Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect

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A large proportion of right-hemisphere stroke patients show hemispatial neglect—a neurological deficit of perception, attention, representation, and/or performing actions within their left-sided space[1], inducing many functional debilitating effects on everyday life, and responsible for poor functional recovery and ability to benefit from treatment[2]. The frequent parietal locus of the lesion producing neglect reflects the impairment of coordinate transformation used by the nervous system to represent extrapersonal space. Given that adaptation to a visual distortion can provide an efficient way to stimulate neural structures responsible for the transformation of sensorimotor coordinates, the aim of our study was to investigate the effect of prism adaptation on various neglect symptoms, including the pathological shift of the subjective midline to the right. All patients exposed to the optical shift of the visual field to the right were improved on their manual body-midline demonstration and on classical neuropsychological tests. Unlike other physiological manipulations used to improve neglect, this improvement lasted for at least two hours after prism removal and thus could be useful in rehabilitation programmes. The positive effect found for both sensorimotor and more cognitive spatial functions suggests that they share or depend on a common level of space representation linked to multisensory integration.

The manifestations of hemispatial neglect may be temporarily improved by several sensory manipulations (caloric stimulation[3,4], neck vibration[5] or optokinetic stimulation[6]), whereas other manipulations have failed to produce a consistent improvement of neglect[7]. Despite over twenty years of extensive research efforts, however, in all such cases the effects are usually transitory, lasting no more than 10–12 minutes. One classical feature of neglect is a pathological shift of the subjective midline to the right, as measured by straight-ahead demonstration in the dark[8]. Psychophysical manipulations can be used to alter straight-ahead demonstrations in normal healthy subjects. Exposure to an optical alteration of the visual field is known to produce an initial disorganization of visuo–motor behaviour, which can be corrected through visuo–motor adaptation[9]. Such adaptation has been widely used to demonstrate the plasticity of coordinate transformations involved in multisensory and sensori–motor integration[10,11]. One major compensative effect of short-term wedge-prism exposure is a shift of proprioceptive representations, which can be demonstrated by asking subjects to point straight ahead in the dark (see ref. 9, for example). After adaptation, this finger straight-ahead demonstration is shifted in a direction opposite to the optical deviation, indicating that internal visual and proprioceptive 'maps' have been realigned. The aim of our study was thus to investigate the effect of prism adaptation on various neglect symptoms, including the manual demonstration of the subjective midline.

Sixteen right brain-damaged patients with a persistent, left hemispatial neglect participated in the study (nine males and seven females; mean age, 62). All had been admitted to a neurological rehabilitation hospital for a moderate to severe hemiplegia and various degrees of somatosensory dysfunction (see Table 1 of Supplementary Information). All patients were right-handed and had a documented, single unilateral hemispheric lesion, and no past history of previous stroke. None of the patients suffered from impaired vigilance, confusion, general mental deterioration or psychiatric disorders. Testing took place between 3 weeks and 14 months post-onset (average, 9 weeks).

Experiment 1 was aimed at measuring the adaptability of neglect patients to a lateral shift of the visual field. Manual body-midline demonstration was used to evaluate adaptation to base-left wedge prisms (inducing a 10° shift of the visual field to the right) by a simple target-pointing task. A group of eight neglect patients and a group of five control subjects produced 10 straight-ahead pointing trials before and after a short period of adaptation. Figure 1 shows that the patient's mean straight-ahead was initially shifted to the right. Following the adaptation, both patients and controls demonstrated straight-ahead shifts to the left, and thus the patient's pathological deviation was greatly improved. This first result demonstrated that neglect patients can easily adapt to a lateral shift of the visual field to the right, and that prism adaptation, acting against the rightward bias of straight-ahead demonstration (on average), allows these patients to show a close-to-normal post-test performance. (Interestingly, patients did not adapt to a shift of the visual field to the left, whereas normals adapted with the same amount to the left and the right shift.)

Experiment 2 investigated whether prism adaptation could also improve the main clinical manifestations of neglect[12]. Twelve neglect patients were randomly assigned to the prism group and the control group. All patients underwent a similar procedure. A series of traditional neuropsychological tests[2] was performed on three sessions. After the first session (pre-test), patients had to perform the elementary pointing task with the prismatic goggles used in experiment 1, in order to adapt to the visual–proprioceptive discrepancy. Patients in the 'prism' group were exposed to the 10-degree optical deviation to the right. Patients in the control group

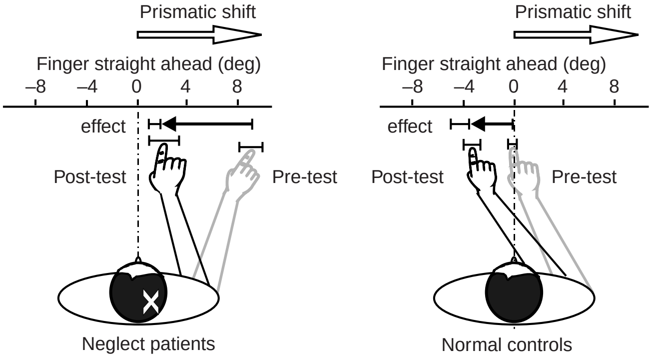

Figure 1 Midline demonstrations. Blindfolded subjects were required to point straight ahead while their head was kept aligned with the body's sagittal axis. Ten pointing trials were run in the pre-test (without goggles) and in the post-test (immediately upon removal of the 10-deg prism (white arrow)). As expected, the midline demonstrations made by the neglect group were initially shifted to the right, whereas control subjects pointed to their actual straight ahead. A two-way repeated-measures analysis of variance with the factors Group ('neglect' vs controls) and Session (pre-test vs post-test) was performed on midline demonstrations (mean of ten responses) obtained for each subject in each condition, and showed a main effect of Session ($P < 0.05$) and a Group by Session interaction ($P < 0.05$) indicating that the two groups were not affected by the prisms in the same way. Additional comparison showed that the differential effect (pre-test minus post-test) was significantly higher in the neglect group ($F(1, 11) = 8.70$; $P < 0.05$). Patients were thus more affected by the adaptation than controls (black arrows), and the magnitude of this effect was less variable in the patients (arrow extensions).

wore neutral goggles with thick flat glasses. Immediately after removing the goggles, a second session was performed with the same battery of tests (post-test). Patients were again tested after a delay of about two hours following the goggles exposure (late test). The standard neuropsychological procedure included: line bisection[13], line cancellation[14], copying a simple drawing made of five items[15], drawing of a daisy from memory, and reading a simple text. All patients in the 'prism' group exhibited a clear improvement following prism exposure. A Group by Session interaction effect ($F(2,8)$, $P < 0.01$) showed that 'prism' and control patients were differentially affected by the goggles exposure. Post-hoc Sheffé's tests demonstrated that the post-test and the late test provided significantly better scores than the pre-test (both $P < 0.05$) in the 'prism' group, whereas no significant difference was found between testing sessions for the control group (both $P > 0.90$). Figure 2 shows results obtained for the Gainotti copying test[15] by one representative patient of each group and the two group values. Figure 3 allows further group comparison for cancellation and bisection tasks. A dramatic improvement was seen in all tests following prism exposure and was fully maintained two hours later. By contrast, there was no significant improvement in the control group.

Unlike other physiological manipulations used to improve neglect, patients demonstrating the classical features of severe visual neglect after right-brain damage showed a strong and reliable improvement after a short adaptation period to a prismatic shift of the visual field to the right. These results indicate that the process of prism adaptation, long considered as a relatively passive process involved in the recalibration of visuo-motor coordination, can also affect the organization of higher levels of spatial representation, such as those impaired in neglect patients. This finding also stands in contrast with the usual specificity of wedge prisms after-effects in normal subjects, found to be arm-specific or even task-specific under several experimental conditions. It should stimulate the search for higher-level after-effects in healthy subjects as well as investigations about why a patient with a lesion of the parietal network may be more permeable to prism adaptation than normals. If prism adaptation can influence higher-level spatial representations, then this result raises an intriguing question regarding the putative causal role of subjective midline shift on the other common features of neglect. In the current debate, such an explanation has been put forward (see ref. 5, for example) but has been challenged by experiments providing evidence for the lack of a consistent relationship between neglect and a change in the egocentric reference[16,17]. The co-occurrence of a positive effect of prism adaptation on the manual straight-ahead (independent of vision) and on conventional tests of visual neglect suggests that a common level of space representation (linked to multisensory integration) may be shared in both sensorimotor (for example, straight-ahead pointing) and more cognitive spatial functions (such as copying, reading). Whether prism adaptation can also improve such higher functions as mental imagery or anosognosia remains to be investigated.

This robust effect of prism adaptation cannot be attributed solely to an effect of attention, nonspecific activation of the right lesioned hemisphere, or improvement of defective left-sided sensory processes, all of which are factors that have been proposed to account for the effect of sensory stimulation on neglect[18]. Rather, it would seem that the improvement of patients depended upon a central mechanism, which may be mediated by a left hemisphere activation[19]. Therefore the effect of the prism is not merely to act as a passive, prosthetic modulator, modifying sensory afferents (see refs 18, 20 for example), but can be conceived of as stimulating active processes involved in the plasticity of sensorimotor correspondences, by activating brain functions related to multisensory integration and space representation. In this respect, our results contrast with those obtained when Fresnel prisms were used to shift the left visual field towards the central retina, rather than to study the effect of adaptation[20]. Under these latter conditions, no significant improvement of neuropsychological testing was observed after the patients kept using the goggles daily during four weeks. A permanent exposure to a shift of the visual field in a direction compensating for the left hemispatial neglect is thus less effective on neglect than the adaptation to this optical deviation, because it produces mainly a sensory, peripheral effect rather than a central effect on space representation.

Two non-exclusive mechanisms can be proposed to account for the strong improvement of neglect after prism adaptation: a general plasticity induction and a lateralized warning signal. First, stimulating the short-term plasticity of brain functions related to coordinate transformations and space representation may favour the neural restoration of the right-hemisphere functions when they have been impaired by a lesion. Indeed, adaptation to visual field reversal is able to induce functional reorganization of early visual processing[11].

Second, a direction-specific mechanism has to be evoked to account for the direction-specific alteration of the egocentric reference seen in experiment 1, and for the overcompensation of neglect observed with the bisection task in experiment 2 (Fig. 3; Schenkenberg test, right side). There is a natural tendency of the brain to compensate for distortions occurring at either the sensory[9] or the motor side[21]. The natural velocity of such processes strongly contrasts with the very slow spontaneous recovery classically observed for hemispatial neglect. Whereas neglect patients are

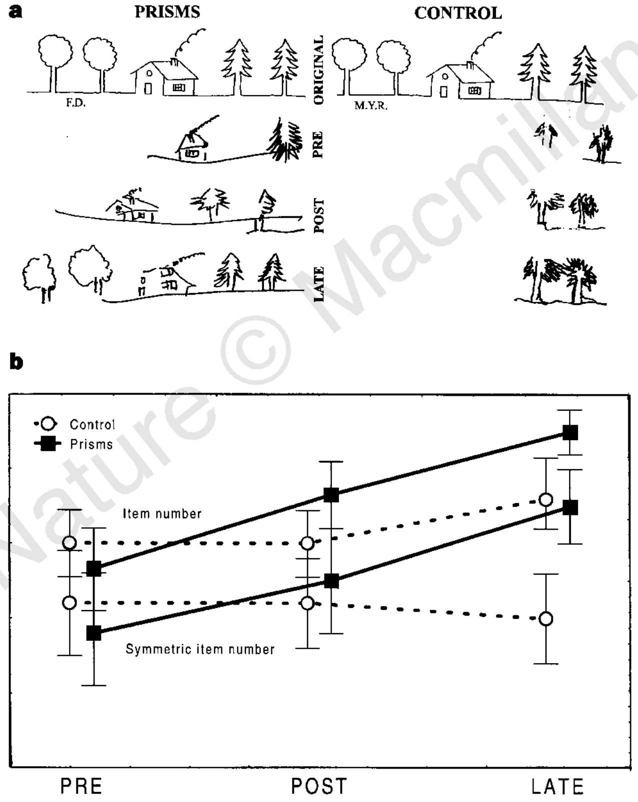

Figure 2 Copying test. One of the classic tests used to assess hemispatial neglect is referred to as the Gainotti test[15], in which the patient is required to copy a drawing made of five items. **a**, A representative example from patient F.D. (left panel) in which the drawing made before prism exposure (pre-test) demonstrates the complete neglect of three items. In the post-test (on prism removal), one item is added to the patient's drawing; in the late test (after 2 h), all items are drawn. By contrast, patient M.Y.R. (right panel) was exposed to neutral goggles and she did not improve in the post and late tests. **b**, The mean number of items drawn (± s.e.m.) and the mean number of items drawn symmetrically (± s.e.m.) in the two groups. Note that these two scores, respectively reflecting space-based and object-based hemineglect, are improved in the same way in the 'prisms' group. No decrease in performance was seen between the post-test and the late test in this particular test, or in others.

typically biased towards the right side, they usually seem to maintain some coherence between various aspects of brain functions related to space, which could prevent them from compensating their biases. The coherent disorganization of space representation in neglect does not seem to produce effective disparity signals, whereas the visual–proprioceptive discrepancy induced by prism exposure alters the coordinate transformations used by the nervous system to represent extrapersonal space. The dramatic improvement induced by prism adaptation suggests that a signal is given to the brain that stimulates the natural recovery process. The main signal for this adaptation is the discrepancy observed between the expected position of the hand and its shifted, seen position as it enters in the visual field. This signal precisely indicates to the subject that his actual action is biased towards the right as compared with his intention. The lateralized information introduced by prism exposure may break the biased coherence and introduce a signal useful for stimulating the correction of left neglect. This should also explain why the neglect patients showed a stronger adaptation than the controls in experiment 1, and a prolonged effect. (Preliminary results suggest that the effect of prism adaptation on neglect may last over four days for the two types of tasks used here.)

Neural structures considered to be involved in prism adaptation have long been restricted to the cerebellar region (reviewed in ref. 22). However, the posterior parietal cortex contralateral to the acting hand might be activated during adaptation to a prism-induced shift of the visual field[19]. Therefore the question arises of the respective contributions of these two brain structures in the sensory realignment and in the more strategic aspects of prism adaptation. Intraparietal areas are well known for being involved in sensorimotor transformations[23]. These early transformations could provide the basis for higher-level spatial representations, including the level of sensorimotor interface required by action planning[24].

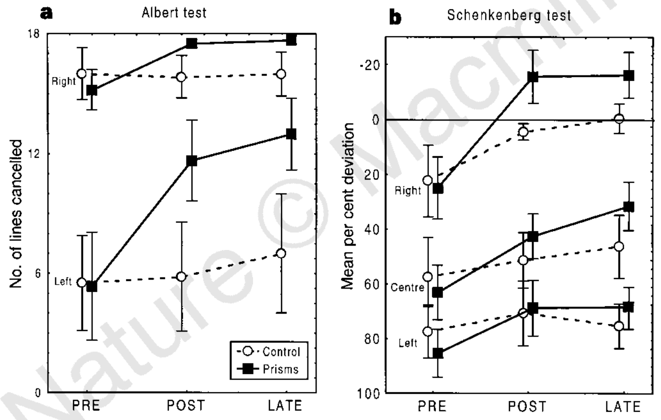

Figure 3 Line cancellation and bisection. **a**, Results obtained by the two groups on a line cancellation task[14] for the two sides of the test sheet (means ± s.e.m.). The results were classic in that patients performed initially less well in the left half than in the right half (pre-test). The 'prism' group is dramatically improved compared to the control group; this positive effect is not reduced after two hours. The analysis of variance performed for this particular test showed a Group by Session interaction ($F(2,20) = 5.98$; $P < 0.05$), and the post-hoc Sheffé's tests revealed that the pre-test differed from the post-test and the late test (both $P < 0.01$), whereas this was not the case in the control group ($P < 0.95$ for both). A difference between the post-test and the late test was not found in either group (both $P > 0.95$). **b**, Results of the two groups in a line bisection task[13] for the three parts of the test sheet. The mean deviation (% ± s.e.m.) is initially shifted to the right in both groups: patients tend to omit lines on the left side (values close to 100%). Following exposure while wearing goggles, this initial deviation is shifted to the left in the 'prism' group. The analysis of variance showed a Group by Session interaction ($F(2,20) = 5.23$; $P < 0.05$), and the post-hoc Sheffé's tests revealed that the pre-test differed from the post-test and the late test (both $P < 0.01$), whereas this was not the case in the control group (for both, $P > 0.25$). Again, no group exhibited a difference between the post-test and the late test (for both, $P > 0.95$). Note that the post and late values obtained in the right side show a deviation to the left, which strongly supports a directional effect of prism adaptation on space representation in neglect patients.

An attractive aspect of prism exposure lies in its non-invasive nature, its acceptability to patients, and its ease of use. In addition, the duration of the effects described here, owing to central active processes stimulated by the adaptation, indicates that this technique may come to have a major role in the neuropsychological rehabilitation of hemispatial neglect. ☐

Methods

Prism adaptation. The prism exposure condition was identical in the two experiments. The goggles were fitted with wide-field, prismatic lenses, creating an optical shift of 10 deg. The exposure period consisted in making 50 pointing responses to visual targets presented 10 deg to the right or left of the objective body midline. During the prism exposure, subjects were asked to point at a fast but comfortable speed; they could see the target, the second half of their pointing trajectory and their terminal error. Their head was kept aligned with the body's sagittal axis by a chin-rest and controlled by an investigator. The duration of this exposure ranged from 2 to 5 min. By contrast with a previous study, which used a shift of only the left half of the visual field to draw attention to the neglected field[13], our experiment evaluated the effect of prism adaptation, and all subjects were subsequently tested without prisms.

Subjects. All patients and subjects were right-handed. Patients presented a unique lesion of the right hemisphere, sparing the cerebellum and other brainstem structures. On computed tomography (CT) scan, 11 cases presented with a cortico–subcortical hypodense lesion involving the right parieto–temporo–occipital carrefour; three cases with a subcortical lesion that included the right capsulo–lenticular region, and two cases with a right frontal lesion sparing the parietal lobe. Neurological examination revealed no optic ataxia, cerebellar dysfunction, somatoparaphrenia. Five patients initially showed an anosognosia for hemiplegia and hemianopia, which had disappeared at the time of testing. Nine patients presented a left hemianopia on the Goldman testing. Patients participating to both experiment 1 and experiment 2 were enrolled with a minimal time interval of one week and in a random order.

Control subjects participating in experiment 1 were inpatients with no neurological history, matched for age (mean: 59.6 years), sex (3/2) and handedness.

Experiment 1. All subjects participating in experiment 1 were randomly subjected to two different wedge prism exposure conditions (base left, base right) with a minimal time interval of two days. The order of presentation was counterbalanced. They were seated blindfolded in front of a horizontal box that permitted measurement of the finger movement endpoints with an accuracy of 1 deg. The cover of the experimental box allowed them to perform free pointing movements without vision of the arm, or with a partial sight of the arm trajectory (exposure condition).

Experiment 2. Five classical tests were used in experiment 2. All testing was carried out in the midsagittal plane. The line-bisection test allowed the computation of three scores, reflecting the bias in bisecting horizontal lines in the right, centre and left part of the testing sheet. The line-cancellation test provided two scores that reflected omissions made in the right and left halves of the page. Two scores were extracted from the copying test, respectively reflecting the number of items drawn by the patient and the number of items drawn symmetrically. Drawings of a daisy made by each patient were ranked from 1 to 3 in order of symmetry quality by two independent judges. The number of word omissions or alterations was counted for each reading performed. This series of tests thus provided nine scores for each session and for each patient. None of these nine scores showed a significant difference between the two groups of patients during the pre-test (all $P \geqslant 0.20$).

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Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness

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Patients with extensive damage to the right hemisphere of their brain often exhibit unilateral neglect of the left side of space. The spatial attention of these patients is strongly biased towards the right[1], so their awareness of visual events on the left is impaired[2]. Extensive right-hemisphere lesions also impair tonic alertness (the ability to maintain arousal)[3–5]. This nonspatial deficit in alertness is often considered to be a different problem from spatial neglect[5,6], but the two impairments may be linked[7,8]. If so, then phasically increasing the patients' alertness should temporarily ameliorate their spatial bias in awareness. Here we provide evidence to support this theory. Right-hemisphere-neglect patients judged whether a visual event on the left preceded or followed a comparable event on the right. They became aware of left events half a second later than right events on average. This spatial imbalance in the time course of visual awareness was corrected when a warning sound alerted the patients phasically. Even a warning sound on the right accelerated the perception of left visual events in this way. Nonspatial phasic alerting can thus overcome disabling spatial biases in perceptual awareness after brain injury.

Attention has at least two components: nonspatial alertness and spatial selectivity[3,5,9,10]. Alertness is a state of general readiness[11–13], whereas selective attention operates to enhance perception at particular spatial locations[14]. Spatial attention may depend on a predominantly right-lateralized cortical network[15,16] that becomes unbalanced following large lesions centred on the right parietal lobe. The resulting stronger activation of the left hemisphere rather than the right hemisphere in the lesioned network biases spatial attention rightwards, producing left neglect[17,18]. Functional imaging data[19] show that sustaining alertness also relies on a right-lateralized cortical network, involving frontal and parietal lobes. Consistent with this, extensive right-hemisphere damage produces a nonspatial deficit in maintaining alertness[4,5,7,8,20–22]. Although the effortful maintenance of tonic alertness over prolonged periods relies on this cortical, right frontal–parietal circuit (which is damaged in neglect patients with extensive right-hemisphere lesions), phasic alerting by salient external events depends instead on ascending thalamic–mesencephalic projections (which should remain intact in such patients)[7,8,10,16,19,23,24]. Hence, it should be possible to phasically activate what remains of the right-lateralized cortical networks for attention and alertness[10] in neglect patients, through alerting events (for example, warning tones). This should effectively shift spatial attention leftwards in neglect patients[7,8], thus compensating for their deficit.

Here we tested this theory by playing occasional warning sounds to phasically alert left-neglect patients, as they performed a task that directly measures their speed of awareness for left visual events relative to right events[2,25]. We predicted that the warning sound should accelerate their perception of left visual events, by shifting attention leftwards because of phasic activation of the damaged right-hemisphere through the intact thalamic–mesencephalic ascending circuit. In every trial, a central fixation cross was presented, followed by a visual bar on either the left or right (see Methods, Fig. 1). This visual bar was followed, at a variable stimulus onset asynchrony (SOA), by a second bar on the other side. The patient had to judge which bar came first. The patients were 'warned' in a random 25% of trials, by a 300-ms central-tone

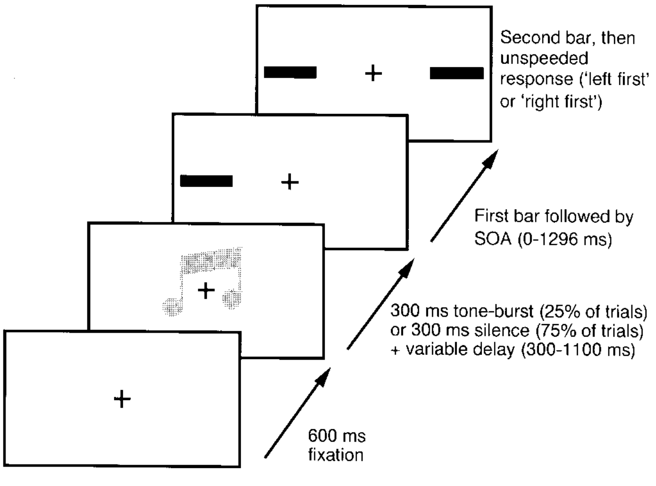

Figure 1 The sequence of events for a single trial, with time running from bottom left to top right. The trial began with the patient fixating the central cross for 600 ms. After a delay, a salient tone of unpredictable pitch sounded in warned trials (as indicated by the musical notation, which was not presented visually, in the second frame); there was silence in the intermingled, and more common, unwarned trials. After a variable, random delay, a visual bar appeared on one side (left in the figure), followed by a bar on the other side at a variable SOA. Both bars then remained until the patient judged verbally whether the left or the right bar had appeared first. In the main experiment, the occasional alerting sounds were always central. In the follow-up study, they were always to the far right of the visual screen.