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Reviews and perspectives

Experimental remission of unilateral spatial neglect

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Abstract

Over the past several decades a growing amount of research has focused on the possibility of transiently reducing left neglect signs in right brain-damaged patients by using vestibular and/or visuo-proprioceptive stimulations. Here we review seminal papers dealing with these visuo-vestibulo-proprioceptive stimulations in normal controls, right brain-damaged (RBD) patients, and animals. We discuss these data in terms of clinical implications but also with regards to theoretical frameworks commonly used to explain the unilateral neglect syndrome. We undermine the effect of these stimulations on the position of the egocentric reference and extend the notion that the positive effects of these stimulation techniques may stem from a reorientation of attention towards the neglected side of space or from a recalibration of sensori-motor correlations. We conclude this review with discussing the possible interaction between experimental rehabilitation, models of neglect and basic spatial cognition research.

Keywords: Unilateral neglect; Vestibular caloric stimulation; Optokinetic stimulation; Prismatic adaptation; Vision; Proprioception; Nystagmus; Attention

Contents

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1. Introduction

Unilateral spatial neglect (USN) is a failure to report, respond, or orient to stimuli that are presented contralateral to a brain lesion, provided that this failure is not due to elementary sensory or motor disorders (Heilman & Valenstein, 1979). Symptoms of this bias range from a slowing in leftward responding to a complete lack of awareness of one half of space, at which point, patients behave as if that half of the world does not exist (Fig. 1). A left neglect syndrome is most commonly observed in right brain-damaged patients and is often dramatic enough to constitute a major handicap (Heilman & Valenstein, 1979; Vallar, 1993). These patients often get lost in familiar environments, repeatedly bump into objects on their left side, and, as a result, often hurt themselves (Bartolomeo & Chokron, 2001).

Over the last few years a number of behavioural experimental remediation techniques have been developed to treat left neglect symptoms in right brain-damaged (RBD) patients. These techniques include training patients in visual (Pizzamiglio et al., 1992; Seron & Tissot, 1973; Weinberg et al., 1977; Wiart et al., 1997) and tactile (Weinberg et al., 1979) exploration, to enhance a voluntary, endogenous orientation of attention towards the left neglect hemispace, and suppressing visual feedback to reduce the pathological rightward attraction of attention (Chokron, Colliot, & Bartolomeo, 2004; Smania, Bazoli, Piva, & Guidetti, 1997). Although these procedures have shown some success in laboratory settings, they often fail to generalize to real-life environments (Heilman, Watson, & Valenstein, 1997).

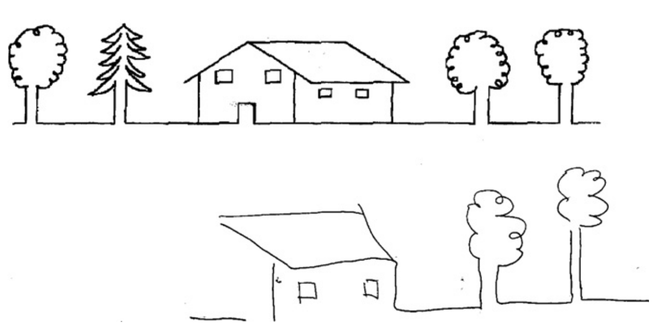

Fig. 1. Copy of a figure by a right brain-damaged patient presenting a left unilateral spatial neglect (top: model, bottom: patient's copy).

Recently, a number of visual, vestibular and/or proprioceptive stimulation techniques have been developed (Karnath, 1994, 1995, 1996; Karnath, Christ, & Hartje, 1993; Karnath, Schenkel, & Fischer, 1991; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990; Robertson & North, 1992, 1993; Vallar, Antonucci, Guariglia, & Pizzamiglio, 1993; Vallar, Bottini, Rusconi, & Sterzi, 1993; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995; Vallar et al., 1995b; Vallar, Sterzi, Bottini, Cappa, & Rusconi, 1990) to treat left neglect. These techniques have been shown to induce transient reductions in left neglect signs during visuo-spatial and imagery tasks involving both extra-personal and personal space. These visuo-vestibulo-proprioceptive stimulation techniques include caloric vestibular stimulation (CVS), optokinetic stimulation (OKS), vibration of neck muscles on the left side, leftward trunk rotation, transcutaneous electrical stimulation (TES) of the left hand or neck muscles, limb activation, and prismatic adaptation (PA). There is some evidence to suggest that these techniques reduce symptoms of anosognosia and somatophrenia (Rode et al., 1992) as well as enhance auto-correction and awareness (Rubens, 1985).

A number of studies have demonstrated that vestibulo-proprioceptive stimulations can affect the position of one's egocentric reference, which is a hypothetical frame of reference used in everyday life to localize objects with respect to one's trunk (see Karnath, 1997; Perenin, 1997 for review). It has been suggested that the spatial bias observed in left neglect patients following a right-sided lesion stems from a rightward deviation of this egocentric frame of reference (Fig. 2). Such a rightward shift would eliminate one's awareness of all objects that occur beyond the left boundary of the shifted or skewed reference frame. This hypothesis has led to a commonly held view that the left neglect syndrome is a disturbance of one's egocentric frame of reference and that vestibulo-proprioceptive stimulations reduce the leftward neglect by restoring a normally oriented spatial frame of reference (Karnath, 1997; Karnath & Dieterich, 2006). However, more recent studies have repeatedly shown that there is no significant correlation between

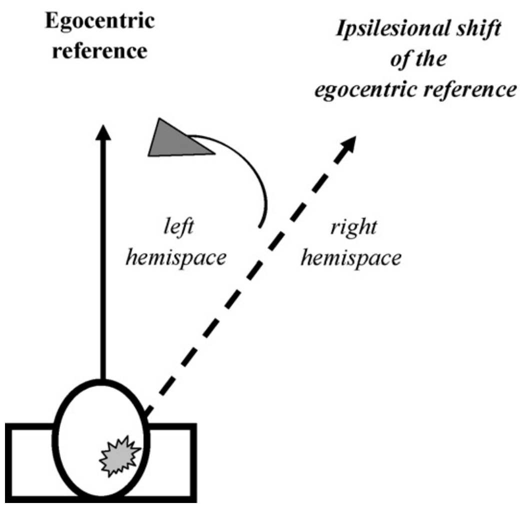

Fig. 2. Egocentric shift hypothesis of neglect. In normal subjects, the position of the egocentric reference (ER) is seen to be superimposed to the sagittal middle. After a right parietal lesion, there would be an ipsilesional deviation of the position of the ER thus defining a new *left hemispace* and *a* new *right hemispace*. The vestibulo-proprioceptive experimental stimulations (CVS, OKS, trunk rotation, neck muscles vibration) are seen to reduce left neglect behaviour by transiently restoring a sub-normal position of the ER (indicated by the arrow).

the position of this egocentric reference and the presence and severity of left neglect signs (see Chokron, 2003 for review and discussion). In light of this, Gainotti (1993, 1996) has proposed an alternative hypothesis which suggests that the positive effects of vestibulo-proprioceptive stimulation stem from a reorientaion of attention towards the neglected side of space rather than a restoration of one's egocentric frame of reference.

Given the profound implications of these stimulation techniques for the remediation of neglect and for elucidating the neural mechanisms and processes underlying spatial cognition, each of the vestibulo-proprioceptive stimulation techniques mentioned above will be critically evaluated in the current review. First, each technique will be presented in terms of the aims, procedures, and main findings of relevant studies that include normal subjects and/or right brain-damaged patients. In addition, Table 1 summarizes the most relevant papers for each technique in terms of population, stimulation and effects. We also discuss studies that have examined vestibulo-proprioceptive responses with electrical stimulation (i.e., cortical and peripheral), electrophysiological (i.e., evoked potentials and single recordings), and/or neuroimaging (e.g., regional cerebral blood flow) paradigms. Following this review of the literature, we will engage in a general discussion that will critically examine the theoretical construct that has been most commonly used to interpret the palliative although transient effects of vestibulo-proprioceptive stimulation techniques in right brain-damaged patients (see above). We then discuss the attentional hypothesis first proposed by Gainotti (1993, 1996) which suggests that the positive effects of vestibulo-proprioceptive stimulation stem from a reorientation of attention towards the neglected side of space rather than a restoration of one's egocentric frame of reference and propose a new hypothesis based on the idea that these stimulations could play a role on a possible recalibration of sensori-motor contigencies. Finally, we conclude with a discussion of how the vestibulo-proprioceptive data fit in with the overall neglect literature and make suggestions for future research.

2. Caloric vestibular stimulation (CVS)

2.1. CVS in normal controls

CVS is a routine diagnostic technique used by neurologists to assess vestibulo-proprioceptive functioning. The technique involves the irrigation of the ear canal with either cold or warm water. In normal individuals, the application of cold water to the ear canal produces a vestibulo-ocular reflex in which the slow phase of the nystagmus moves toward the stimulated ear. Head turning is also induced in the same direction as the slow phase of the nystagmus. These automatic responses are mediated by way of vestibulo-spinal activity. The same effect is obtained only in the reverse direction by applying warm water to the opposite side.

2.2. CVS and rehabilitation in RBD patients

The link between parietal lesions and vestibular defects has been known for a long time. In 1951, Hécaen and coworkers (1951) first reported the existence of a vestibulo-ocular bias in the direction opposite to the side of a brain lesion. In addition, when blindfolded, patients suffering from a right parieto-occipital lesion were unable to maintain their arms in position while pointing straight ahead. Instead, the arms of the patients tended to drift toward the ipsilesional side. When CVS was applied to the labyrinths of these patients, an asymmetrical vestibulo-ocular response was elicited. That is, the slow phase of the caloric nystagmus was stronger when it moved in the same direction as that of the ipsilesional arm drift. The authors also reported on a series of 14 parietal lesion cases following head trauma. A large proportion of these patients presented segmental deviations (e.g., arm drift and Romberg sign), directed as a rule toward the side of the lesion. The authors interpreted these data as reflecting impaired function of the inputs from the vestibular nucleus to the cortex. They reasoned that the lack of integration of vestibular inputs at the cortical level would result in the visuo-constructive deficits observed after right-sided parietal lesions. These deficits would manifest themselves in the misperception of spatial coordinates (Hécaen et al., 1951). This hypothesis has been confirmed via numerous animal lesion studies (see Jeannerod & Biguer, 1987).

The relationship between CVS and neglect was first suggested by Silberpfennig (1949) who observed improvements in reading words during the occurrence of vestibular nystagmus, when the slow component moved to the left, in a right frontal lobe tumor patient with right-sided deviation of gaze. More recently, Marshall and Maynard (1983) also reported improvements of leftward gaze after weekly administrations of left cold caloric irrigation in a patient who demonstrated a fixed gaze deviation to the right several months after suffering from a right hemi-

Table 1
Selection of studies using each kind of experimental stimulation in healthy controls and brain-damaged patients with or without neglect

Reference	Treatment	Procedure	Duration of treatment	Population	Time post-injury	Interval between stimulation and post-test	Absence of effect negative effect (increasing the spatial bias in N+ patients or inducing a spatial bias in controls)	Positive effects (reducing the spatial bias in N+ patients)	Long lasting effects (>1 h)
Rubens (1985) [case study]	CVS	Cold left ear CVS for 1 min followed 30 min after by warm right ear CVS for 1 min and the reverse the next day	One session	Eighteen RBD LN+, five healthy young controls	In the first 2 weeks post-stroke	Before, immediately after, 5 min later, 4–7 days later (for seven patients retested on the line crossing-test)	Left warm-water and right cold-water CVS showed no effect on RBD LN+	Left cold-water and right warm-water stimulation improved, gaze in all RBD LN+. Visual neglect in all RBD LN+ measured by cross line, reading, point and count people around him. Greater improvement after left cold-water than right warm-water stimulation	Return to baseline after 5 min delay Improvement in the line crossing test for the seven patients retested 4–7 days after treatment
Rode et al. (1992) [case study]	CVS	Cold (20°) left ear caloric stimulation for 1 min	Two sessions (48 h interval)	One RBD LN+	Six months post-stroke	Before, immediately after, 1 day after the first stimulation and 2 days after the second one	No effects on: hemianesthesia, hemianopia	Motor deficit: hemiplegia for the left leg, head and gaze deviation, detection of auditory stimuli, visual neglect: line crossing test and detection of visual stimuli, personal neglect, anosognosia, somatoparaphrenia, logorrhea	Informal observation showed improvement after 1 day delay on: anaosognosia, logorrhea
Rode & Perenin (1994) [statistical analysis]	CVS	Cold (20°) left ear CVS for 30 s	One session	Eight RBD LN+, six healthy age-matched controls	Between 3 weeks and 4 months post-onset	Before, immediately after		Representational neglect (mentally evocation of the map of France and name as many towns as possible in 2 min)	Return to baseline few days or few weeks after
Pizzamiglio et al. (1990) [statistical analysis]	OKS	Horizontal background (80 cm × 40 cm) of luminous dots fixed (baseline condition) or moving leftward vs. rightward at a speed of 50 cm/s	One session	Ten RBD LN+, 10 RBD LN, 10 healthy age-matched controls	Up to several month post-onset	During stimulation	Negative effect on spatial bias (40 cm line bisection task) during right OKS	Spatial bias (40 cm line bisection task) during left OKS	
Vallar et al. (1993a) [statistical analysis]	OKS	Vertical background of luminous dots fixed (baseline condition) or moving leftward vs. rightward at a speed of 45° (s^{-1})	One session	Ten RBD LN+, 10 RBD LN, 10 LBD, 10 healthy age-matched controls	Up to several month post-onset	During stimulation	–	Position sense of both arms was improved during left OKS and deteriorated during right OKS	
Bisiach et al. (1996) [statistical analysis]	OKS	Background of alternating yellow and blue vertical stripes fixed (baseline condition) or moving leftward vs. rightward at a speed of 13° (s^{-1})	One session	Ten RBD left neglect patients, 10 RBD patients without neglect	From one to 93 months post-onset	During stimulation	Right OKS deteriorated performance level in line bisection test. left OKS deteriorated performance level of task requiring to set both endpoint of the line only the midpoint was shown	Left OKS induced a leftward bias in line bisection test (reducing the rightward bias of RBD LN+)	
Kerkhoff, Keller, Ritter & Marquardt (2006) [statistical analysis]	R-OKS	Background of leftward moving dots at a speed of 7.5–50° (s^{-1}) vs. visual scanning training (VST)	Five sessions (8 days)	Five RBD LN+ (R-OKS), five RBD LN+ (VST)	>2 months post-onset	Before and after stimulation		R-OKS induced an improvement in line bisection (perceptual and visuo-motor), digit cancellation, visual size distorsion and reading, VST induced an improvement in visuo-motor line bisection only	Improvement 2 weeks later
Karnath et al. (1991) [statistical analysis]	Trunk orienta-tion	Either both head and trunk were centred (baseline condition) or either the head or the trunk was turned 15° to the left vs. to the right (four test conditions)	One session	Four RBD LN patients, 4 LBD patients without neglect, 13 healthy controls	From 20 days to 21 months post-onset	During stimulation	Turning the trunk to the right or turning the head to the right or the left did not affect reaction time of ocular saccades in response to stimuli displayed in the left hemifield	Turning the trunk to the left holding the orientation of all others axes constant improved reaction time of ocular saccades in response to stimuli displayed in the left hemifield	
Chokron & Imbert (1995) [statistical analysis]	Trunk orienta-tion	Either both head and trunk were centred (control group: baseline condition) or the trunk was turned 15° to the left vs. to the right (two exp. groups)	One session	Thirty healthy controls, 1 RBD LN+		During stimulation	Turning the trunk to the left holding the orientation of all others axes constant induced a left deviation on straight ahead pointing task while turning the trunk to the right induced a right deviation in healthy controls	Turning the trunk to the left holding the orientation of all others axes constant induced a left deviation on straight ahead pointing task while turning the trunk to the right induced a right deviation in RBD LN+	
Taylor & McCloskey (1991) [statistical analysis]	Neck muscles vibration	Vibration (100 Hz) of the posterior muscles of the neck (applied below the left occiput just lateral to the spine)	One session	Nine healthy controls		During stimulation		Illusory displacement of a visual target consciously reported, Illusory alteration of head posture (non reported consciously except one participant)	

Karnath et al. (1993) [statistical analysis]	Trunk orientation and Neck muscles vibration	Head and trunk centred (baseline condition) or trunk turned 15° to the left vs. to the right or Vibration (100 Hz) of the left vs. right posterior neck muscles (four test conditions)	One session	Three RBD LN+, 5 LBD RN−, 15 healthy controls	From 3 days to 43 months for LBD patients and from 20 to 54 days post-stroke for RBD LN+	During stimulation	No effects for both control groups. For RBD LN+, turning the trunk to the right or vibrating the right posterior neck muscles induced no effects	Informal observation showed for certain subjects of the three groups illusory displacement and movement of a visual target consciously reported (to the left during right posterior neck muscles vibration and to the right during left posterior neck muscles vibration), Turning the trunk to the left or vibrating the left posterior neck muscles improved visual identification (for two RBD LN+ and visual detection (for one RBD LN+) performance for left visual field stimuli tachistoscopically displayed	
Karnath (1995) [case study]	Neck muscles vibration (NMV) and TENS	Vibration (100 Hz) vs. transcutaneous electrical stimulation (100 Hz) of the left posterior neck muscles (two test conditions) and vibration (100 Hz) of the left-hand muscles (as control condition)	One session	Four RBD LN+	From 5 days to 115 days post-onset	Before, during, after NMV, during transcutaneous electrical stimulation	TENS did not show effect on cancellation test and copying a simple drawing	Vibrating the left posterior neck muscles improved: cancellation test, copying a simple drawing	
Rossetti et al. (1998) [statistical analysis]	PA	Pointing task for about 3 min during exposure to neutral goggle (control group) or to a rightward vs. leftward 10° optical shift of the visual field (two exp. groups)	One session	Sixteen RBD LN+, healthy controls	Between 3 weeks and 14 months post-onset	Before (baseline condition), immediately after, 2 h later	No adaptation in the group submitted to the leftward shift of the visual field.	Improvement after rightward PA on: proprioceptive straight-ahead pointing, line cancellation, visuomotor bisection task, reading a simple text, copying a simple drawing, drawing a daisy from memory	Improvement until 2 h later on all tests
Colent et al. (2000) [statistical analysis]	PA	Pointing task for about 20 min during exposure to a rightward vs. leftward 15° optical shift of the visual field (two exp. groups)	One session	Fourteen healthy controls		Before (baseline condition), immediately after	Rightward or leftward prismatic adaptation did not show effects on visuomotor bisection task, Rightward prismatic adaptation did not show effects on perceptual bisection task	Leftward prismatic adaptation induced a rightward bias on perceptual bisection task	
Girardi et al. (2004) [statistical analysis]	PA	Pointing task for about 20 min during exposure to a leftward 15° optical shift of the visual field	One session	Eleven healthy controls (in exp. 1), 12 healthy controls (in exp. 2)		Before (baseline condition), immediately after	Induction of rightward bias in visual circle centring task, rightward bias in haptic circle centring task, rightward bias in visual proprioceptive pointing task, rightward bias in proprioceptive straight-ahead pointing task, leftward bias in visual straight-ahead estimation task		
Frassinetti et al. (2002) [statistical analysis]	PA	Pointing task for about 15 min during exposure to a rightward 10° optical shift of the visual field vs. no treatment (control group)	Two daily sessions (10 sessions a week) during 2 weeks	Thirteen RBD LN+ (seven in exp. group and six in control group)	From 3 to 27 months post-onset	Before, 2 days after the end of the treatment, 1 week after, 5 weeks after	No significant effect on fluff test (find and remove paper pieces attached to their clothes on the left part of their body), No improvement for one patient who showed no adaptation effect	Improvement on: behavioural Inattention Test (Wilson, Cockburn, & Halligan, 1987), bell cancellation, neglect dyslexia, Room description test (name items seen in the room for 2 min) and objects reaching tests (touch and name all the objects on a table for 2 min)	Improvement until 5 weeks after the end of treatment on all tests
Rode et al. (2001) [statistical analysis]	PA	Pointing task for about 3 min during exposure to rightward 10° optical shift of the visual field	One session	Two RBD LN+, two healthy controls	One month post-onset	Before (baseline condition), immediately after, 24 h later	No effects for healthy controls on mental imagery	Improvement for NL patients on: drawing a daisy from memory, Representational neglect: mental evocation of the France map and name as towns as possible in 2 min, leftward shift in pointing task	Improvement 24 h later on: drawing from memory
Angeli et al. (2004) [statistical analysis]	PA	Pointing task for about 15 min during exposure to neutral goggle (control group) or to rightward 10° optical shift of the visual field (exp. group)	One session	Thirteen RBD LN+ (eight in exp.group and five in control group)	From 2 to 72 months post-onset	Before (baseline condition), immediately after		Improvement on: neglect dyslexia: decrease of reading errors, Leftward shift of the landing position the first ocular saccade, increase of the ocular fixation time on the left part of words and decrease of the ocular fixation time on the right part of words	

CVS: caloric vestibular stimulation, OKS: optokinetic stimulation, ROKS: repetitive optokinetic stimulation, PA: prismatic adaptation, RBD LN+: right brain-damaged patients with left neglect (LN−: without left neglect), LBD: left brain-damaged patients, exp.: experiment, NMV: neck muscle vibration, TENS: transcutaneous electrical neck stimulation.

sphere stroke. This CVS regime resulted in a permanent ability to look to the left and thus to compensate for a left homonymous hemianopia.

The first systematic research on the relationship between unilateral spatial neglect and CVS was conducted by Rubens (1985). Rubens, along with others (Chain, Leblanc, Chedru, & Lhermitte, 1979; Hécaen, 1962; Hécaen et al., 1951; Heilman & Valenstein, 1979) noted that, in the acute phase of visual neglect, patients tend to overtly look and turn away from the defective hemispatial field. Based on this observation, Rubens set out to test if USN is due, at least in part, to a [ipsilesional] bias of gaze and postural turning. He reasoned that, if this were so, then CVS could be used to force eye deviation and past-pointing in the direction opposite to the pathologically acquired bias and hence may reduce signs of visual neglect. Rubens tested this hypothesis on 18 patients suffering from left-sided visual neglect during the acute phase (i.e, during the first 2 weeks) following a right-hemisphere stroke. Rubens monitored a number of measures, including the patient's direction of gaze, their capacity to point to and count people standing around the bed, their ability to read and visually cross lines placed at the patient's bedside, immediately before, during, and immediately after CVS treatment. Moreover, Rubens systematically tested all the possible treatment conditions of CVS (i.e, caloric stimulation was carried out with 20 ml of warm versus cold water on both sides). The order in which the different conditions were administered was counterbalanced across subjects. Results demonstrated a significant improvement on the part of all patients who had a brisk vestibulo-ocular response in their ability to direct their gaze to the left side of space and in their performance on all tests of neglect. The improvement occurred more quickly and was more intense with left ice water than with right warm water stimulation. Unfortunately, within a 5 min post-stimulation period, gaze direction and signs of neglect returned to pre-stimulation levels. Rubens also noted some other intriguing behavioural changes. In the prestimulation period, all the neglect patients began their visual exploration of space at the extreme right, working from right-to-left, and then stopping at, or short of, the midline. During slow phase nystagmus to the left, 14 of the 17 patients changed direction and proceeded from left-to-right as they carried out the task. Ice water stimulation seemed to produce discomfort in all patients even when the left ear was stimulated, but most patients could not say why they were uncomfortable. Immediately after ice water irrigation, all patients seemed more alert, more attentive than before, and performed more quickly on a line crossing task. Patients also became more aware of what they were doing, checking their performance more often. Only a few patients experienced vertigo, oscilloscopia, or some other types of movement related sensation, even during brisk nystagmus.

A number of more recent studies have also investigated CVS as it relates to left unilateral neglect following right brain-damage. Using 20 and 60 ml of ice water, respectively, applied only to the left ear, Cappa, Sterzi, Vallar, and Bisiach (1987) and Rode et al. (1992), demonstrated that following CVS right brain-damaged patients experienced a significant decrease of anosognosia, somatoparaphrenic delusions, and left-sided personal neglect.[1] These studies were the first to investigate the effects of CVS on long-term neglect related phenomena (e.g., anasognosia) that went beyond contralesional visuo-spatial impairments (Rode et al., 1992).

These effects of CVS on tasks that do not involve visuo-spatial control were confirmed by Geminiani and Bottini (1992) and Rode and Perenin (1994) using tasks that require representational imagery (i.e., creating a mental image of a familiar scene). Earlier studies (see Bartolomeo & Chokron, 2001, and Chokron et al., 2004b for review) had demonstrated that the neglect syndrome also extends to visuo-spatial imagery, such that patients with leftward neglect were unable to verbally report on landmarks that occurred to their left while they visualized themselves walking through a highly familiar area of their hometown. Using a similar task Geminiani and Bottini (1992) and Rode and Perenin (1994) showed that applying ice water to the left ear significantly reduced left neglect on a visuo-spatial imagery task in which subjects had to verbally describe the Piazza del Duomo and the map of France.

In addition, in a series of studies, Vallar and colleagues (Vallar et al., 1990, 1993b; Vallar, Guariglia, & Rusconi, 1997) were able to demonstrate that left somatosensory deficits like hemianesthesia or left tactile extinction following stroke can also be improved by left CVS. Along the same lines, Bisiach, Rusconi, and Vallar (1991), investigated the effects of vestibular stimulation on somatoparaphrenic delusion in a patient suffering from a fronto-temporo-parietal infarction located in the right hemisphere. The authors were able to demonstrate a transitory remission of the patient's delusional belief that was consistently observed immediately after unilateral vestibular activation obtained by means of cold-water irrigation of the left (contralesional) ear. This positive effect of CVS on somatosensory deficits led the authors to suggest that these deficits may also be manifestations of the neglect syndrome that could also be sensitive to CVS.

Together, studies investigating CVS have provided strong evidence to suggest that this technique represents an effective way to ameliorate, although only transiently, contralesional visuo-spatial deficits that apply to extrapersonal, personal or representational space and also to somatosensory deficits. Interestingly, the positive effects of CVS on somatosensory impairment imply that these deficits may also be, at least in part, attentional (i.e., part of the neglect syndrome) rather than perceptual-motor (i.e., manifestations of primary sensory or motor impairment) in nature. As we will further discuss in the last section, the positive effects of CVS on non-visual manifestations in left neglect patients, such as somatoparaphrenic delusion or somatosensory deficits challenge any explanation restricted to an enlargement of visual orientation to the left hemispace due to the nystagmus.

[1] Anasognosia refers to the patient's lack of awareness of his own deficit. The somatophrenic delusion refers to a misrepresentation of the left half of the body. For example, when asked to point to their left arm with their right hand, left neglect patients commonly answer that their left arm is gone or outside of the examination room. Personal neglect corresponds to neglect behaviour for the left half of the patient's body or personal space. Patients suffering from left personal neglect usually do not attend (i.e., shave) the left half of their face.

2.3. Neurophysiological correlates of CVS

On the basis of neurophysiological studies, in monkeys and humans, several cortical projection areas for vestibular afferents, that are thought to mediate CVS, have been proposed. A number of studies using monkeys have all implicated the parietal lobe as being the primary projection area of vestibular inputs (Buttner & Buettner, 1978; Ödkvist, Schwarz, Fredrickson, & Hassler, 1974; Schwarz & Fredrickson, 1971). For example, cortical vestibular projections were studied by measuring single cortical neuronal activity (Buttner & Buettner, 1978) and evoked potentials (Fredrickson, Scheid, Figge, & Kornhuber, 1966; Schwarz & Fredrickson, 1971) following electrical stimulation of the vestibular nerve. These studies suggested that a cortical projection from the vestibular nerve is located in area 2 of the parietal lobe. On the other hand, using evoked potentials, Ödkvist and co-workers (1974) found cortical activation of area 3 in the parietal lobe, again following vestibular nerve stimulation. Some monkey studies have also reported a vestibular projection to the retroinsular cortex (parieto-insular-vestibular cortex: PIVC) (Akbarian, Grusser, & Guldin, 1993) in which the PIVC neurons behave like polymodal vestibular units. It should be noted that the primary vestibular area and the retro-insular cortex have been implicated as playing a critical role in orienting one's head in space (Akbarian et al., 1993; Fredrickson et al., 1966).

In contrast to the animal studies cited above, Penfield and Jasper (1954) found that electrical stimulation of the superior temporal gyrus in humans evoked a "true" vestibular sensation. Friberg et colleagues in 1985 (Friberg, Olsen, Roland, Paulson, & Lassen, 1985) examined regional cerebral blood flow (Xenon-33 method) in normal human subjects during CVS. In this study, the authors estimated that the location of the primary vestibular cortical area to be a little above and posterior to the auditory cortex within the temporal lobe, but bordering on the parietal lobe. Moreover, the same location was confirmed in all individuals, irrespective of the hemisphere examined.

Using positron emission tomography, (PET), Bottini et al. (1994) measured regional cerebral perfusion in humans with various vestibular stimulation techniques in order to map the central vestibular projections and to investigate the cerebral basis of spatial disorientation. The temporo-parietal cortex, the insula, the putamen, and the anterior cingulate cortex were found to be the cerebral projections of the vestibular system in humans. In addition, by using fMRI during CVS, Suzuki et al. (2001) found that vestibular stimulation increased neural activity in the intraparietal cortex. Notably, vestibular stimulation with cold water in the right ear induced activation of the same anatomical structures activated by cold vestibular stimulation in the left ear, but in the opposite hemisphere. Along those lines, using fMRI during vestibular stimulation in healthy subjects, Dieterich and co-workers (Dieterich et al., 2003) showed an asymmetric pattern of activation across the hemispheres. Cortical activation during CVS seems to be dependent upon three factors: the subject's handedness, the side of the stimulated ear and the direction of the induced vestibular symptoms. As a matter of fact, these authors demonstrated that activation was stronger in the non-dominant hemisphere, in the hemisphere ipsilateral to the stimulated ear, and in the hemisphere ipsilateral to the fast phase of the vestibulo-caloric nystagmus.

3. Optokinetic stimulation (OKS)

3.1. OKS in normal controls

The vestibular system may be viewed as a sensor of head accelerations that cannot detect motion at constant velocity, and thus requires supplementary visual information (Brandt and Dieterich, 1999). Visual perception of self-motion induced by large-field optokinetic stimulation is thus essential. Vestibular stimuli invariably lead to the sensation of body motion. Stimuli of visual motion, however, can always have two perceptual interpretations: either self-motion or object-motion. The subject who observes moving stimuli may perceive either himself as being stationary in space (egocentric motion perception) or the actually moving surroundings as being stable while he is being moved (exocentric motion perception). Visual self-motion can be perceived while gazing at moving clouds or a train moving on the adjacent track in a train station. Vestibular information about motion is elicited only through acceleration or deceleration; it ceases when the cupulae within the semicircular canals or the otoliths have returned to their resting position during constant velocity (see for review, Brandt and Dieterich, 1999). Our perception of self-motion during constant-velocity car motion is completely dependent on optokinetically induced vection. In natural settings, the vestibulo-oculo reflex (VOR) is functionally and synergistically coupled with the optokinetic response (OKR). This interaction favours gaze stabilisation on visual targets during head–body rotation. As we will describe below, optokinetic stimulation (OKS) induces the VOR which can be used either for clinical purpose, in order to assess vestibulo-proprioceptive functioning or as presented here as an experimental technique.

The technique involves the presentation of a visual moving stimulus (i.e., background moving in a given direction across the screen) which triggers a nystagmus in which the slow phase is coherent with the movement of the triggering stimulus and the quick phase reverts eyes to the initial point of fixation (Howard & Ohmi, 1984). In normal individuals, the function of this reflex is to maintain a constant image of the moving stimulus on the retina as the stimulus moves though external space. In contrast to CVS, OKS evokes a continuous (tonic) signal from the retina rather than a phasic labyrinthine signal. For this reason, OKS effects do not decay after 20–30 s, as is the case with with vestibular reflexes, but can be generated over long periods of time.

3.2. OKS and rehabilitation in RBD patients

The first study to examine the effects of OKS in RBD patients was conducted by Pizzamiglio and co-workers (1990). These authors sought to investigate the possibility of inducing a shift in the spatial coordinates of normal individuals and in brain-damaged subjects without neglect, as well as, realigning the spatial coordinates of neglect patients (i.e., correcting their spatial bias), by exposing them to OKS. Pizzamiglio and co-workers measured the displacement of the subjective midpoint produced by a moving background while subjects conducted a line bisection task in which they were asked to simply mark the midpoint of a visually presented line.[2] Their results can be summarized as follows. First, OKS entailed a displacement of the subjective midpoint in the same direction as the moving background. This effect was observed for all subject groups for both directions of movement. The presence of a focal brain lesion without neglect did not increase or modify the OKS effect from that observed in normal subjects. In contrast, neglect patients were more susceptible than normal and brain-damaged (without neglect) subjects to the influence of the OKS. Also, in neglect patients, the displacement toward the right side tended to be greater than the displacement toward the left side. Further, these data also showed that those neglect patients who demonstrated greater impairment in space exploration, as assessed by the degree of error in the line bisection task without movement, also were more susceptible to the influence of OKS in displacing their subjective midpoint in either direction.

In the Pizzamiglio study, 13 out of the 33 neglect patients were re-tested after 1 week. Results demonstrated that the effect of OKS on line bisection remained constant in most of the neglect cases. The correlation between the results of the two test sessions was 0.85 for the rightward and 0.64 for the leftward OKS conditions.

In a subsequent series of studies, Pizzamiglio et al. (1990) and Vallar and colleagues (Vallar et al., 1993a; Vallar et al., 1995a), examined the effects of OKS on position sense in right brain-damaged patients with left neglect (RBDN+ patients), right brain-damaged patients without left neglect (RBDN− patients), and left brain-damaged patients without neglect (LBD patients). Results from these studies (Vallar et al., 1993a; Vallar et al., 1995a) showed that OKS did affect the position sense of only the RBDN+ group. Moreover, position sense errors were directional in that movement in the leftward direction improved accuracy, while movement in the rightward direction brought about a major decline in performance. Vallar and co-workers concluded that in patients with neglect, the disorder of position sense is produced at least in part by a shift of the egocentric reference system into the ipsilesional side of space.

Karnath (1996) also examined the effects of OKS on pathological perception of body position in space. Three patients with right hemisphere damage and unilateral neglect were asked to direct a laser pointer to the position which they felt falling exactly "straight ahead of their body's orientation". Results demonstrated that without stimulation all three patients localized the sagittal midplane of their bodies markedly to the right of the objective midpoint. However, while undergoing OKS, the subjective horizontal displacement of the sagittal midplane was reduced only when the stimulus moved to the left. Performance worsened with rightward movement.

Although the above cited studies all demonstrate a transient reduction of neglect due to OKS, Bisiach, Pizzamiglio, Nico, and Antonucci (1996) suggested that the effect of OKS may simply reflect a temporary suppression or mitigation of neglect symptoms without restoring the underlying spatial representation of the patients (i.e., restoring the neural circuits involved to a normal functional level). They addressed this question by requiring RBD patients with and without left neglect to execute a modified line bisection task during leftward or rightward OKS. Based on the midpoint of an imaginary line with a specific horizontal length, subjects were required to mark the imaginary line's end-points. During rightward movement, left neglect patients most frequently misplaced the end-points leftwards. When the task was executed during leftward OKS, the disproportion increased instead of vanishing. In addition, confirming previous findings (Pizzamiglio et al., 1990), neglect patients were abnormally susceptible to OKS whatever its direction, as compared to patients without neglect.

Based on the positive but transient effects of OKS above-mentioned, Kerkhoff (2001) and Kerkhoff et al. (2006) tested if repetitive OKS (R-OKS) could provide long term positive effects in RBD patients with left unilateral neglect. The authors described a multimodal (visual and auditory) improvement after five sessions of OKS (45 min each) delivered in a period of 2 weeks and this improvement was found to be stable after a 2-weeks follow-up. In the more recent study (Kerkhoff et al., 2006) the improvement after R-OKS was found to be more efficient than conventional visual scanning training using static visual displays.

3.3. Neurophysiological correlates of OKS

A number of studies have investigated the neurophysiological basis of OKS in both monkeys and humans. Using a single cell recording technique, Kawano (Kawano & Sasaki, 1984; Kawano, Sasaki, & Yamashita, 1984) has conducted a series of studies in macaques that have demonstrated that area 7a contains neurons that fire selectively in response to OKS, but not during smooth pursuit eye movements. Further a number of studies in monkey have also demonstrated that visual areas MT and MST in the superior temporal sulcus, which are commonly known to be involved in visual motion processing, show an enhancement of activity for both OKS and smooth pursuit eye movements (Dürsteler & Wurtz, 1988; Komatsu & Wurtz, 1988a, 1988b; Newsome, Wurtz, & Komatsu, 1988). In primates, it has been shown that unilateral lesions of the inferior parietal lobule (IPL) and peristriate cortex produce a significant reduction of the speed of the ipsilesional optokinetic slow phase nystagmus (Lynch & McLaren, 1983). Human studies of OKS have also revealed that parietal lesions, particularly when they extend into white matter regions, impair the slow phase of the optokinetic nystagmus in the ipsilesional direction. The ipsilesional optokinetic nystagmus impairment was associated with normal voluntary and reflex saccades (Baloh, Yee, & Honrubia, 1980). Similarly, Incoccia and colleagues (Incoccia, Doricchi,

[2] In the line bisection task, the subject is asked to mark the midpoint of a visually presented line.

Galati, & Pizzamiglio, 1995) found that left neglect patients with right brain damage centred around area 37 and with partial extension of the lesion to areas 19, 39, and the underlying white matter, also suffered an impairment of the optokinetic slow phase nystagmus. In addition to the slow phase component, these patients also demonstrated a reduction in the amplitude and speed of the quick phase component. Together with the animal studies cited above, these human data suggest that parietal damage results primarily in a reduction of the optokinetic slow phase nystagmus which is directed ipsilaterally to the lesion (Lynch & McLaren, 1983).

Using fMRI, Boileau et al. (2002) investigated the overlap of activity between optokinetic stimulation and a task of midline computation. Results confirmed that the right posterior parietal and frontal cortices were involved in both tasks ($p < 0.0001$). In the same vein, Bense et al. (2006), recently used fMRI to investigate (1) whether stimulus direction-dependent effects can be found, especially in the cortical eye fields, and (2) whether there is a hemispheric dominance of ocular motor areas. In a group of 15 healthy subjects, optokinetic nystagmus in rightward and leftward directions was visually elicited and statistically compared with the control condition (stationary target) and with each other. Direction-dependent differences were not found in the cortical eye fields, but an asymmetry of activation occurred in paramedian visual cortex areas, and there were stronger activations in the hemisphere contralateral to the slow optokinetic nystagmus phase (pursuit). Furthermore, and contrasting with the preponderance of left neglect after right hemisphere damage, no hemispheric dominance for optokinetic nystagmus processing was found in right-handed volunteers.

4. Trunk rotation (TR)

4.1. TR in normal controls

Trunk rotation has been proposed as another method by which one's egocentric reference frame can be displaced in normals or transiently realigned in neglect patients while performing various visuo-spatial tasks (Bradshaw, Nettleton, Pierson, Wilson, & Nathan, 1987; Chokron & Imbert, 1995). The use of trunk rotation for this purpose is based on the notion first proposed by Ventre, Flandrin, and Jeannerod (1984) that external objects in space are represented within the organism in terms of an internal egocentric reference frame that is aligned along the midline or longitudinal axis of the body. It is thought that this egocentric reference frame, superimposed on the mid-sagittal plane, divides the corporeal and extracorporeal spaces into left and right hemispaces (Jeannerod, 1988; Jeannerod & Biguer, 1987). Chokron and Imbert (1995) and Chokron, Colliot, Atzeni, Bartolomeo, and Ohlmann (2004a) by asking normal subjects to point straight ahead while blindfolded have confirmed that the orientation of the trunk in space divides our normal space into egocentric "left" and "right" and may thus determine the "neglected" contralesional space. In these studies the authors imposed a leftward or rightward trunk rotation while the head remained fixed and found that normal subjects pointed in the orientation of the trunk position, with a relatively good accuracy.

4.2. TR in RBD patients

To evaluate the effects of trunk rotation with respect to displacements in the egocentric reference frame commonly observed in neglect patients, Karnath et al. (1991) manipulated trunk relative to the head positions of right brain-damaged patients with neglect (RBDN+) while studying saccadic reaction times (SRT). Their aim was to examine whether the midline of the trunk and/or head serves as a plane for dividing space into a "right" and "left" sector, and thus forms the basis for the neglected controlateral vs. normal ipsilateral side of neglect patients. This study was conducted among four RBDN+, four left brain-damaged (LBD) patients, and 13 normals. The subject's trunk and head were either rotated together or the trunk was rotated 15° to the left or right relative to the position of the head. Alternatively, the subject's head could be deviated 15° left or right relative to the trunk. Results of the study demonstrated that when head, trunk, and visual fields were aligned and corresponded to the middle of the projection screen, SRTs were longer in the left visual field (LVF) compared to right visual field (RVF). However, the LVF deficit could be compensated for by solely turning the trunk of the patients to the left while holding the orientation of the head and visual fields (aligned and corresponding to the middle of the projection screen). In contrast, turning the head to the left side relative to the trunk did not compensate for the LVF deficit. Moreover, LBDs and normal controls did not show the compensatory effects of trunk rotation on SRT. This study demonstrates that in left neglect patients the trunk position in space may determine the boundaries of the neglected field. This confirms that USN may be defined in egocentric coordinates.

5. Transcutaneous mechanical muscle vibration (TMV)

5.1. TMV in normal controls

An organism's ability to execute coordinated movements requires that ongoing information about muscle length be transmitted to the vestibulo-proprioceptive system. In normals, precise information about muscle length is signaled via the discharge rate of muscle spindle afferents. Moreover, when a muscle or its tendon are made to vibrate, the afferent discharge of the muscle spindle increases. While this increased firing rate is interpreted by the proprioceptive system as a lengthening of the muscle, muscle length actually remains constant. Thus, in normal subjects, transcutaneous mechanical muscle vibration (TMV) produces illusory sensations of the position and shape of body parts (Goodwin, McCloskey, & Matthews, 1972; Lackner & Levine 1979). Moreover, Lackner (1988) was able to show that a visual target attached to a fixed limb also appears to move when the limb muscles are vibrated. Similarly, when left neck muscles are vibrated, normal subjects experience illusions of rightward displacement and movement of visually presented targets (Biguer, Donaldson, Hein, & Jeannerod, 1988; Taylor & McCloskey, 1991). Under such conditions, normal subjects also show a leftward displacement of their subjective midline when asked to stop the displacement of a point in front of their subjective straight ahead (Karnath et al., 1993). However, Rorden, Karnath, and Driver (2001) demonstrated that this egocentric deviation was not associated to a bias in covert orienting of attention in normal subjects, which argues against explanations of neglect solely in terms of a pathological misperception of body orientation as we will further discuss.

5.2. TMV and rehabilitation in RBD patients

Based on the illusory effects of neck muscle vibration observed in normals (see above), some authors have proposed that this illusional effect may reflect a displacement of one's egocentric visuo-spatial frame of reference. More specifically, it was hypothesized that similar to the stimulation techniques already discussed, left neck muscle vibration should improve left visuo-spatial neglect in RBD patients displacing the egocentric coordinates leftward. Such a leftward displacement during vibration would run counter to the rightward pathological displacement of these egocentric coordinates following a right hemisphere lesion (Karnath et al., 1993; Vallar et al., 1995b).

Based on the transcutaneous muscle vibration findings (see above), Karnath and co-workers (1991) reasoned that the compensatory effects of deviating the trunk (i.e., 15° to the left) relative to head/eye position on left-sided saccadic reaction times in RBDs with neglect (see above) were due to the fact that turning the trunk under these test conditions led to a lengthening of left posterior neck muscles. Moreover, they reasoned that if this hypothesis is correct, then it should be possible to induce a remission of neglect not only by turning the trunk relative to the head to the contralateral side, but also by vibrating the contralateral posterior neck muscles, since both of these conditions would induce the same afferent signal. Karnath et al. (1993) tested this hypothesis in 3 RBDLN+ patients, 5 LBD patients and 15 non brain-damaged dermatological patients.

The procedure used in this study was the same as the one described above (Karnath et al., 1991), only in addition to trunk orientation, they tested the effect of left and right neck muscle vibration, and compared each experimental condition to three control conditions: baseline (no vibration, no rotation), left hand vibration, and turning the head 15° to the left. Posterior neck muscles were vibrated during a visuo-spatial detection task. In terms of the RBDN+ patients, results demonstrated an improvement in the neglect patients' performance, both while turning the trunk and vibrating left neck muscle, that seemed independent of the presence of a conscious illusion of movement and displacement of the visual stimuli. Although the compensatory effect of the vibration could be seen in all three patients, only one reported a visual illusion. Curiously, there was no worsening of the deficit in left neglect patients either when the trunk was rotated to the right or when right neck muscles were vibrated. According to these authors, these findings indicate that trunk rotation and neck muscle vibration may act on left neglect signs by manipulating the position of the egocentric reference via proprioceptive inputs.

6. Transcutaneous electrical neural stimulation in RBD patients (TENS)

In the same vein, Vallar et al. (1995b) tested the effect of transcutaneous electrical neural stimulation (TENS) on left neglect signs. This stimulation technique provides a somatosensory input to the vestibulo-proprioceptive system. The main clinical application of TENS has been for pain relief, and suggestions have been made that this effect involves the stimulation of larger myelinated cutaneous afferent fibres (α and β), and local spinal non-opiate mediated mechanism (Tardy-Gervet, Gilhodes, & Roll, 1989). Vallar et al. (1995b) hypothesized that if TENS provides proprioceptive inputs through large diameter afferents, then similar to transcutaneous mechanical vibration, this form of stimulation should positively affect left neglect. Fourteen RBDN+ patients performed a letter cancellation task while applying transcutaneous electrical stimulation to neck muscles. Thirteen patients improved when the left neck muscle was stimulated, even when head movements were prevented by a chin-rest. Conversely, stimulation of the right neck had no positive effect, rather it worsened exploratory performance in nine patients. Moreover, in contrast to the findings of Karnath (1995) using muscle vibration, stimulation of both the left hand and the left neck, had comparable positive effects on visuo-spatial hemineglect.

In a subsequent study, Vallar et al. (1997) tested the effect of TENS on contralesional tactile perception deficits, in 10 RBD patients and 4 LBD patients. Transient somatosensory improvement was noted after stimulating contralesional neck in all RBD patients, both with and without left somatosensory neglect, and in one LBD patient with right somatosensory neglect. In three LBD patients without neglect, the treatment had no detectable effects. In one RBD patient, stimulation of the ipsilesional neck temporarily worsened the somatosensory deficit.

This pattern of positive results is similar to that found in patients with hemineglect by using vestibular and optokinetic stimulations producing a nystagmus with leftward slow phase. Also, the finding that stimulation of the right side of the neck tends to worsen exploratory performance agrees with the results of studies using vestibular and optokinetic stimulations bringing about a nystagmus with a rightward slow phase. Unfortunately, unlike above-mentioned stimulations but like prismatic adaptation, we will not present the neurophysiological correlates of this stimulation which remain unclear.

7. Limb activation in RBD patients

Twenty years ago, Joanette, Brouchon, Gauthier, and Samson (1984, 1986), demonstrated that when using the left hand in manual pointing, left neglect patients exhibited better performance than when using the right hand. Subsequently, Robertson and co-workers (Robertson & North, 1992, 1993; Robertson, North, and Geggie, 1992) also showed that left neglect patients can be ameliorated during active movements of the contralesional limb in the contralesional hemispace. More specifically, the most beneficial effect was obtained when moving left fingers in the left hemispace without any visual feedback. These findings argue in favour of the close link between visual attention and motor function and confirm Rizzolatti's premotor theory of neglect. Spatial attention would not be a supramodal function controllong the whole brain but rather a modular function present in several independent circuits. According to this theory and in agreement with Robertson's findings, activating the premotor circuits of the damaged hemisphere may in some way facilitate the sensory cells connected with them, and hence improve perception in the neglected hemispace. Many of the stimulations presented here share in common this close link between motricity (gaze, limb activation, visuo-motor adaptation) and attention, for this reason we will further develop this point in the discussion section.

8. Prismatic adaptation (PA)

8.1. PA in normals

It is possible to optically alter the surrounding visual field by asking subjects to wear goggles fitted with wide-field, prismatic lenses creating an optical shift (usually about 10°). Exposure to such an optical alteration of the visual field is known to produce an initial disorganization of visuo-motor behaviour. This disorganisation can be assessed by asking subjects to perform a coordination task, e.g., target pointing. Usually, when people perform this kind of task while wearing prismatic lenses, the pointing error is initially large but quickly declines because of visuo-motor adaptation (Redding & Wallace, 1996). One major compensatory effect of short-term prismatic exposure is a shift of the egocentric reference which can be demonstrated by asking subjects to point straight-ahead in an open loop (Rossetti et al., 1998). Colent, Pisella, Bernieri, Rode, and Rossetti (2000) employed this protocol on 14 normal subjects which were divided in 2 groups in order to test opposite prismatic shifts of visual field on perceptual and visuo-motor bisection tasks. Results indicated a rightward deviation of the subjective middle in visual line bisection following prism adaptation to leftward optical shift. In addition, no bias was produced after rightward prismatic shift adaptation despite explicit measures of after-effects. Given the leftward specificity of visuo-motor adaptation and the perceptual predominance of these effects, the authors concluded that this directional shift mimics the spatial bias observed on left neglect patients. These results were subsequently confirmed by Michel et al. (2003) and prompted Girardi, McIntosh, Michel, Vallar, & Rossetti (2004) to extend this result to spatial haptic judgements. They assessed the subjective centre estimation of haptically explored circles on 11 normal subjects before and after exposure to leftward optical shift of field. Performances indicated rightward deviation suggesting that prismatic adaptation may affect sensori-motor level as well as higher levels of spatial representation. Using a landmark task with normal participants, Berberovic and Mattingley (2003) also confirmed the presence of a rightward bias in peripersonal space following leftward prismatic adaptation and a leftward deviation of the subjective sagittal midline whereas the right shift prismatic adaptation did not produce any deviation of the perceptual estimation of the centre of line. According to the authors, these results suggest that both straight-head pointing and landmark judgments were performed using different frames of reference which would be differentially affected by prismatic treatment. Finally, exploring eye movements during emotional expression judgments, Ferber and Murray (2005) showed that prismatic adaptation produces a bias in the pattern of oculomotor exploration of a scene in healthy participants. This bias occurred toward the right hemispace without affecting the leftward perceptual bias in judgements about happy/neutral chimeric faces. The authors thus assumed that a change in the oculo-motor pattern of exploration can occur in the absence of any change in higher cognitive spatial representations.

8.2. PA in RBD patients

Given that adaptation to a visual distortion can provide an efficient way to stimulate neural structures responsible for the transformation of sensory motor coordinates, the aim of Rossetti et al. (1998) was to investigate the effect of prismatic adaptation on left neglect signs. After exposition to wedge-prisms that shifted the optical field 10° to the right, left neglect patients were improved in a straight ahead pointing task and on classical neuropsychological tests (copying test, line cancellation, line bisection test). Unlike the short-lived remission induced by both CVS and OKS, this improvement lasted for at least 2 h after prisms removal. More recently, it has even been shown that these benefits may persist over a period ranging from 4 days (Pisella, Rode, Farne, Boisson, & Rossetti, 2002) to 5 weeks (Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002) which is the longest lasting effect observed among all the experimental stimulations presented here.

A positive feature of this method was large gains compared to the brief period of visuomotor adaptation. For instance, Rossetti et al. (1998) registered immediately after treatment benefits corresponding to about 7° leftward shift in straight head pointing, thus correcting the initial rightward shift. Since this seminal study, an increasingly important amount of research had focused on this visuomotor adaptation procedure regarding its possible implications on neglect recovery and understanding its therapeutic effects. An important consideration was the direction-specific effect of prismatic adaptation: beneficial effects were only observed following adaptations to rightward visual shift and not for leftward ones (Rossetti et al., 1998; Tilikete et al., 2001). In addition, prism exposure had shown regression of neglect signs only when adaptation to lateral deviation of visual field (confirmed by explicit measures of after effects) was obtained. Recently, Vallar, Zilli, Gandola, & Bottini, (2006) tested the effects of prism adaptation on omission errors, on rightward perseveration and on other graphic productions in a line cancellation task in nine right brain-damaged patients with left unilateral spatial neglect. In this study, prism adaptation improved both neglect, as indexed by omission errors, and perseveration behaviour, up to a delay of 60 min.

Effects of prismatic adaptation are not limited to clinical measures of neglect. In a recent study, Tilikete et al. (2001) have shown that improvement extends to postural control, such that the lateral displacement of centre of pressure measured by posturographic evaluation was reduced after prismatic adaptation. On the other hand, Rode, Rossetti, and Boisson (2001) generalized the effects of prism exposure over mental imagery. Two RBD patients with left unilateral neglect were asked to name towns during mental map exploration. Immediately after adaptation treatment, results revealed an increasing number of towns located on the left part of the map, but these effects did not last up to 24 h after prismatic adaptation. In addition, eye movements were not controlled and it was thus impossible to assess the effect of a possible leftward ocular exploration while performing the task. As we will further develop in the discussion section, given the fact that visual parameters such as visual feedback or eye position have been shown to influence the exploration of mental representations (Anderson, 1993; Chokron et al., 2004a; Chokron et al., 2004b), one cannot exclude that the positive effect of PA even in representational tasks is not linked to the compensatory leftward gaze deviation pattern (see Serino et al., 2006 for discussion).

McIntosh, Rossetti, and Milner (2002) assessed non-visual components of neglect in order to address the assumption that higher levels of spatial representations may be affected by adaptation treatment. They reported a single case study of a severe case of left neglect with 9-months chronicity. Results confirmed beneficial effects of treatment across many visuo-spatial tests of neglect, like star cancellation, scene copying and line bisection as well as in haptic spatial judgements. Indeed, when the patient was asked to estimate the centre of a haptically explored circle, a decrease of the rightward lateral deviation was observed 2 h post-treatment. These findings were confirmed and extended by Maravita et al. (2003). These authors have demonstrated a decrease in tactile extinction during bilateral stimulation following a 10-min period of visuomotor adaptation to 20° rightward shift of the visual field. More recently, Angeli, Benassi, and Ladavas (2004) have tested the effect of prismatic adaptation to the ipsilesional oculo-motor bias exhibited by some left neglect patients. The eye movements patterns of eight left neglect patients were recorded during reading. Results indicated a decrease of neglect dyslexia signs, with a reduction of reading errors after prismatic adaptation, as well as a positive effect on oculo-motor patterns during reading. According to the authors, the reduction of the oculo-motor bias observed in left neglect patients may stimulate low-order visuo-motor processes which may, in turn, induce a reorganization of higher-order spatial processes. Along the same lines, Serino and co-workers (2006) recently investigated the positive effects of PA on left neglect signs in conjunction with eye movement analysis. These authors found a significant correlation between leftward oculomotor deviation produced by PA and recovery of neglect. As a matter of fact, they observed that in left neglect patients, the greater the leftward deviation of the first saccade, the greater the imporvement in visuo-spatial tasks. According to Serino et al. (2006), the increase in amplitude of the first leftward saccade obtained after PA produced also a shifting of visual attention towards the left side of the visual field.

However, using the same prismatic exposure procedure with a left neglect patient, Ferber, Danckert, Joanisse, Goltz, & Goodale (2003) failed to report any improvement in explicit detection of stimuli located in the contralesional space, despite a dramatic increasing of leftward eye fixations after prismatic adaptation. Although significant improvements were reported in the bells and the letter cancellation tests, this case study revealed the persistence of a rightward perceptual bias in emotional expression judgement of chimerical faces following successful adaptation to visual shift.

The fact that prismatic adaptation does not increase perceptual awareness in the neglected hemispace favors the hypothesis that visuomotor adaptation may improve selective spatial judgments but probably does not restore the whole spatial representation. The link between gaze direction and neglect remission during all experimental stimulations described in this review will be further addressed in the discussion section.

8.3. Neurophysiological correlates of PA

Luauté et al. (2005) designed a positron emission tomography (PET) study in five neglect patients after a prism exposure period to investigate the neuroanatomical substrate of PA. Results showed a strong implication of the cerebellum probably linked to the realignment of visuo-motor coordinates. Other activations in several ipsilesional and contralesional cortical and subcortical structures were found such as the left thalamus, the right temporo-occipital cortex, the left medial temporal cortex and the right posterior parietal cortex. These activation patterns suggest that PA may activate a distributed network that include the cerebellum, cortical and subcortical areas both in the healthy and lesioned hemisphere and raise the question of the complexity of the possible adaptative and compensatory mechanisms at work in PA.

9. Use of multiple stimulation techniques

Based on previous studies showing remission of left neglect symptoms after vestibular, proprioceptive and optokinetic stimulation, Karnath (1994) hypothesized that the afferent information obtained from visual, vestibular and proprioceptive signals are combined and elaborated into an egocentric, body-centred, visuospatial frame of reference. To test this hypothesis, Karnath conducted a series of experiements using RBDN+, LBD, and non-brain-damaged control subjects to investigate the effects of both neck muscles proprioception and CVS on the expected shift of the egocentric reference. Normal subjects were asked to actively direct a laser point towards the position of their subjective straight ahead (active visual straight ahead task) while patients had to stop the displacement of a pointer directed by the experimenter in front of their subjective sagittal middle (passive visual straight ahead task). The procedures for the stimulations were the same as in previous studies.[3] For RBDN+ patients, as

[3] The procedures for the stimulations were the same as in previous studies: vibration of posterior neck (100 Hz), and 30 ml of cold water in the left ear during 1 min for the CVS. In the "vibration condition" the testing procedure started as soon as the subject had a clear illusion of target movement. CVS induced a brisk nystagmus in all subjects, with the slow phase towards the left side. The two baseline conditions consisted in no stimulation at all, respectively in the light

well as for both control groups, only those subjects who experienced an illusion of target motion also showed a deviation of their subjective body orientation.

The neglect patients' spontaneous horizontal displacement of sagittal midline to the right could be compensated for by either neck muscles vibration or by left CVS. With both types of stimulation, the subjective body orientation lay close to the objective position and to the judgements observed for the control groups in "baseline" condition, with no additional stimulation. Vibration of the right neck muscles led to a transient worsening of the ipsilesional displacement of subjective body orientation in two out of three neglect patients.

When neck muscle vibration and vestibular stimulation were combined and were simultaneously applied on the left side, the shift of the neglect patients' subjective body orientation to the left further increased compared with the deviation observed when any of the stimulations was applied in isolation.

Moreover, when the left-sided vestibular stimulation was combined with the vibration of the posterior neck muscles on the right side, the effects neutralized each other. Again, only in the neglect patient who reported no apparent movement of the stationary target when vibrated on the right, left-sided vestibular stimulation had no additional effect on the subjective body orientation. It is likely that there was a displacement of the subjective body orientation to the left as was seen with exclusive left-sided vestibular stimulation.

10. General discussion

The different stimulations presented here have fostered various explanations going from an improvement of ocular movements paralleled by the presence of nystagmus to a restoration of the space representation or a facilitation in orienting spatial attention to the left hemispace.

As we will see, it is difficult both to reconcile any of these hypotheses with what we already know from the body of work on unilateral neglect, and to find an explanation that fits all the reported effects of stimulations. However, we attempt to discuss the different hypotheses that had been proposed (see also Kerkhoff, 2003; Redding and Wallace, 2006; Rossetti and Rode, 2002 for reviews) and propose a new explanation in terms of a restoration of sensori-motor correlations.

10.1. Experimental stimulation as a means to restore space representation in left USN patients

After the seminal study of Rubens (1985), most of the authors testing the effect of experimental stimulations on left USN refer to a particular model of neglect relying on Jeannerod and coworkers' experimental work (Jeannerod & Biguer, 1987, 1989; Ventre & Faugier-Grimaud, 1986; Ventre et al., 1984).

and in darkness. In the experimental conditions, the vibration of neck muscles could be applied alone, either to the right or to the left, or combined with CVS of the left ear, the last experimental condition consisted in CVS of the left ear alone.

On the basis of neurophysiological data, Ventre et al. (Ventre & Faugier-Grimaud, 1986; Ventre et al., 1984) hypothesized that a body reference that allows a reconstruction of body position in space with respect to external objects is built as an internal representation of body midline or longitudinal axis. In keeping with Jeannerod and Biguer (1987, 1989) this internal representation of the sagittal axis would be the egocentric reference (ER) segmenting body and space in two halves: a left and a right hemispace. The position of the ER is conceived as an equilibrium position between information arising from both sides of space, that guides actions directed towards those sides. This position is thus assumed to be a result of symmetric activity of associative neural structures. Unilateral lesions of these structures are supposed to produce a permanently asymmetric activity, inducing in turn a displacement of the egocentric coordinates to a new position located in the ipsilesional hemispace, thus provoking contralesional neglect (Fig. 1).

For most of the authors using stimulations in neglect patients, the appropriate stimulation may modify the pattern of sensory input on which the internal representation of the body is constructed. This, in turns, would lead to a temporary displacement of the egocentric representation towards the contralesional side. The stimulation therefore, by running counter to the unbalancing effect of the lesion, restores at least in part the appropriate correspondence with the somatotopic representation (Fig. 2). Patients become then temporarily aware of otherwise neglected stimuli delivered to the affected side. This model implies three distinct assertions. Firstly, it takes for granted the existence of an ipsilesional deviation of the egocentric reference in left USN patients. Secondly, this deviation is seen as the cause of the neglect behaviour. Thirdly, the stimulation is only seen as a means to restore the position of the reference. If some physiological and clinical evidence appears to support these assertions, other experimental findings have not. As we have seen before, the vestibular system is a component part of cerebral circuits including cortical and sub-cortical structures. Its main cortical projections are directed to the parietal cortex (Fredrickson et al., 1966) which in turn has efferent projections to the vestibular nuclei in the brainstem (Ventre & Faugier-Grimaud, 1986). According to these anatomical data, the vestibular system could be involved in maintaining orientation in egocentric space (Karnath & Dieterich, 2006).

In addition, some neurophysiological studies suggest that the cortical projection area of the vestibular system is a posterior-superior temporal region. This area is adjacent to the infero-posterior parietal cortex which is frequently damaged in patients with controlateral hemineglect (Stein, 1989; Vallar & Perani, 1986).

Concerning experimental studies among neglect patients, a constant "directional" error which would fit the hypothesis of an ipsilesional deviation of the egocentric reference has been described by various authors. Heilman et al. (1983) reported in five left neglect patients a large deviation of the subjective straight-ahead to the right ipsilesional hemispace. This was replicated by Karnath (1994) and Karnath et al. (1991) and Chokron and Imbert (1995). Along the same lines Chokron and Bartolomeo (1999) showed that in left brain-damaged patients there is a correlation between the position of the egocentric reference and the presence and severity of right neglect signs (Chokron & Bartolomeo, 1999).

But there is also clinical evidence of a significant deviation of the egocentric reference in non-neglect patients suffering from hemianopia (Fuchs, 1920), ataxia (Perenin, 1997), or primary motor deficit (Chokron & Bartolomeo, 1997). Moreover, it was recently shown that unlike left brain-damaged patients, there is no significant correlation between left neglect signs and either the presence or the side of a deviation of the egocentric reference position (Bartolomeo & Chokron, 1999; Chokron & Bartolomeo, 1997). We thus recently concluded that the position of the egocentric reference plays no crucial role in the behavioural consequences of spatial bias induced by right-hemisphere lesions (Bartolomeo & Chokron, 1999; Chokron, 2003). In addition, the fact that left neglect signs may arise in other frames of reference than the egocentric one (Behrmann & Moscovitch, 1994; Driver & Halligan, 1991; Reuter-Lorenz, Drain, & Hardy-Morais, 1996; Tipper & Behrmann, 1996) as well as the presence of revisiting behaviour in the right, ispilesional hemispace (Pisella & Mattingley, 2004) also contradict the egocentric reference hypothesis.

However, a deviation of the egocentric reference may follow the presence of an extensive parietal lesion (Chokron & Bartolomeo, 1999; Hasselbach & Butter, 1997).

If there is no systematic and specific deviation of the position of the egocentric reference in left neglect patients, the positive effect of the above-cited stimulations cannot stem from a restoration of the egocentric frame of reference.

Bisiach et al. (1996) showed that OKS does not restore space representation in neglect. The authors thus proposed that manipulations such as OKS may remove neglect without normalizing the representational medium itself. In the same way, we showed that left-to-right scanning of a to-be-bisected line may induced a pathological leftward deviation of the subjective middle in neglect patients, thus reversing their left neglect behaviour without reducing it (Chokron, Bartolomeo, Perenin, Helft, & Imbert, 1998). Along those lines, given the fact that these stimulations induce a directional bias of either the gaze, the trunk or the left arm towards the left neglected hemispace, one could propose that the positive effects are simply resulting from this motor and proprioceptive orientation towards or in the left hemispace.

10.2. *Experimental stimulation as a means to reduce lateral gaze bias and directional hypokinesia in left USN patients*

As we have seen before, the first description of a positive effect of a stimulation on left USN was reported by Rubens (1985) using CVS. The temporary remission of extrapersonal neglect signs after left cold or right warm stimulation, led him to hypothesize that most, if not all of the improvement of USN patients was clearly the result of the leftward eye movements permitted by the nystagmus. He thus proposed that this transient remission was mediated quasi-entirely through vestibulo-ocular and vestibulo-spinal mechanisms.

His other proposition was that CVS also acts on directional hypokinesia, the unwillingness to produce arm movements toward the contralesional hemispace (Heilman, Bowers, Coslett, Whelan, & Watson, 1985). According to Heilman et al. (1985, 1983) the cortico-limbic system is implicated in the maintenance of hemispheric arousal and readiness to respond towards the controlateral hemispatial field. The unilateral destruction of this system leads to directional hypokinesia and impaired attention to the controlateral hemispace. In line with this framework, Rubens (1985) proposed that the stimulation of the vestibular system, with its rich connections to the reticular system could have lightened general attention and diminished left-sided hypokinesia. This idea was also defended by Storrie-Baker, Segalowitz, Black, McLean, and Sullivan (1997) who showed that while during caloric stimulation both hemispheres increased in EEG activation, the right hemisphere increase is significantly greater, supporting an activation-arousal hypothesis of neglect (Heilman, Watson, & Valenstein, 1993). According to the subsequent studies that employed CVS in left neglect patients during non-visual tasks, Rubens' low level explanation can only account for the remission of extrapersonal visual neglect. The positive effects obtained with CVS, OKS, neck muscle vibration and TENS (see above sections), on the remission of both personal, extrapersonal, representational neglect and somatosensory deficits led the respective authors, to propose an interpretation in terms of a higher-level effect of the experimental stimulation used on space representation. However, as seen before, the effect of leftward gaze orientation consecutive to the nystagmus may be interpreted not only as a primary low-level effect, but also as a mechanism acting at a higher level of integration, such as the orientation of attention in space. This question was also addressed by Serino, Angeli, Frassinetti, and Ladavas (2006) who recently targeted the mechanisms underlying neglect recovery after prism adaptation. As above-mentioned, during the adaptation process under prism exposure, patients perform pointing movements to a visual target and receive visual feedback concerning the final position of the hand with respect to the target. In the very first trials patients show a rightward deviation when pointing to the visually perceived target. As explained by Serino et al. (2006), a possible strategy to adapt to the prismatic deviation consists in pointing to the side of the target by an amount sufficient to reduce the visual error. As proposed by the authors, since there is evidence that, during pointing, eye movements are yoked to hand movements and vice versa, it is possible to speculate that under prism exposure condition, due to this eye-hand coordination, the leftward deviation of hand movements could induce a leftward deviation of the oculo-motor system. This link is confirmed by the fact that the authors found a positive correlation between the first saccade deviation and the improvement in visuo-spatial tasks obtained at the end of the treatment. Thus after the treatment eye movements remain leftwardly oriented, at variance with the hand movement after effects that are known to vanish after few days (Farnè, Rossetti, Toniolo, & Ladavas, 2002). This dissociation might be explained by the fact that after the removal of the prisms, the leftward deviation of the oculomotor system could enhance in neglect patients the detection of stimuli presented in the contralesional side of the space. Therefore, as above discussed, it is also possible to speculate that the increase in the amplitude of the first leftward saccade obtained after PA produces also a shifting of visual attention towards the left side of the visual field, thus mediating the recovery of visual neglect. This hypothesis could also account for the improvement of neglect patients during representational tasks. As a matter of fact, it has been shown that rotating the eyes towards the left may improve the recall of left-sided items suggesting that the direction of eye movements can influence the formation or retrieval from spatial representations (Meador, Loring, Bowers & Heilman, 1987; and see for discussion, Chokron et al., 2004b). In this way and as pointed by Serino et al. (2006), the positive effect of lateral gaze orientation towards the left hemispace by means of CVS, OKS or PA as well as the interpretation of left limb activation in terms of spatio-motor cueing (Robertson and North, 1992; Robertson & North, 1992, 1993) raise the question of the role of these stimulations on the orientation of endogenous and exogenous attention in space.

10.3. Experimental stimulation as a means to restore a biased automatic orienting of attention

Neither Rubens (1985) nor the authors who have replicated and extended his findings have entirely attributed the observed remission of hemineglect to that of an improved capacity to explore visually the contralesional half-space.

However, the general mechanism through which vestibular stimulation acts upon personal and extrapersonal neglect, ansognosia, and hemianesthesia might well consists in a contralesional orientation of attention (Gainotti, 1993, 1996).

As a matter of fact, Gainotti (1993, 1996) proposed that the facilitation of ocular movements towards the neglected half-space leads to a reduction of neglect and of related phenomena not only because it allows a better visual exploration of the neglected half-space but also because it automatically orients attention towards this space. This hypothesis was subsequently confirmed in various protocols including the Posner paradigms (see for review, Bartolomeo & Chokron, 2002) as well as drawing objects from memory (Chokron et al., 2004b).

Several lines of evidence, concerning both normal and brain-damaged patients, confirm that eye movements may orient the subject's attention towards the appropriate part of space. This effect was shown in normal subjects in several tasks that are not under visual control: in dichotic listening both verbal (Gopher, 1973) and non-verbal (Larmande, Blanchard, Sintes, Belin, & Autret, 1984; Larmande, Elghozi, Bigot, Sintes, & Autret, 1983) and in the detection of tactile stimuli (Honoré, 1982). In these experiments, the direction of eye movements towards the part of space stimulated improved both the subject's performance and the reaction times, confirming the hypothesis of a link between the gaze direction and the spatial allocation of attention. Regarding brain-damaged patients, Larmande and Cambier (1981) showed that in patients with left tactile extinction the incidence of extinction decreased when the gaze was oriented towards the left half space and increased when it was directed to the right. On the other hand, two patients presenting a pathological rightward gaze deviation were submitted to a non verbal dichotic task (Belin, Perrier, Cambier, & Larmande, 1988) where conversely to normal subjects they showed a right ear advantage as if the right gaze deviation had oriented their attention to the right. In the same way, Meador et al. (1987) reported a patient with left neglect whose recall from memory of items located in the left hemispace improved when his head and eyes were physically directed toward the left. From the above-mentioned results, Gainotti (1994) concluded that the direction of eye movements leads to a corresponding spatial orienting of attention towards the corresponding parts of personal and extrapersonal space. If this can explain the positive effects of the stimulations which induce a nystagmus what about the prismatic adaptation, the trunk rotation, the neck vibration or the transcutaneous electric stimulation which are not accompanied by ocular movements?

One could easily argue that these stimulations all include a sensory or motor stimulation occuring in the left hemispace that could be responsible for a left orientation of attention, similar to the effect of cueing procedures (Riddoch & Humphreys, 1983). While trunk rotation, neck muscle vibration and transcutaneous electric stimulation all comprise an explicit proprioceptive stimulation of the left corporeal hemispace, the prismatic adaptation is designed to force the patient to point leftward to a seen target. As several authors have shown, orienting left neglect patients' attention to the left by using either visible or invisible cues (Mattingley, Pierson, Bradshaw, Phillips, & Bradshaw, 1993; Riddoch & Humphreys, 1983) as well as spatio-motor cues (Robertson & North, 1992) or using the movement of a background or of a stimulus as a cue (Chokron et al., 1998; Dunai, Bennett, Fotiades, Kritikos, & Castiello, 1999; Kerkhoff, Schindler, Keller, & Marquardt, 1999; Mattingley, Bradshaw, & Bradshaw, 1994) (even in the absence of optokinetic nystagmus) may reduce the amount of left neglect signs. In addition, it was recently demonstrated that rightward prismatic adaptation reduced both the rightward attentional bias and the disengage deficit in patients with right brain damage irrespective of the presence of neglect (Striemer and Danckert, 2007).

The hypothesis that visuo-vestibulo-proprioceptive stimulations act by re-orienting attention towards the leftward neglected hemispace is confirmed, as described below, by the presence of nonspecific positive effects when using these experimental stimulations.

10.4. Nonspecific effects of experimental stimulations

In his seminal paper, Rubens (1985) reported that left neglect patients appeared more 'alert' while carrying out tasks during ice-water stimulation. Along the same lines, several authors reported some nonspatial, positive effects of CVS, OKS and PA in brain-damaged patients, raising the question of both the nature and the specificity of these effects. Left cold CVS was thus found to be effective on both left and right hemianesthesia (Vallar et al., 1990; Bottini et al., 2005) and proposed by Ramachandran and McGeoch (2007) for the treatment of apotemnophilia because of its positive effects on somatophrenia (Rode et al., 1992). In addition, an effect of vestibular stimulation on dichotic lexical decision performance was found by Schüeli, Henn, and Brugger, (1999). These authors reported a shift of right ear advantage (REA) in right-handed men during a dichotic listening task with words and non-words as stimuli, using vestibular stimulation by using a rotating chair. There was a reliable REA for lexical decision accuracy in the baseline and right-to-left trials but not during left-to-right rotation. In this condition, whereas the performance of the right ear was not affected, there were more correct lexical decisions to left-ear targets. As we have discussed before, the authors interpreted this effect in terms of a leftward attentional shift induced by left-to-right rotation, and put together this effect and what is observed in left neglect patients with cold water in the left ear.

Along the same lines, Kerkhoff (2003), Kerkhoff (2003, 2006) demonstrated that the positive effect of repetitive OKS on left neglect patients was not restricted to the visual modality since both auditory neglect and neglect dyslexia were substantially improved and remained stable after a 2-week follow-up in all cases. These improvements were thus obtained in two different sensory modalities (vision and audition) which underline the multimodal efficiency of OKS that was already documented with short-term optokinetic stimulation.

Apart from its positive effects on left neglect, PA had also been proved to rehabilitate patients suffering from a various range of deficits. As a matter of fact, RBD patients without left neglect signs were found to benefit from PA regarding their postural imbalance (Tilikete et al., 2001). Moreover, as above-described for CVS and R-OKS, PA was shown to affect performance in other modalities than vision such as haptic perception (Girardi et al., 2004; McIntosh et al., 2002)) and audition (Maravita et al., 2003). These multimodal effects have been interpreted by the different authors as an indirect effect of PA on the central level of space representation. However, the fact that PA had been found to decrease visuo-constructive disorders in RBD patients (see Rode, Klos, Courtois-Jacquin, Rossetti, and Pisella, 2006 for review) suggests that PA does not act specifically on the ipsilesional bias characteristic of unilateral neglect but rehabilitates the visual functions more generally attributed to the right cortical hemisphere. More surprising is the recent study of Sumitani et al. (2007) among five patients with complex regional pain syndrome (CRPS). The patients adapted to wedge prisms, producing a 20° visual displacement toward the unaffected side. PA toward the unaffected side alleviated pathologic pain and other CRPS pathologic features, when measured at post-test. In the longitudinal study, sham PA and 5° PA did not produce any effects, and PA toward the affected side actually exacerbated the subjective pain. The authors propose that vision, and in this way PA may influence pathologic pain and perhaps also other CRPS pathologic features, suggesting that prism adaptation could be a viable cognitive treatment for CRPS. However, these findings are difficult to reconcile with the idea that the prismatic adaptation acts specifically on the ipsilesional bias characteristic of unilateral neglect or that PA rehabilitate more generally the visuo-spatial functions attributed to the right hemisphere. The fact that PA may affect pathologic pain could either argue in favor of an attentional effect modulating painful sensations or indicate that the lateralized visuo-motor adaptation modify the whole perception and representation of extrapersonal as well as personal space. In this way and regarding the fact that all stimulations involve a sensori-motor component (lateral gaze orientation, visuo-motor adaptation, trunk deviation or limb activation) we propose in the next section a new hypothesis in terms of a restoration of sensori-motor correlations leading to neglect remission.

10.5. Experimental stimulation as a means to restore spatial remapping and sensori-motor correlations

Recently, Redding and Wallace (2006) reviewed the positive effects of prismatic adaptation and proposed an alternative hypothesis. Prism adaptation realignment would shift the egocentric coordinates of a sensory-motor reference frame, thereby bringing at least part of the neglected hemispace into the dysfunctional task-work space. According to these authors, prism adaptation would substitute for dysfunctional positioning, but not sizing of a task-work space. This hypothesis is closed to the referential hypothesis of neglect above discussed, but these authors proposed in addition that ‘such amelioration of dysfunctional positioning may enable relearning strategic processes (calibration) perhaps, even partially restoring the ability to appropriately size the task-space’ (see Redding and Wallace, 2006, p. 16). This idea of a ‘recalibration’ of space decreasing neglect signs seems can be connected to the hypothesis of spatial remapping impairments in left neglect. Indeed, Pisella and Mattingley (2004) proposed that manifestations of neglect can be accounted for by spatial remapping impairments due to parietal dysfunction. According to their view, in normal subjects primary visual areas contain retinotopic maps that are renewed and overwritten at each new ocular fixation. These remapping processes are seen to operate in higher-level oculocentric visual maps of the parietal cortex thus ensuring visual integration of the successive retinal images over time and space, and create a constantly updated representation of stimulus locations in terms of distance and direction from the fovea. In left neglect patients, due to the right parietal lesion these processes would be deficient, generating thus deficits that could be interpreted in terms of a spatial remapping impairment within the left visual field following a saccade to a left-side target. According to the authors, proprioceptive information from head and body may influence the remapping mechanisms and in this way, visuo-proprioceptive stimulation such as prismatic adaptation could improve neglect by influencing the gain of the remapping mechanisms. But as the authors underline, information concerning the neural substrates of prismatic adaptation is still lacking to confirm this hypothesis.

Following the idea that sensori-motor contingencies influence visual awareness, O’Regan and Noe (2001) have recently proposed that visual consciousness is not the result of having built a detailed mental representation of the visual environment, but is nothing over and above the mastery of the laws which govern the sensorimotor contingencies associated with visual exploration. For example, our consciousness of the presence of an object on our left would principally result from our capacity to direct a saccade toward that object. There is no need to build a detailed mental representation of the visual environment, because the visual world is already outside there, each detail being immediately available for visual exploration. As a matter of fact, consideration of the neglect behaviour and of its rehabilitation with experimental stimulations bring substantial support to these notions. Much of the empirical evidence reviewed here suggests that a crucial mechanism leading to reduction of the spatial bias in neglect patients is the sensori-motor component of the experimental stimulation. Moreover, as repeatedly underlined in prismatic adaptation studies, the more the left neglect patients adapt to the prismatic deviation, the greater the improvement (see for discussion, Serino et al., 2006). Thus, in the same vein than O'Regan and Noe hypothesis, the positive effects of the different stimulations above-mentioned might be understood as temporarily restoring patients' knowledge of sensorimotor contingencies associated with leftward orienting. It has indeed to be noted that all these experimental stimulations are both perceptual and motor in nature, and one could propose that they reduce neglect by providing new sensori-motor contingencies either by the visual or proprioceptive or vestibular disturbance they induce.

Contrary to the hypothesis of Redding and Wallace (2006) which states that a realignment of a sensory-motor reference frame accounts only for the effect of prismatic adaptation, our hypothesis is more about the effect of acquiring new sensori-motor rules in the left neglect hemispace by adaptation to the perturbation induced by the vestibulo-proprioceptive stimulation, whatever its nature (all stimulations described in the present paper may elicit such effects). The positive effect of these stimulations could be seen as resulting from such 'sensori-motor' learning in the left hemispace and could be interpreted either in terms of a compensation of the existing rightward bias or as an additional leftward bias that counterbalances the existing spatial bias in neglect. Indeed, as suggested by Girardi et al. (2004) on prismatic adaptation, transient modification of sensori-motor contengencies creates a temporary leftward spatial bias which compensates for the massive rightward bias of left neglect patients. Consistent with this hypothesis is the fact that healthy subjects do not show long-lasting effects of PA as compared to left neglect patients. For this reason, the decrease of left neglect signs after experimental stimulations could be interpreted as the result of a pathological, leftward sensori-motor bias created by the new sensori-motor contingencies generated by the vestibulo-proprioceptive stimulation. From a neuroanatomical perspective, this hypothesis is in accordance with the sensori-motor function of the right parietal cortex which has been extensively described by numerous authors (see for review Andersen et al., 1997; Grefkes and Fink, 2005). According to our hypothesis, if left neglect signs might be reduced by new sensori-motor contingencies, one could propose that unilateral spatial neglect is due to a kind of sensori-motor decorrelation. As proposed by Andersen et al. (1997), the role of the right posterior parietal cortex (PPC) is to perform sensory-motor transformations and an important aspect of this transformation process is to convert spatial information between several coordinates. The PPC thus represents an interface between sensory and motor areas where cognitive functions related to sensory-motor transformations such as attention, intention and selection of targets are performed. In this view, visuo-vestibulo-proprioceptive stimulations by both inducing a sensori-motor conflict and requiring an adaptation to it could give a chance to left neglect patients to recalibrate sensory-motor information in their left hemispace, by learning a new relationship between perception (especially visual perception and proprioception) and action. Regarding this hypothesis, even if all stimulations described here can promote the acquisition of new sensori-motor rules by adaptation to the perturbation, PA could be the more effective stimulation (with long-lasting effects) because this stimulation requires an *active* adaptation to the induced deviation compared to other stimulations like CVS, OKS, TMV or TENS which induce a more passive adaptation. In turn, according to O'Regan and Noe (2001) this active adaptation (and, to a lesser extent, passive adaptation) to the imposed distortion could restore spatial awareness of the left hemispace by the way of a recalibration of the left hemispace. According to our present hypothesis, if these stimulations decrease left neglect signs by inducing a re-correlation of sensori-motor information in the left hemispace, one could propose that left neglect behaviour is the consequence of a sensori-motor decorrelation (or loss of sensori-motor rules) in the contralesional hemispace. From a neuroanatomical point of view, this sensori-motor decorrelation hypothesis of neglect is confirmed by recent studies showing that the disruption of a fronto-parietal network could be the determinant in the severity and recovery of left neglect signs (He et al., 2007; Thiebaut de Schotten et al., 2005).

Some studies using prismatic adaptation in normals (Colent et al., 2000; Michel et al., 2003) have shown some lateralized spatial bias in healthy participants. To confirm our present hypothesis, further experimental studies are needed to investigate the extent to which a lateralized sensori-motor decorrelation is able to induce a 'neglectlike' spatial bias in healthy subjects.

10.6. Conclusions and implications for future research

In this review different stimulations that have been reported to transiently reduce left neglect signs were discussed. The mechanisms by the way these stimulations act are still unknown, however the understanding of the processes implicated in their effects may be helpful in defining the levels of impairment in left neglect patients and in designing rehabilitation techniques with lasting positive effects. As pointed out by Kerkhoff and Rossetti (2006) and more recently by He et al. (2007), animal experiments, functional imaging studies and longitudinal outcome studies suggest that injured brains can change their function and connectivity, both on the behavioural and neural level, and both spontaneously (i.e. without intervention) as well as in response to specific treatments. However, many questions in this context still remain open. First of all, it would be interesting to understand what these stimulations share with other techniques that had also been reported to decrease left neglect signs such as cueing procedures (Riddoch & Humphreys, 1983), imposing a left-to-right visual scanning direction (Chokron et al., 1998; Mattingley et al., 1994; Reuter-Lorenz & Posner, 1990), imagery tasks (Smania et al., 1997) reducing the visual guidance (Chokron et al., 2004b; Hjaltason & Tegner, 1992) and using devices that supposedly reduce the ipsilesional colliculus activation (Butter & Kirsch, 1992). There might either be a link between these different effective stimulations or their diversity could simply reflect the heterogeneity of neglect signs (or neglect syndromes?) as discussed by several authors (Binder; Marshall, Lazar, Benjamin, and Mohr, 1992; Bartolomeo & Chokron, 2001; Chaterjee, 1998; Halligan & Marshall, 1992, 1994; Vallar, 1994). Moreover, as pointed out by Kerkhoff (2003), given the large cortical and subcortical network involved in spatial neglect, the search for multimodally effective treatments is probably a challenge for the future. In the same way, in addition to testing new therapeutical tools, researchers could also design longitudinal studies where long-lasting effects of experimental stimulations, as well as the natural course of the deficits, can be more thoroughly studied. Furthermore, the possibility of the better efficacy of certain treatments during acute stages of neglect versus in the chronic stage of neglect can be explored. Advances in anatomical knowledge are likely to inspire and guide the development of such studies. New neuroimaging techniques, such as diffusion tensor imaging, are now shifting the focus from the prevalent consideration of cortical modules, to that of large-scale brain networks and of their white matter connections (Catani, 2006). The network approach may prove particularly relevant for complex entities such as neglect and attention (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007; Thiebaut de Schotten et al., 2005). New experimental tools such as TMS will permit to refine this structural knowledge by studying the functional aspects of the explored networks (Fierro, Brighina, and Bisiach, 2006; Rounis, Yarrow, and Rothwell, 2007; Valero-Cabre, Russhmore, and Payne, 2006).

Finally, in order to elucidate how the experimental stimulations reviewed here lead to neglect remission, future research should also include experiments in which in addition to neglect patients, normal subjects are confronted with these stimulations, as well as patients suffering from a peripheral perceptual disorder (caused by a vestibular lesion for example). Therefore, attention should be paid to the brain-damaged patients who do not have any deviation of their subjective straight ahead position, (Chokron & Bartolomeo, 2000; Farne, Ponti, & Ladavas, 1998), patients in whom neglect signs arise in other frames of reference than the egocentric one (Behrmann & Moscovitch, 1994), and patients who do not respond to these stimulations. Finally, the link between the cerebral activation and the effect of these stimulations, should be thoroughly studied by the way of functional studies as well as experiments where the correlation between the lesion localization and the effects of the different above-mentioned stimulations is explored.

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