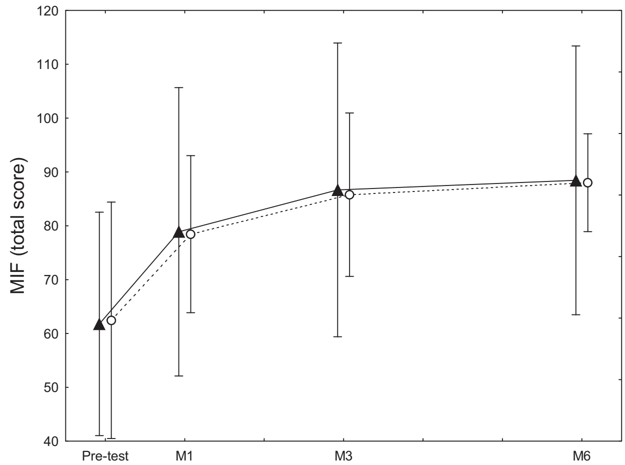

Fig. 7. Total FIM scores for the patients in the "prism" (black triangle) and the "control" (white circle) groups. FIM score evolution was not significantly different between the two groups. At 6 months, a comparable autonomy is obtained for the patients in the two groups. Score increases essentially occur during the first month, after which the scores evolve more slowly. The vertical bars represent confidence intervals set at 0.95.

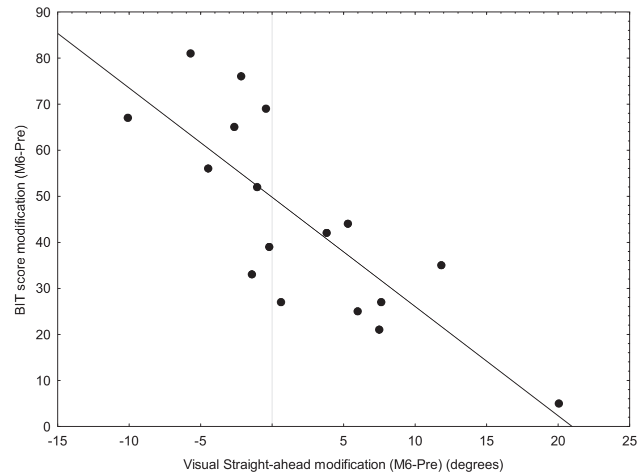

Fig. 8. Correlation between BIT variation and VSA variation from pre-test to M6. Highly significant correlation is observed between the differential values (post-pre) of the sensory-motor parameters and the BIT score. Only for VSA is the partial regression highly significant, thereby illustrating the finding that heightening of the BIT score between inclusion and M6 can be predicted by VSA evolution. Concretely, all patients show BIT score improvement at 6 months and all of the patients ($n = 7$) showing leftward VSA variation, and only these patients, exhibited an increase of their BIT score by at least 50 points.

3.5.2. BIT score

Initially pathological with scores of 70.2 ± 37.6 for the "prism" group and 76.7 ± 38.2 for the "control" group, by the end of follow-up the BIT average was 113.4 (± 28.0) for the 'prism' group and 117.4 (± 23.7) for the "control" group, scores corresponding to values exceeding the threshold. Repeated measurements variance analysis ("session" factor (pre, M6) and 'group' (prism, control) did not show significant interaction (F(1.1–) = 0.82); $P > 0.05$). The increased BIT score observed at 6 months illustrates SN improvement during monitoring that is similar in the two groups of patients (F(1.16) = 53.1; $P < 0.0001$) with an overall average rising from 73.4 (± 36.9) to 115.4 (± 25.3).

3.6. Predictive value of the sensory-motor parameters

An initial series of analyses explored the predictive value of the sensory-motor parameters for the BIT and FIM scores collected in pre-test and at M6. The three multiple regression analyses carried out with the sensory-motor parameters for inclusion (pre-test1, pre-test for Expo.1, or pre-test 2) and the average scores for the two pre-tests (mean pre) are not significant (Rs < 0.6; $P > 0.3$). Only one of the nine partial correlations is significant, showing that the dependant variable BIT is correlated only to the VSA measured in pre-test 1 (t(13) = 2.17; $P < 0.05$); while this result corroborates the above-mentioned variability between the two VSA pre-tests, it also suggests that the score for the BIT, an essentially visual test, is potentially related to VSA. Multiple regression analysis carried out using the three sensory-motor parameters measured at M6 showed that the relationship observed in pre-test has disappeared by the end of 6-month follow-up (ts(13) < 0.9; $P > 0.4$). As regards the FIM score, no significant correlation was observed, either for the pre-tests or at M6 (ts < 2.0; $P > 0.05$).

A second series of analyses explored the predictive value of the sensory-motor parameters on the evolution of the BIT and FIM scores. The differential values (M6-pre) for each parameter were used as dependent (FIM or BIT) or independent (MSA, VSA, OLP) variables of the multiple regression. For BIT, multiple regression is very significant (R = 0.86; F(3.13) = 12.5; $P < 0.0005$). The BIT modification evidences a correlation that is highly significant with regard to the modification of VSA (t(13) = 4.91); $P < 0.0005$ (Fig. 8), but only marginally significant with regard to the modification of OLP (t(13) = 2.09; $P = 0.057$), and non-significant with regard to MSA (t(13) = 0.88). No significant result was obtained with the FIM scores.

4. Discussion

This is the first double-blind monocentric randomized controlled trial to evaluate the long-term effects of a mild PA treatment consisting of one weekly session over a 4-week period involving patients presenting with chronic SN after a stroke. Differential development of the sensory-motor effects and of SN and functional disability showed that the sensory-motor effects of PA were not necessarily accompanied by long-term therapeutic effects. In this discussion, we address the sensory-motor and the therapeutic dimensions of the effects reported, and hope to draw lessons that may prove useful for the clinical management of patients and for the conception of future therapeutic trials.

The MSA of all but two of the patients measured in pre-test was systematically deviated rightward. This observation is in agreement with the pre-test deviation values reported in several previous studies [21,27,33,41]. The shift of the proprioceptive straight-ahead on the brain-injured side is of pathophysiological significance as it concerns SN [42,58,60,64], even if dissociations producing challenging views [19,33]. In any event, this parameter constitutes a pertinent clinical disturbance to be measured. The test-retest correlation achieved here underscores the reliability of this measurement, and as such may be recommended in clinical practice as a marker to be used not only in PA quantification, but also for monitoring patients' egocentric frames of reference [42]. For VSA and OLP, on the other hand, patients' performances are not easily reproducible from one pre-test to the next. Even though SN is primordially considered as a visually manifested pathology, the reliability of the above-mentioned proprioceptive measurement can be linked to somesthetic manifestations of the syndrome [22–24]. It can likewise be linked to the leftward somesthetic effects also observed after PA in healthy subjects [65,66].

Some authors have put forward the idea that error reduction during PA treatment constitutes an index of therapeutic efficacy

[67]. This proposition is weakened by the fact that the parameters used in previous analyses represent a confused patchwork of pointing errors having been measured during a single session or over the course of several successive sessions. The results of our study confirm that error reduction curves do not allow for prediction of the quantity of after-effects and consequently of adaptation, either in the healthy [53] or in the brain-damaged [46] subject.

Systematic measurement of the sensory-motor effects of prism exposure also shed light on the physiological foundations of the therapeutic action of PA. All of the patients having undergone prism exposure presented sensory-motor after-effects following exposure: 100% after the first three sessions and 67% after the fourth with regard to the effects measured by MSA; 100% after the first two, 89% for the third and 67% after the fourth with regard to the effects measured by OLP. On conclusion of the 4th and last exposure, the patients no longer presented a displacement of their representations on the right side. Just as the pre-tests had revealed the predominant interest of proprioceptive straight-ahead measurement, the most solidly attested sensory-motor effects observed in our study likewise involve the latter. Initially deviated rightward, the parameter is displaced leftward after each PA session. In comparison to several previous studies [21,44,45], we did not observe an exaggeration of proprioceptive after-effects together with the normal total after-effect [43]. Contrastingly, the VSA, at first only mildly deviated, moving as expected toward the optical deviation during the first exposure session only. It is surprising to note that later on, this visual parameter evolves in the opposite direction (Fig. 4B), as though it was finally following the proprioceptive straight-ahead pointing, and drawn toward negative values. This apparently paradoxical result offers confirmation that proprioceptive straight-ahead pointing is a clinical marker of the clinical efficacy of PA on SN. It is generally initially deviated rightward; the measurement it provides is reliable; it is modified in a compensatory direction (leftward for a rightward optical deviation) by the adaptation; and the modification is reproducible in spite of the progressive reduction of the amplitude of the effects. Conversely, VSA is not reliable; it is modified rightward by the right optical deviation used for therapeutic purposes. Its overall evolution in the direction opposite to the optical deviation appears to indicate that it is modified secondarily subsequent to action at another level, namely proprioceptive.

OLP, which classically reflects alignment of the visual and proprioceptive frames of reference and is used to quantify adaptation [43,60,61], does not seem to present the same advantages of reliability and reproducibility during the pre-tests as MSA. We initially concluded that the after-effects measured in neglect patients using MSA, which were twice as sizable as those observed in healthy subjects, signified that the adaptive reaction was amplified in SN, thereby producing more substantial after-effects [21,68]. The idea that the overall compensation in optical deviation could be based on strategic reactions and on true adaptive reactions (spatial realignment) [21,43,53] allowed Michel et al. [69] to postulate that the absence of a strategic component in SN resulted in increased mobilization for realignment, which was measured by after-effects and constituted the only proof of adaptation [18,68]. The gain in adaptation could result from the lack of awareness of the deviation evidenced in neglect patients and confirmed by their lack of galvanic skin response to prism introduction [18]. In this respect, the conditions of progressive prism exposure reproducing this loss of awareness in healthy subjects likewise augment the after-effects of adaptation [70]. In an interesting study of the sensory-motor and cognitive consequences of PA in neglect patients, Sarri et al. [44] confirmed that while the amplitude of the proprioceptive after-effects of PA was heightened in neglect patients [21], OLP was similarly modified in neglect patients and healthy subjects (also see: [45]), thereby suggesting a normal total shift as an after-effect in SN. One explanation for exaggerated MSA is that this parameter could be impacted both directly by the after-effects of adaptation, and indirectly by the repercussions on the egocentric frame of reference for cognitive expansion of the effects of adaptation [33,44]. However, in the group of patients monitored in this study, exaggerated visual and normal proprioceptive after-effects were shown to exist instead, in what might be considered as an anti-therapeutic direction.

How can this finding be explained? Our study of visuo-proprioceptive alignment during the pre-tests (Fig. 5) revealed the existence of visuo-proprioceptive misalignment in cases of SN, since the rightward shift of MSA is not compensated by an opposite shift of VSA. While the shift calculated by the additivity hypothesis is not reflected in OLP, its existence could provide an explanation for the peculiar asymmetry of the adaptive capacities of neglect patients, who adapt normally and even better than normally to rightward optical deviation [21], but not to leftward optical deviation [71]. In this respect, the direction of the visual and proprioceptive after-effects induced by rightward deviation serves to compensate for the preexisting visual and proprioceptive deviations in our patients, while leftward deviation is likely to induce effects in the opposite direction that can probably not be added on to the preexisting deviations, which are consequences of the brain injury.

Since our study has not rendered possible an analysis of the concomitant variations of the sensory-motor and cognitive variables for each PA session, we cannot be more conclusive on this point. Study of the correlation between sensory-motor and cognitive effects in healthy subjects may facilitate the exploration of the fundamental question pertaining to the mechanisms connecting the sensory-motor and cognitive areas [28,69,72,73] from which the therapeutic effects of PA originate [68]. It is nevertheless worthwhile to note that from one treatment session to another, spontaneous improvement of the sensory-motor variables in the "control" group makes up for the transitorily acquired advantage of the "prism" group. Even though the benefits brought by PA are maintained once the treatment has been concluded, a single weekly PA session fails to produce additional long-term sensory-motor gain. These observations suggest that in order to bring about a benefit that would be significant in comparison with spontaneous recovery, optimal PA treatment should be more intensive.

Correlation analyses between the sensory-motor parameters and the BIT and FIM scores during the pre-tests and in terms of evolution from the pre-tests to M6 throw more light on the pathophysiology of SN and on the effects of PA. In fact, the low correlation between the initial BIT scores of the 18 patients and the sensory-motor pre-test results is shown to have disappeared at M6, i.e. when BIT values are no longer pathological. This finding suggests that VSA deviation is associated with the existence of marked SN. As for reported scores on the BIT, which is in essence a visual negligence test, their evolution over 6 months is strongly correlated to VSA modification during the same period. In spite of its initial variability, our study reveals that VSA evolution is the best predictor of patients' amelioration at 6 months.

Even though the sensory-motor effects of prism adaptation observed in our study are astonishingly durable given the non-intensive organization of the treatment sessions, they did not yield long-term functional improvement. Our results do not show a significant benefit with regard to the FIM and the BIT after PA rehabilitation. As a result, this randomized clinical trial does not permit the extension of results reported after a single PA session with regard to visual neglect [33], spatial dyslexia [19] spatial dysgraphia [29] and wheelchair driving [30,31] into more durable after-effects. In case studies [29,30,33] and in series with non-randomized control groups [19], the reported improvement was maximal 24 hours after the prism exposure session and subsequently persisted, only to disappear after a week, thereby suggesting that a single weekly PA session may suffice. In our trial, no mid-term evaluation of SN was carried out after each exposure session before and after each PA session and it was not possible to describe the short-term effects of each exposure session on SN improvement. Our results only demonstrate that a single weekly PA session is not sufficient to reduce long-term SN manifestations. Indeed, it is important to point out that the regime applied in our study was much lighter, in terms of both frequency and number of prism exposure sessions, than those used in other studies having produced interesting therapeutic results (review: [15]).

Similar dissociated effects have been described in other studies [41,74]. In a controlled study assessing the efficacy of 4 PA sessions over the course of the first month following a stroke, a more rapid improvement was observed in the PA group, but only during the first weeks. A month after the treatment, the additional benefit of the PA group had not been maintained, thereby suggesting, as in our study, that ''dosage'' of the sessions had not been sufficient to produce long-lasting effects [40]. Finally, dissociations have been reported in case studies demonstrating reduced sensory-motor (including oculo-motor) bias and a lack of cognitive effect after one PA session [75,76]. In fact, the different after-effects of PA reflect a realignment of spatial coordinates. While this particular component of PA presupposes cerebellar integrity [77], cognitive and functional effects seem to depend on the activation of a network initially involving not only the cerebellum, but also some cortical areas [68,78–80]. In this study, no patient presented with cerebellum injury, and this factor helps to explain why all of the patients in the ''prism'' group presented after-effects.

The studies reporting lasting PA effects generally implemented a rehabilitation program involving two exposure sessions a day for 2 weeks. More specifically, long-term effects have been reported in several non-randomized [20,34–37] and randomized [38,40] studies, including a multicentric controlled randomized study [39], and they have clearly shown that the improvement produced through PA-intensive rehabilitation (20 exposure sessions over 2 weeks) mainly involved patients presenting with moderate SN.

One of the limits of our trial consists of the choice of primary outcome measure. The FIM is a generic scale evaluating activity limitations, and it is not specific to SN. While it is designed to measure the functional consequences of various deficiencies, its specific sensitivity to SN improvement remains limited in cases with associated major sensory-motor deficit, which were prevalent in our trial (80% of the patients in the 2 groups presented with severe deficits; see Table 1).

In terms of practical recommendations, our result suggests that weekly PA sessions are not propitious to secure optimal cumulative gain. Fig. 6 shows that the effects of a given session tend to be negated by the time of the pre-test of the following session, which means that progressive accumulation of favorable effects is unlikely to be sustained. It could even be the case that the terminal effects of our treatment are no greater than those of a single adaptation session. It may be reasonably assumed that rather than supposedly inadequate duration of treatment, insufficient frequency of treatment was also responsible for the lack of long-term supplementary functional benefit [40]. The doses having entailed therapeutic benefit range from 10 to 20 sessions and from 2 per week to per day [15]. Two weekly PA sessions appear to represent the minimal dose conducive to durable therapeutic gains. The relationship between PA effectiveness and treatment duration/number of sessions remains to be studied through future clinical trials.

Our study also enhances the definition of the significance and value of the three sensory-motor parameters. In spite of its variability, VSA distinguishes itself as the one index of neglect improvement. To a greater extent than its absolute value, its progression predicts the evolution of the BIT score. As for OLP measurement, which is marked by the particularly high significance of adaptation outcome, our results support the idea that OLP remains the most suitable means of describing and quantifying the after-effects of PA in cases of SN [43,44,62]. Finally, MSA is a robust measurement, stably deviated rightward in the event of neglect. It also helps clarify the mechanism of action of PA on neglect. The therapeutic efficacy of PA trends not towards visual after-effects, but rather in the direction of manual after-effects, i.e. the prisms effects at the proprioceptive level. Despite of this, SN improvement follows the variation of VSA, which paradoxically moves leftward over the course of repeated PA sessions (Fig. 4A). We may consequently speculate that the way the prisms act at the proprioceptive level serves as a key entry onto the disturbed coordination of the spatial frames of reference, which represent the level at which the prisms produce the reorganization effect objectified by the VSA modification. The proprioceptive mechanism could constitute the primary action producing subsequent secondary multimodal spatial realignment of which the amplitude might be measurable in terms of its repercussions on VSA. Our results allow us to put forward the idea that the improvement in the cognitive parameters of spatial neglect could be derived from modified patient VSA, congruent with influential vision of Marc Jeannerod [42,59,60,81].

At this time a sizable number of studies are available that show the extent to which SN management can be improved through PA rehabilitation (see review in: [10,12,15,82]), even if the long-term effects remain to be confirmed by multicenter randomized trials [11]. More studies are also needed to determine optimal frequency and modalities of exposure, maximum amplitude of the prism deviation, and criteria for selection of the patients likely to benefit from this technique rather than from other SN rehabilitation methods. Since in most cases spatial neglect is associated with and tends to aggravate the severity of hemiplegia, hemi-anesthesia or hemianopsia [10], it would be equally interesting to associate PA with other methods targeted at specific rehabilitation of motor or sensory deficits, so as to optimize the remission of disability. The association of complementary methods has been considered for SN rehabilitation in non-randomized studies drawing attention to long-term effects, thereby suggesting a synergy between different strategies [51,83,84]. Cumulative effects have also been achieved by associating PA with vibratory stimulation of the muscles at the back of the neck [85]. Future investigations should help clarify which associations are the most effective and how to select them according to the symptomatic and anatomic profiles of each patient.

Disclosure of interests

The authors declare that they have no conflicts of interest concerning this article.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rehab.2014.10.004.

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