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Lateralized visuospatial and postural imbalances associated with spatial neglect: a neuropsychological study on assessment and intervention in right-hemispheric stroke patients

Nathalie Vaes

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Administratively responsible promoter: Prof. Dr. Guy Vingerhoets
Promoters: Dr. Kristine Oostra, Dr. Gudrun Nys

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Vaes, N., Lafosse, C., Hemelsoet, D., Van Tichelt, E., Oostra, K., & Vingerhoets, G. (2015). Contraversive neglect? A modulation of visuospatial neglect in association with contraversive pushing. *Neuropsychology, 29*(6), 988-997.

Vaes, N., Nys, G., Lafosse, C., Dereymaeker, L., Oostra, K., Hemelsoet, D., & Vingerhoets, G. (2016). Rehabilitation of visuospatial neglect by prism adaptation: Effects of a mild treatment regime - a randomized controlled trial. *Neuropsychological Rehabilitation*. Advance online publication. doi: 10.1080/09602011.2016.1208617

List of Main Abbreviations

CG	Control Group
CoC	Center of Cancellation
CoD	Center of Drawing
CoN	Center of Navigation
CP	Contraversive Pushing
EG	Experimental Group
MDIS	Metrisquare DiagnoseIS
NP^-	Neglect without CP
NP^+	Neglect with CP
PA	Prism Adaptation
PP	Posterior Pushing
PPS	Peripersonal Space
RCT	Randomized Controlled Trial
SCP	Scale for Contraversive Pushing
SLBT	Schenkenberg Line Bisection Test
SN	Spatial Neglect
T0	Baseline measurements
T1	Effect measurements within 2 to 24 hours after PA
T2	Effect measurements 3 months after PA
VNT	Visuospatial Navigation Test
VNTB	Visuospatial Neglect Test Battery

Chapter 1: Preface

1 General introduction

Stroke is a major public health problem globally, with large personal, family and health care costs. Fifteen million people worldwide suffer a stroke annually, of which 5 million people are permanently disabled (World Health Organization, 2016). A better understanding of the impairments associated with functional disabilities after stroke, helps to identify the requirements to reduce the personal, social and community burden of stroke (Barrett & Muzaffar, 2014). Spatial neglect (SN) is a proper example in this respect. SN is a disabling condition with an unfavorable impact on daily functioning in stroke patients with unilateral hemisphere lesions. The reported occurrence rates of SN vary widely across different studies: up to two thirds and from 13 to 81% of right-hemispheric stroke patients respectively, in Stone et al. (1991) and Buxbaum et al. (2004), 43% of right-hemispheric and 20% of left-hemispheric patients in Ringman, Saber, Woolson, Clarke and Adams (2004), 23.5% taking right- and left-hemispheric patients together (Tatuene et al., 2016). Based on a systematic review, Bowen, McKenna and Tallis (1999) concluded that they could not determine a reliable estimate of the frequency rate of SN. The following literature-based range of the occurrence of SN is a better alternative: between 30 – 70 % of right-hemispheric and 20 – 60 % of left-hemispheric stroke patients (Chen, Hreha, Fortis, Goedert, & Barrett, 2012). Reasons for the variability in the reported rates are methodological differences (Bowen et al., 1999). First, a detection bias might be introduced when severe aphasia in left-hemispheric patients interferes with the assessment instructions. Second, the time of assessment post stroke varies. A certain reduction of the frequency occurs with time, especially in left-hemispheric patients. Third, the frequency varies with the assessment tool used. The tools differ in their test sensitivity and regarding the type of SN process that they measure. Finally, the reported occurrence rates may be influenced by motivation, internal or external distracters and tiredness. Nevertheless, a degree of SN is extremely common at presentation after stroke (Ringman et al., 2004) and frequently associated with an important overall disability (Jehkonen, Laihosalo, & Kettunen, 2006). SN also is a predictor of poor functional performance and rehabilitation outcomes after stroke (Gillen, Tennen, & McKee, 2005;

Jehkonen et al., 2006; Katz, Hartman-Maeir, Ring, & Soroker, 1999). It adversely affects patients' personal and social life, and their progress and length of stay in rehabilitation. Gillen et al. (2005) found that SN patients' length of hospitalization is on average 11 days longer, and that they showed more depressive symptoms and less functional improvement per day, compared to patients without SN. Such findings stress the importance of timely and thoroughly mapping and treating SN. This dissertation is a small contribution to the large body of scientific literature about SN assessments and interventions. Despite the extensive literature about SN (see paragraph 1.1), further research is indispensible to deepen the understanding of its diverse symptoms and their cerebral substrates on the one hand. On the other hand, continued investigations are essential for the fine-tuning of targeted neglect treatments. We hope that our contribution, together with all other scientific efforts in the field, will eventually lead to a reduction of the personal and community costs of SN. By translating a pool of experimental outcomes into solid clinical practice, we might be able in the end to improve patients' quality of life. More specifically, the current thesis contributes to the field of SN in the following ways. Adequate neglect measures are a prerequisite to investigate SN symptoms and treatment effects. In this digital era, an electronic measuring method offers more benefits to experimental, as well as clinical neuropsychologists. We designed a digital Visuospatial Neglect Test Battery (VNTB) that allows for sound peripersonal visuospatial neglect diagnostics. It was developed in collaboration with Metrisquare DiagnoseIS. The VNTB is thoroughly explained and depicted in Chapter 2. The different tests enabled us to adequately measure prism training effects in a randomized controlled trial (RCT) as described in Chapter 3, and posture-related visuospatial behavior in a case-control study as elucidated in Chapter 4. As such, Chapter 2 embodies a method article related to digital SN measurements, Chapter 3 a treatment article related to prism adaptation in SN, and Chapter 4 a theoretical article related to a newly discovered neuropsychological characteristic in SN patients with a specific body posture. In general and brief terms, the relevance of our work lies in the experimental underpinnings for assessing, treating and understanding specific SN processes, in an attempt to eventually contribute to the common clinical goal of reducing the adverse impact of SN on patients' lives. The precise aim of each article will be introduced at the beginning of each chapter, and summarized concisely in the sequel of this introductory Chapter 1. The core concepts of the dissertation are clarified below.

1.1 Spatial neglect

Spatial or unilateral neglect is a neurologic condition in which patients fail to orient, report, or respond to stimuli in contralesional space (Heilman, Valenstein, & Watson, 1985; Heilman, Watson, & Valenstein, 1993). In addition to the shortage of responses contralesionally, neglect patients may also show an excess of responses in ipsilesional space, such as perseverations (Nys, Van Zandvoort, Van der Worp, Kappelle, & de Haan, 2006; Ronchi, Algeri, Chiapella, Spada, & Vallar, 2012; Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009). SN is not caused by primary sensory or motor dysfunction; rather, it is a higher-order disorder (Heilman et al., 1993). Neglect patients seem unaware of their contralesional side and seem to act as if it does not exist. Moreover, they often are not aware of this condition (Vallar, Bottini, & Sterzi, 2003), which makes compensating for it difficult.

SN is a heterogeneous disorder, manifesting itself in many different ways and degrees of severity (Heilman, Valenstein, & Watson, 1994; Robertson & Halligan, 2000; Stone, Halligan, Marshall, & Greenwood, 1998). Patients differ from each other in terms of their symptoms and the various combinations thereof. Many symptoms can be dissociated from each other. Examples include contralesionally neglecting the visual, auditory (Sinnett, Juncadella, Rafal, Azañón, & Soto-Faraco, 2007), and tactile (Bisiach et al., 2004) modalities; neglect for the imaginary (Beschin, Basso, & Della Sala, 2000; Coslett, 1997), sensory, and/or motor (Aimola et al., 2013; Na et al., 1998) domains; hemineglect with or without extinction (Cocchini, Cubelli, Della Sala, & Beschin, 1999; Vossel et al., 2011); and neglect for personal (Guariglia & Antonucci, 1992), peripersonal, and/or extrapersonal space (Aimola, Schindler, & Venneri, 2013; Halligan & Marshall, 1991). Personal space refers to the body, peripersonal space (PPS) to the region immediately surrounding the body, where objects can be grasped and manipulated, and extrapersonal space is the space beyond reaching distance (di Pellegrino & Làdavas, 2015; Guariglia & Antonucci, 1992). Extinction refers to the inability to detect the contralesional item when two stimuli are presented simultaneously on opposite sides, while a single stimulus can be detected on either side (de Haan, Karnath, & Driver, 2012). Even within one of the above listed modalities, patients can differ considerably from each other. Within the peripersonal visual dimension, for instance, a patient’s test performances can be hemispatially distorted in one type of task, but not in another kind of task. For example, Binder, Marshall, Lazar, Benjamin, and Mohr (1992) and Milner and McIntosh (2005) described a double dissociation between performance regarding cancellation and bisection. In cancellation, patients search for and cross out certain stimuli presented on a page in front of them. SN patients typically fail to cancel stimuli on the contralesional side. In line bisection, patients estimate and indicate the midpoint of horizontal lines presented on a paper in front of them. Bisection deviations from the true midpoint to the ipsilesional side are indicative of SN (Plummer, Morris, & Dunai, 2003). An example of SN performance in cancellation and bisection can be found in Figure 1, next to an example of SN in figure copying. Typically, SN manifests more severely with increasing task complexity, illustrated in Figure 1 by the performance difference between an easy and a complex drawing. When the attentional system is loaded more heavily by increasing task complexity in a certain way, the contralesional performance deficit increases (Bonato, Priftis, Marenzi, Umiltàa, & Zorzi, 2010; Taylor, 2003).

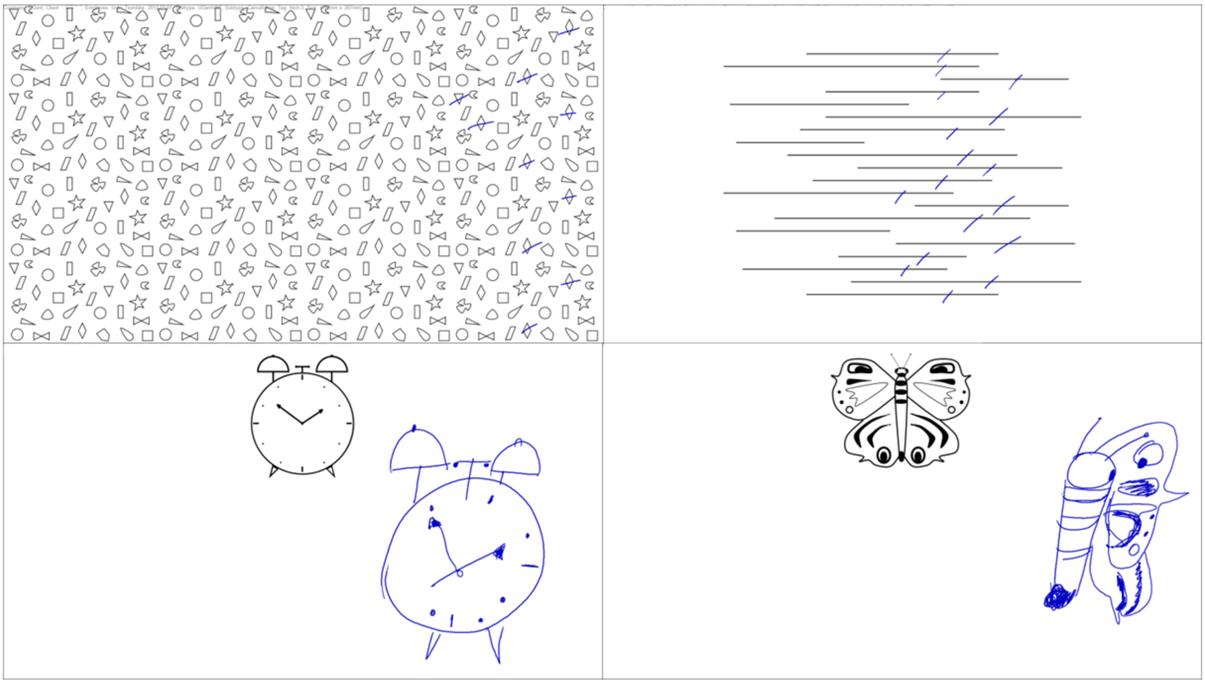

Figure 1. The contralesional performance deficit in severe SN, as illustrated by the cancellation of targets on the ipsilesional side only (top left), the ipsilesional shift in line bisection (top right), and copying less details on the ipsi- than on the contralesional side in drawing (bottom). The drawings further demonstrate some characteristics that can be observed regularly in SN patients: an aggravation of the deficit when a test is more demanding (cf. bottom left versus right), a preference to use the ipsilesional workspace (patients are instructed to copy the drawing beneath the example).

Although different neglect symptoms can stand alone, SN mostly concerns a cluster of lateralized deficits encompassing a clinical syndrome (Robertson & Halligan, 2000; Stone et al., 1998; Striemer & Danckert, 2010). It can originate from damage to different neural mechanisms (Stone et al., 1998), but manifests more frequently and significantly after right hemisphere pathology (Halligan & Marshall, 1994). According to many authors, the predominance of right hemisphere damage in the etiology of SN reflects the dominance of the right hemisphere for spatial attention (Jacobs, Brozzoli, & Farnè, 2012). Because hemispatial attentional systems are phylogenetically older than language systems, it seems that the dominance for spatial attention is anchored more firmly to the right hemisphere than the dominance for language to the left hemisphere, with a smaller tendency to shift in left-handed persons. At one week post-stroke, Ringman et al. (2004) found a similar right hemisphere predominance of lesions in left-handed and ambidextrous than in right-handed SN patients, while aphasia after right hemisphere infarction was more common in non-right-handers than in right-handers. One well-known theory explains the hemispheric asymmetry in SN by proposing that the right hemisphere represents and directs attention to both sides of space, while the left hemisphere only accounts for the right side of space. By consequence, the right hemisphere can compensate for a left brain lesion, while a massive asymmetric representational and attentional bias is introduced after a right brain lesion (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996; Posner, Walker, Friedrich, & Rafal, 1984). Another influential theory proposes that SN stems from the imbalance between both hemispheres, when a lesion disrupts the reciprocal connections that normally exert inhibitory control on the opposite hemisphere. Consequently, the ipsilateral hemisphere is hypo-activated and the contralateral one hyper-activated. According to this point of view, SN occurs more frequently after right brain damage because the contralateral orienting bias of the left hemisphere is stronger than that of the right hemisphere (Kinsbourne, 1993). A third important theory is proposed by Corbetta and Shulman (2011). They question the asymmetry of spatial attention, and plea for a symmetrical organization of spatial attention in the dorsal fronto-parietal regions instead (regions centered around the intraparietal sulcus (IPS), superior parietal lobe (SPL) and frontal eye fields). These regions of each hemisphere mainly represent the contralateral side of space. In contrast, regions of the ventral attention network (centered around the temporo-parietal junction and ventral frontal cortex) regulate the non-spatial processes of reorienting, target detection and arousal, and are strongly right hemiphere dominant. The authors argue that the interaction of the lateralized ventral regions with the dorsal regions causes the hemispheric asymmetry of SN. Damage that deregulates the non-spatial ventral mechanisms hypo-activates the right hemisphere, leading to less interactions between the right non-spatial ventral and spatial dorsal attention networks and within the right dorsal network. The resulting unbalanced inter-hemispheric activity favors the left hemisphere, which in turn causes spatial attention and eye movements to be directed to the ipsilesional field.

Which area is indicated as critical depends on the diagnostic definition adopted for neglect, but the damage is mostly situated around the parieto-temporal junction (Milner & McIntosh, 2005). Husain and Rorden (2003) enumerate the parietal, temporal and frontal cortical regions that frequently have been implicated in SN, as shown in Figure 2. However, SN is reported after insular lesions as well, and at the subcortical level after thalamic, basal ganglia and white matter lesions (Karnath, Fruhmann, Küker, & Rorden, 2004; Ringman et al., 2004). SN most likely evolves from subcortical lesions provided that they cause malperfusion or malfunction in cortical regions (Hillis et al., 2002; Karnath, 2001; Karnath, 2009).

Many authors associate the attentional-perceptual component of SN with parietal lesions, and the motor component with frontal damage (Bisiach, Geminiani, Berti, & Rusconi, 1990; Verdon, Schwartz, Lövblad, Hauert, & Vuilleumier, 2010). Husain, Mattingley, Rorden, Kennard and Driver (2000) challenge this conventional view by demonstrating that the inferior parietal lobe does not only play a role in spatial perception, but also in the initial stages of planning for spatial movements, such as reaching towards visual and auditory targets.

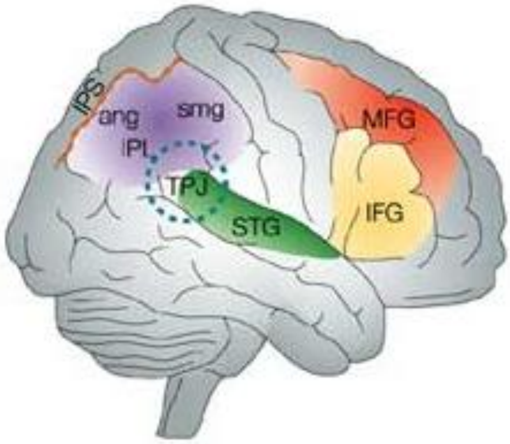

Figure 2. Representation of the cortical regions that can lead to SN when damaged: the temporo-parietal junction (TPJ), the inferior parietal lobe (IPL, consisting of the angular (ang) and supramarginal gyrus (smg)), the intraparietal sulcus (IPS), the superior temporal gyrus

(STG), the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG) (Husain & Rorden, 2003).

1.2 Digital measurements in spatial neglect

Computer-based tests can offer more advantages in SN than are possible in non-computerized tests, such as a higher sensitivity (Deouell, Sacher, & Soroker, 2005; Schendel & Robertson, 2002). However, software to develop these tests is insufficiently known or so far has been unavailable (Bonato, 2012). We used user-friendly software (DiagnoseIS) to develop the VNTB, a battery of diverse types of peripersonal visuospatial tests and measures for SN. Because neglect patients' task performance can be very diverse and even dissociated from each other (as discussed above), it is important to use a battery that gauges various neglect modalities via different tests. The tests are intended for administration on an electronic pen display, preferably with a wide interactive field. As far as we know, the VNTB is novel in its breadth of digitally capturing different modalities of visuospatial neglect on a tablet. It is applicable in any situation that requires mapping peripersonal neglect severity. Originally, though, it was designed to capture treatment effects. Since SN is incapacitating, it is meaningful to examine whether neglect treatments can influence certain components of the syndrome. Two of the VNTB tests do not measure motor modalities, which can shed light on the debate whether or not prism adaptation affects only SN processes with an intentional-motor component (cf. infra). Furthermore, improvements in diverse neglect measures are important, because deficits in these measures are associated with poorer performance in rehabilitation outcomes and functionality (Gillen et al., 2005; Jehkonen et al., 2006; Katz et al., 1999). The different tests of the VNTB are explained in the results section of Chapter 2, because they are the product of the test development process that is based on the method that is clarified there.

1.3 Prism training in spatial neglect

In attempting to reduce neglect symptoms, many different interventions have been proposed. Kerkhoff and Schenk (2012) and Luauté, Halligan, Rode, Rossetti, and Boisson (2006) have reviewed the different neglect interventions and their effectiveness. Meanwhile, sensorimotor realignment by prisms or prism adaptation (PA) is a well-known treatment procedure for SN. It produces a shift in the proprioceptive reference frame to the neglected side by stimulating sensorimotor reorganization (Jacquin-Courtois et al., 2013; Rossetti et al., 1998). During PA with a rightward visual displacement, an observer wears spectacles with prism lenses that shift the visual field to the right (mostly 10º). At the same time, the observer reaches for certain targets such as dots, starting from a central spot (e.g. at the trunk). At first he will reach too far to the right side. This pointing error is gradually reduced, known as "error reduction". After reaching to targets for about five minutes, the prismatic glasses are removed, and an "after-effect" is observed in which the observer reaches too far to the left of a target. Please see Figure 3. This procedure of adaptation to rightward deviating prisms is used in left-sided neglect, and to leftward deviating prisms in right-sided neglect. Some authors have suggested that the amount of after-effect corresponds to the neglect improvement after PA (e.g., Farnè, Rossetti, Toniolo, & Làdavas, 2002; Rossetti et al., 1998). On the contrary, others have stated that the level of error reduction corresponds with this improvement (Serino, Angeli, Frassinetti, & Làdavas, 2006). An enormous advantage of PA in neglect rehabilitation is that it is a bottom-up strategy (Jacquin-Courtois et al., 2013). Consequently, patients' frequently impaired awareness of their lateralized symptoms cannot hinder the prism training.

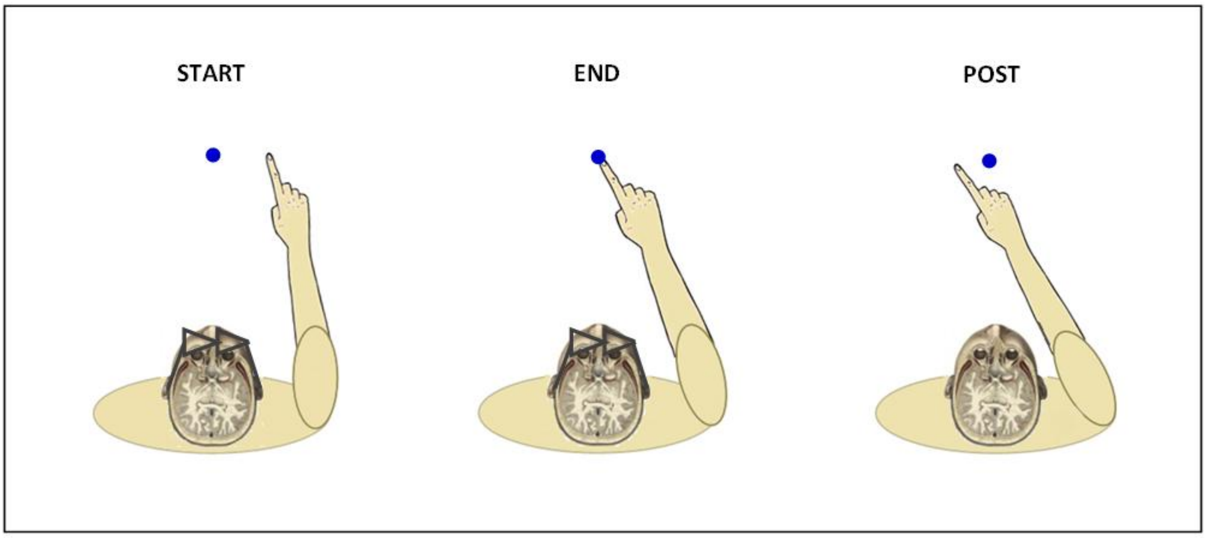

Figure 3. PA with a rightward visual displacement. At start, the observer will misreach to the right of the target. Progressively this pointing error decreases and disappears. The after-effect

is observed post-PA (after removal of the prisms): the observer misreaches to the left of the target.

Certain researchers theorize that PA can affect spatial cognitive processes in the attentional-perceptual as well as the intentional-motor domain, even apart from the modalities that are trained during PA (Jacquin-Courtois et al., 2010; Rode, Klos, Courtois-Jacquin, Rossetti, & Pisella, 2006). Other authors state that PA affects components of the brain network related to spatial action planning and execution (intentional-motor) and not to isolated attentional-perceptual biases (Fortis, Chen, Goedert, & Barrett, 2011; Goedert, Chen, Boston, Foundas, & Barrett, 2014). Still others propose that PA influences attention and visuomotor behaviors that are controlled by the dorsal visual stream, and barely the perceptual biases relying on the ventral visual stream (cf. infra, Striemer and Danckert, 2010; Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003; Sarri, Greenwood, Kalra and Driver, 2011, see Figure 4). The dorsal stream projects from the primary visual cortex to the posterior parietal region and regulates sensorimotor transformations for visually guided actions directed at objects. The ventral stream projects from the primary visual cortex to the inferotemporal cortex and is most important for the perceptual identification of objects (Goodale and Milner, 1992). Event-related fMRI studies in healthy participants demonstrate the involvement of a cortical cerebro-cerebellar network during PA, consisting of the anterior cingulate, anterior intraparietal, parieto-occipital and superior temporal cortices, and the right cerebellum (Danckert, Ferber and Goodale, 2008; Luauté et al., 2009). Patient fMRI data showed increased activation in bilateral parietal, frontal, and occipital cortices after PA, suggesting a transfer from the short-term plastic changes induced by PA to a longer-term reorganization in fronto-parietal networks regulating internal spatial representations (Jacquin-Courtois et al., 2013; Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013, as indicated in Fig. 4).

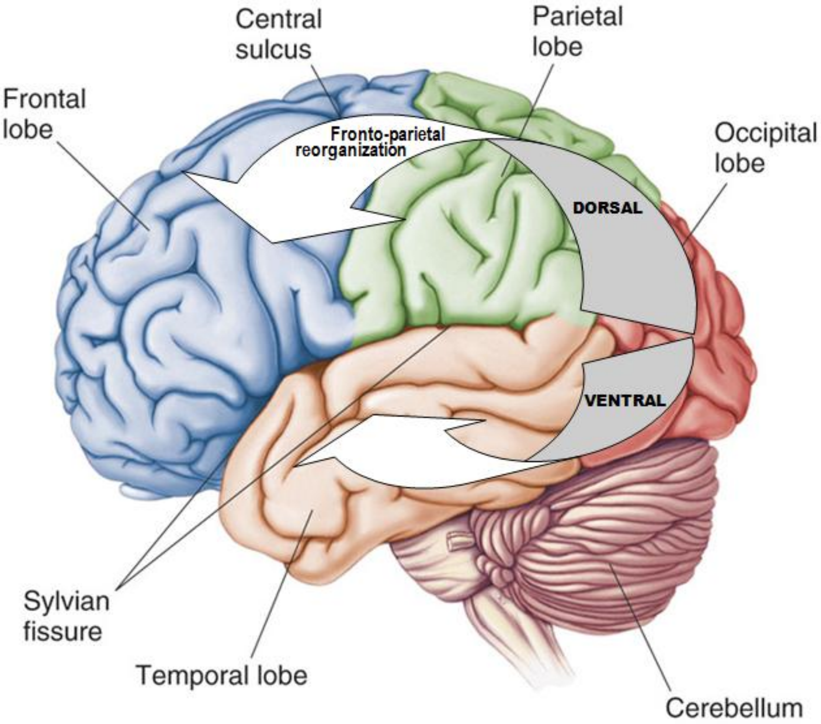

Figure 4. PA induces short-term plastic changes in a cerebro-cerebellar network, leading to a longer-term reorganization in fronto-parietal networks. It is suggested that PA mainly influences attention and visuomotor behaviors controlled by the dorsal stream, and barely perceptual biases relying on the ventral stream.

Striemer and Danckert (2010) propose a parsimonious and plausible neuro-anatomical model to explain the influence of PA on SN. According to their model, during rightward PA, leftward realignment signals are generated in the right cerebellum and transferred to the left SPL and IPS in the dorsal stream. The beneficial after-effects of prisms emerge when the realignment signals from the left SPL/IPS are transmitted through homotopic callosal connections to regions of the right SPL -undamaged in many SN patients- en IPS. Consequently, patients with lesions in SPL/IPS should not show benefits from PA. Furthermore, the inferior parietal lobule and superior temporal gyrus that are frequently damaged in SN, are multimodal association areas important for connecting visual information in the perceptual ventral stream with motor outputs in the dorsal stream. Taking this information together, the authors conclude that PA produces an improvement in spatial attention and visuomotor action, but not in perception.

1.4 Contraversive pushing and postural characteristics in spatial neglect

Patients with contraversive pushing (CP) demonstrate a ‘pusher syndrome’, encompassing a contralesionally tilted posture with severe imbalance, an active pushing away from the ipsilesional side with the non-paretic limbs, and resistance to external attempts to correct their posture (Davies, 1985). CP mainly is reported after stroke, but other cerebral etiologies are possible too (Santos-Pontelli et al., 2004). Most authors observed that CP occurs more frequently after right than after left hemisphere lesions (Davies, 2000; Karnath et al., 2000a; Lafosse et al., 2005). In right-hemispheric patients, CP often is allied with SN (Bateman & Riddoch, 1996; Davies, 2000; Lafosse et al., 2005; Saj, Honoré, Coello, & Rousseaux, 2005). The central transformation of sensory input coordinates to a body centered reference frame is disturbed in SN patients (Karnath, 1994; Ventre, Flandrin, & Jeannerod, 1984). This induces a horizontal deviation of the spatial reference frame, with a corresponding ipsilesional displacement of the subjective body orientation in the axial plane. In line with this, SN patients’ body axis is oriented towards the ipsilesional side, in contrast to the contralesionally tilted body axis in CP patients. Counterintuitively however, Karnath, Ferber, and Dichgans (2000b) found that CP patients’ subjective postural vertical was not displaced contralesionally, but distinctly tilted by 18° towards the ipsilesional side. However, Pérennou et al. (2008) evinced a contralesionally perceived vertical in CP. Furthermore, Honoré, Saj, Bernati and Rousseaux (2009) observed a contralesionally oriented subjective straight ahead in SN patients with CP, as opposed to an ipsilesional subjective straight ahead in SN patients without CP. Table 1 gives an overview of the different characteristics in both patient groups. It is suggested that the pusher syndrome stems from a severe misperception of body orientation in relation to gravity, in the coronal plane. Apparently as a pathological compensation mechanism for this misperception, CP patients push their body *contraversively* (towards the contralesional side) (Karnath, 2007; Karnath et al., 2000b), transferring their center of mass to the contralesional side. On the contrary, the body axis and center of mass of SN patients, reside ipsilesionally (Lafosse, Kerckhofs, Troch, Santens, & Vandenbussche, 2004), as shown in Figure 5. A posterior pusher syndrome is described as well, with similar characteristics as in the CP syndrome, but posterior pushing (PP) is related to the sagittal plane instead of the coronal plane (Davies, 1985; Cardoen & Santens, 2010).

Table 1

Overview of the differences between SN patients with versus without CP

	SN with CP	SN without CP
Body axis	contralesional	ipsilesional
Centre of mass	contralesional	ipsilesional
Subj. postural vertical	contralesional (Pérennou) ipsilesional (Karnath)	ipsilesional
Subj. straight ahead	contralesional	ipsilesional
Hypothetical cause	severe misperception of body orientation in relation to gravity	disturbed sensory based central neurologic generation of body-centered reference frame

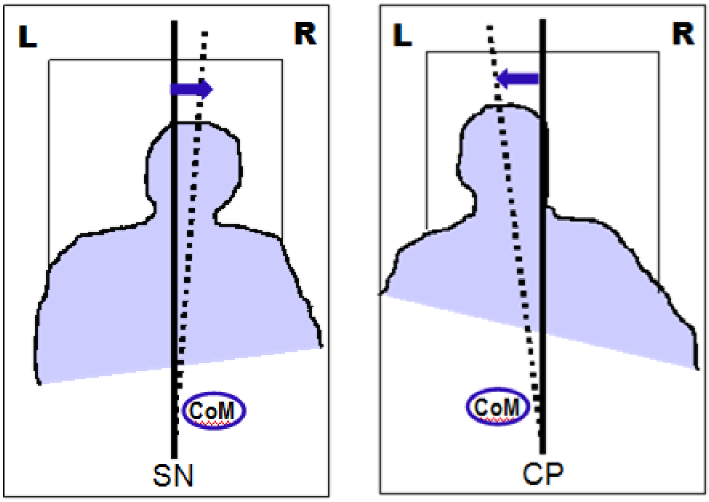

Figure 5. Schematic representation of the difference in body orientation (back of trunk) and center of mass (CoM) between right-hemispheric SN patients (ipsilesional deviation) and CP patients (contralesional deviation), as explained in Lafosse et al. 2004 and 2007.

Given the disturbance in the sensory based central neurologic generation of the body-centered reference frame in SN, Karnath, Christ, and Hartje (1993) manipulated the proprioceptive input (the head-on-trunk signal) in right-hemispheric SN patients. They observed that SN decreases by turning the trunk 15° to the left (real lengthening of the posterior neck muscles) or by vibrating the left posterior neck muscles (apparent lengthening). These results were hypothetically interpreted in line with a contralesional shift in two components necessary for visuomotor coordination and space exploration, namely the subjective midplane localization and the egocentric coordinate system. The trunk midline constitutes the physical anchor for the generation of the egocentric reference frame, allowing the determination of body position with respect to visual space. Hence the spatial orientation of the trunk seems to be determinant for neglecting the contralesional part of space, by dividing space perception into an egocentric “left” and “right” sector (Karnath, Schenkel, & Fischer, 1991). Intrigued by these studies and the distinct postural characteristics of patients with SN on the one hand and CP on the other, the question sets in about the possibility of a correspondingly distinct pattern of visuospatial functioning in these two patient groups. In 2008-2009 we conducted an exploratory investigation (unpublished academic thesis) that was suggestive of a cross-over phenomenon in SN patients with CP. This preliminary finding nourished the implementation of the case-control study which is described in Chapter 4.

2 Overview of the research aims and questions

Table 2 represents a schematic overview of the main characteristics of the three studies that will be discussed in this doctoral thesis. The aim of the first article (Chapter 2) was the development of a digital Visuospatial Neglect Test Battery for administration on an electronic pen display, consisting of various types of tests. The battery was intended for answering the research questions formulated in Chapter 3 and 4, but also for clinical usage. It aims to measure the lateralized attentional and exploration deficits in SN, illustrated in the article by a case study. The related research question regarding the expected differences in test performance between a SN group and an age- and education-matched healthy control group is also answered in Chapter 2. The article further discusses the test properties and the advantages of the digital measurement method in SN.

In Chapter 3, we question whether a mild treatment regime of 7 PA sessions can improve SN processes in hospitalized patients with heterogeneous post-stroke delays. This practically feasible regime enabled us to explore whether it would be beneficial in practice to offer PA during short hospitalization periods, for instance in a stroke unit. We use multiple visuospatial measures of the VNTB (see Chapter 2) and examine which specific SN processes are influenced. From a theoretical point of view, it is relevant to inspect whether PA influences only test performances that require an intentional-motor component, or other cognitive processes as well. The assessments are conducted after a short and long time interval. An explorative research question is formulated about the potential differences in PA effects between acute, subacute and chronic subgroups of patients.

In the article of Chapter 4, we investigate whether right-hemispheric patients' visuospatial behavior and orienting manifest itself differently in SN patients with versus without CP. Their distinct postural pattern, ipsilesionally oriented in SN patients without CP, and shifted from the ipsilesional towards the contralesional side in SN patients with CP, led us to the research question about a contralesionally directed shift in cognitive functioning in SN patients with CP ("contraversive neglect"), compared to SN patients without CP. To be able to monitor whether or not this is the case, we conceived a digital navigation task which allows for quasi unrestricted lateral visuomotor deviation (within the limits of the task surface). In addition, we inspected whether a contralesional instead of ipsilesional deviation (cross-over) in long line bisection is a phenomenon characterizing SN patients with CP, as opposed to SN patients without CP. The navigation and line bisection tasks are part of the digital VNTB that is described in Chapter 2 (Vaes et al., 2015).

Table 2

Schematic overview of the studies in the thesis

Study	**Chapter 2**	**Chapter 3**	**Chapter 4**
Type	methodological	interventional	theoretical
Aim	developing SN assessments to combine with digital tablet	1. studying effects of a mild PA regime on SN 2. exploring PA impact in Ac, SAc, Chr phase	examining peripersonal visuospatial behavior related to postural characteristics
Design	1. CCS to inspect discriminant validity 2. CS as illustration	1. RCT 2. Subgroup comparisons in Ac, SAc, Chr SN	1. CCS 2. CS with PP
Inclusions	1. 20 healthy – 20 SN → 2. 1 SN (casus)	1. 21 EG – 22 CG ← 2. 13 Ac, 18 SAc, 12 Chr	1. 8 NP$^-$ – 9 NP$^+$ 2. 1 SN with PP (casus)

Abbreviations: SN, spatial neglect; PA, prism adaptation; CCS, case-control study; CS, case study; RCT, randomized controlled trial; Ac, acute; SAc, subacute; Chr, chronic; EG, experimental group; CG, control group; PP, posterior pushing; NP$^-$, neglect without contraversive pushing; NP$^+$, neglect with contraversive pushing.

→ : extracted from.

3 The common thread: embodied cognition in peripersonal space

The PPS is critical for behavior, as most interactions between the individual and external world take place in this region. Our brain generates a multisensory representation of PPS, distinguishing stimuli that are close to the body from those that are further away, to enable defensive or approaching responses. This system of multisensory coding of space linked to motor actions, is located in fronto-parietal networks (Serino, in press). The many neurons of this network that are involved in multisensory integration typically have spatially congruent receptive fields in the different modalities that can stimulate them. This means that stimulations from the same external location drive the cell, across the different modalities (Pouget & Driver, 2000). For instance in macaque research, visuo-auditory cells are present in the lateral intraparietal area and parietal reach region, visuo-vestibular cells in the ventral intraparietal area (VIP), visuo-tactile cells in the VIP and the prefrontal cortex. The combination of multisensory integration and movement planning points to the parieto-prefrontal network as a sensorimotor interface in PPS (Noel et al., 2015; Pouget & Driver, 2000). The digital VNTB measurements that are explained in Chapter 2, are developed to capture cognitive functioning in PPS. As will be discussed in Chapter 3, PA is one of the rehabilitation techniques for SN that influences the cerebral plasticity inherent to this sensorimotor PPS representation, leading to a longer-term reorganization in fronto-parietal networks. PA can be seen as an indirect way to correct patients' egocentric reference frame by sensorimotor reintegration, to redefine their sense of where they are in relation to the space around them (Kerkhoff & Schenk, 2012). Serino et al. (2015) suggest that the global egocentric representation of space is formed in relation to the trunk-centered PPS, which integrates not only bodily signals, but also information from external stimuli potentially interacting with the body. They propose that the whole-body reference frame is anchored to the trunk PPS representation, where smaller body-part centered representations are referenced to. This means that a reference to the trunk is incorporated in the construction of a multisensory space representation surrounding, for instance, the head or arm, while the head or arm position is irrelevant for a trunk-centered spatial representation. The trunk-based egocentric PPS representation enables body-object interactions as a multisensory-motor interface. A distortion in this representational system leads to a deviation in humans' behavior in PPS, as seen in SN patients (Karnath et al., 1991; Karnath et al. 1993). In Chapter 4, we investigate whether two different distortions in the egocentric body representation anchored to the trunk are accompanied by correspondingly different patterns of cognitive behavior in PPS.

References

Aimola, L., Schindler, I., & Venneri, A. (2013). Task- and response related dissociations between neglect in near and far space: A morphometric case study. *Behavioural Neurology, 27*(3), 245-257.

Barrett, A.M., & Muzaffar, T. (2014). Spatial cognitive rehabilitation and motor recovery after stroke. *Current Opinion in Neurology, 27,* 653–658. doi: 10.1097/WCO.0000000000000148

Bateman, A., & Riddoch, M.J. (1996). Neuropsychological perspectives on ″pusher syndrome″. *European Journal of Phyical Medicine and Rehabilitation, 6*(3), 93-96.

Beschin, N., Basso, A., & Della Sala, S. (2000). Perceiving left and imagining right: dissociation in neglect. *Cortex, 36*(3), 401-414.

Binder, J., Marshall, R., Lazar, R., Benjamin, J., & Mohr, J.P. (1992). Distinct syndromes of hemineglect. *Archives of Neurology, 49,* 1187-1194.

Bisiach, E., Geminiani, G., Berti, A., & Rusconi, M.L. (1990). Perceptual and premotor factors of unilateral neglect. *Neurology, 40*, 1278-1281.

Bisiach, E., McIntosh, R.D., Dijkerman, H.C., McClements, K.I., Colombo, M., & Milner, A.D. (2004). Visual and tactile length matching in spatial neglect. *Cortex, 40*(4-5), 651-657.

Bisiach, E., Pizzamiglio, L., Nico, D., & Antonucci, G. (1996). Beyond unilateral neglect. *Brain, 119*(3), 851–857. doi: 10.1093/brain/119.3.851

Bonato, M. (2012). Neglect and extinction depend greatly on task demands: a review. *Frontiers in Human Neuroscience, 6*(195). doi: 10.3389/fnhum.2012.00195

Bonatoa, M., Priftis, K., Marenzi , R., Umiltàa, C., & Zorzi, M. (2010). Increased attentional demands impair contralesional space awareness following stroke. *Neuropsychologia, 48,* 3934–3940.

Bowen, A., McKenna, K., & Tallis, R.C. (1999). Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. *Stroke, 30*, 1196–1202. doi: 10.1161/01.STR.30.6.1196

Buxbaum, L.J., Ferraro, M.K., Veramonti, T., Farnè, A., Whyte, J., Làdavas, E., Frassinetti, F., & Coslett, H.B. (2004). Hemispatial neglect: subtypes, neuroanatomy, and disability. *Neurology, 62*, 749-756.

Cardoen, S., & Santens, P. (2010). Posterior pusher syndrome: A report of two cases. *Clinical Neurology and Neurosurgery, 112*(4), 347-349. doi: 10.1016/j.clineuro.2009.12.007

Corbetta, M., & Shulman, G.L. (2011). Spatial neglect and attention networks. *Annual Review of Neuroscience, 34*, 569–99. doi: 10.1146/annurev-neuro-061010-113731

Chen, P., Hreha, K., Fortis, P., Goedert, K.M., & Barrett, A.M. (2012). Functional assessment of spatial neglect: a review of the Catherine Bergego Scale and an introduction of the Kessler Foundation Neglect Assessment Process. *Top Stroke Rehabilitation, 19*(5), 423–435.

Cocchini, G., Cubelli, R., Della Sala, S., & Beschin, N. (1999). Neglect without extinction. *Cortex, 35*(3), 285–313.

Coslett, H.B. (1997). Neglect in vision and visual imagery: a double dissociation. *Brain, 120,* 1163-1171.

Danckert, J., Ferber, S., & Goodale, M.A. (2008). Direct effects of prismatic lenses on visuomotor control: an event-related fMRI study. *European Journal of Neuroscience, 28*, 1696-1704.

Davies, P.M. (1985). *Steps to follow. A guide to the treatment of adult hemiplegia.* New York, NY: Springer.

Davies, P.M. (2000). *Steps to follow. A guide to the treatment of adult hemiplegia.* New York: Springer. doi: 10.1007/978-3-642-57022-3

de Haan, B., Karnath, H.O., & Driver, J. (2012). Mechanisms and anatomy of unilateral extinction after brain injury.". *Neuropsychologia, 50*(6), 1045–53. doi: 10.1016/j.neuropsychologia.2012.02.015

Deouell, L.Y., Sacher, Y., & Soroker, N. (2005). Assessment of spatial attention after brain damage with a dynamic reaction time test. *Journal of the International Neuropsychological Society, 11,* 697-707.

di Pellegrino, G., & Làdavas, E. (2015). Peripersonal space in the brain. *Neuropsychologia, 66*, 126-133. doi: 10.1016/j.neuropsychologia.2014.11.011

Farnè, A., Rossetti, Y., Toniolo, S., & Làdavas, E. (2002). Ameliorating neglect with prism adaptation: Visuo-manual and visuo-verbal measures. *Neuropsychologia, 40*, 718-729.

Fortis, P., Chen, P., Goedert, K.M., & Barrett, A.M. (2011). Effects of prism adaptation on motor-intentional spatial bias in neglect. *Neuroreport, 22*(14), 700-705. doi: 10.1097/WNR.0b013e32834a3e20

Gillen, R., Tennen, H., & McKee, T. (2005). Unilateral spatial neglect: Relation to rehabilitation outcomes in patients with right hemisphere stroke. *Archives of Physical Medicine and Rehabilitation, 86*(4), 763-767.

Goedert, K.M., Chen, P., Boston, R.C., Foundas, A.L., & Barrett, A.M. (2014). Presence of motor-intentional aiming deficit predicts functional improvement of spatial neglect with prism adaptation. *Neurorehabilitation and Neural Repair, 28,* 483-493. doi: 10.1177/1545968313516872

Goodale, M.A. & Milner, A.D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences, 15,* 20-25.

Guariglia, C., & Antonucci, G. (1992). Personal and extrapersonal space - a case of neglect dissociation. *Neuropsychologia, 30*(11), 1001-1009.

Halligan, P.W., & Marshall, J.C. (1991). Left neglect for near but not far space in man. *Nature, 350*(6318), 498-500.

Heilman, K.M., Valenstein, I.E., & Watson, R.T. (1985). The neglect syndrome. In: P.J. Vinken, G.W. Bruyn & H.L. Klawans (Eds.), *Handbook of Clinical Neurology* (Vol. 45, pp. 152-183). Amsterdam, The Netherlands: Elsevier Science Publishers.

Heilman, K.M., Valenstein E., & Watson, R.T. (1994). The what and the how of neglect. In P.W. Halligan & J.C. Marshall (Eds.). *Spatial Neglect: position papers on theory and practice* (pp. 133-141). Hove, UK: Erlbaum.

Heilman, K.M., Watson, R.T., & Valenstein, E. (1993). Neglect and related disorders. In K.M. Heilman & E. Valenstein (Eds.). *Clinical Neuropsychology* (pp. 279–336). New York, NY: Oxford University Press.

Hillis, A.E., Wityk, R.J., Barker, P.B., Beauchamp, N.J., Gailloud, P., Murphy, K., ..., & Metter, E.J. (2002). Subcortical aphasia and neglect in acute stroke: the role of cortical hypoperfusion. *Brain, 125,* 1094–1104. doi:10.1093/brain/awf113

Honoré, J., Saj, A., Bernati, T., & Rousseaux, M. (2009). The pusher syndrome reverses the orienting bias caused by spatial neglect. *Neuropsychologia, 47*(3), 634-638. doi: 10.1016/j.neuropsychologia.2008.11.008

Husain, M., Mattingley, J.B., Rorden, C., Kennard, C., & Driver, J. (2000). Distinguishing sensory and motor biases in parietal and frontal neglect. *Brain, 123,* 1643–1659.

Husain, M., & Rorden, C. (2003). Non-spatially lateralized mechanisms in hemispatial neglect. *Nature Reviews Neuroscience, 4*(1), 26–36. doi: 10.1038/nrn1005

Jacobs, S., Brozzoli, C., & Farnè, A. (2012). Neglect: A multisensory deficit? *Neuropsychologia, 50,* 61029-1044. doi: 10.1016/j.neuropsychologia.2012.03.018

Jacquin-Courtois, S., O'Shea, J., Luaute, J., Pisella, L., Revol, P., Mizuno, K., …, Rossetti, Y. (2013). Rehabilitation of spatial neglect by prism adaptation. A peculiar expansion of sensorimotor after-effects to spatial cognition. *Neuroscience and Biobehavioral Reviews, 37*(4), 594-609. doi: 10.1016/j.neubiorev.2013.02.007

Jacquin-Courtois, S., Rode, G., Pavani, F., O'Shea, J., Giard, M.H., Boisson, D., & Rossetti, Y. (2010). Effect of prism adaptation on left dichotic listening deficit in neglect patients: glasses to hear better? *Brain, 133,* 895-908. doi: 10.1093/brain/awp327

Jehkonen, M., Laihosalo, M., & Kettunen, J.E. (2006). Impact of neglect on functional outcome after stroke – a review of methodological issues and recent research findings. *Restorative Neurology and Neuroscience, 24*(4-6), 209-215.

Ferber, S., Danckert, J., Joanisse, M., Goltz, H.C., & Goodale, M.A. (2003). Eye movements tell only half the story. *Neurology, 60,* 1826–1829.

Johannsen, L., Broetz, D., Naegele, T., & Karnath, H.O. (2006). "Pusher syndrome" following cortical lesions that spare the thalamus. *Journal of Neurology, 253*(4), 455-463. doi: 10.1007/s00415-005-0025-7

Karnath, H.O. (1994). Disturbed coordinate transformation in the neural representation of space as the crucial mechanism leading to neglect. *Neuropsychological Rehabilitation, 4*(2), 147-150. doi: 10.1080/09602019408402273

Karnath, H.O. (2001). New insights into the functions of the superior temporal cortex. *Nature Reviews Neuroscience, 2,* 568-576. doi:10.1038/35086057

Karnath, H.O. (2007). Pusher Syndrome - a frequent but little-known disturbance of body orientation perception. *Journal of Neurology, 254*(4), 415-424. doi: 10.1007/s00415-006-0341-6

Karnath, H.O. (2009) A right perisylvian neural network for human spatial orienting. In: M.S. Gazzaniga (Ed.), *The Cognitive Neurosciences* (Vol. 4, pp. 259–268). Cambridge, MA: MIT Press.

Karnath, H.O., Christ, K., & Hartje, W. (1993). Decrease of contralateral neglect by neck muscle vibration and spatial orientation of trunk midline. *Brain: A Journal of Neurology, 116,* 383-396. doi: 10.1093/brain/116.2.383

Karnath, H.O., Ferber, S., & Dichgans, J. (2000a). The neural representation of postural control in humans. *Proceedings of the National Academy of Sciences of the United States of America, 97*(25), 13931-13936. doi: 10.1073/pnas.240279997

Karnath, H.O., Ferber, S., & Dichgans, J. (2000b). The origin of contraversive pushing: evidence for a second graviceptive system in humans. *Neurology, 55*(9), 1298-1304. doi: /10.1212/WNL.55.9.1298

Karnath, H.O., Fruhmann, B.M., Küker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: a study of 140 patients. *Cerebral Cortex, 14*(10), 1164–1172.

Karnath, H.O., Johannsen, L., Broetz, D., & Küker, W. (2005). Posterior thalamic hemorrhage induces "pusher syndrome". *Neurology, 64*(6), 1014-1019. doi: 10.1212/01.WNL.0000154527.72841.4A

Karnath, H.O., Schenkel, P., & Fischer, B. (1991). Trunk orientation as the determining factor of the contralateral deficit in the neglect syndrome and as the physical anchor of the internal representation of body orientation in space. *Brain: A Journal of Neurology, 114*, 1997-2014. doi: 10.1093/brain/114.4.1997

Karnath, H.O., Suchan, J., & Johannsen, L. (2008). Pusher syndrome after ACA territory infarction. *European Journal of Neurology, 15*(8), e84-e85. doi: 10.1111/j.1468-1331.2008.02187.x

Katz, N., Hartman-Maeir, A., Ring, H., Soroker, N. (1999). Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. *Archives of Physical Medicine and Rehabilitation, 80*(4), 379-384.

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: An update. *Neuropsychologia, 50*, 1072-1079. doi: 10.1016/j.neuropsychologia.2012.01.024

Kinsbourne, M. (1993). Orientational bias model of unilateral neglect: Evidence from attentional gradients within hemispace. In I. H. Robertson, & J. C. Marshall (Eds.), *Unilateral neglect: Clinical and experimental studies* (pp. 63–86). Hove, UK: Erlbaum.

Lafosse, C., Kerckhofs, E., Troch, M., Santens, P., & Vandenbussche, E. (2004). Graviceptive misperception of the postural vertical after right hemisphere damage. *Neuroreport, 15*(5), 887-891. doi: 10.1097/00001756-200404090-00031

Lafosse, C., Kerckhofs, E., Troch, M., Vereeck, L., Van Hoydonck, G., Moeremans, M., . . . Vandenbussche, E. (2005). Contraversive pushing and inattention of the contralesional hemispace. *Journal of Clinical and Experimental Neuropsychology, 27*(4), 460-484. doi: 10.1080/13803390490520463

Lafosse, C., Kerckhofs, E., Vereeck, L., Troch, M., Van Hoydonck, G., Moeremans, M., Sneyers, C., Broeckx, J., Dereymaeker, L. (2007). Postural abnormalities and contraversive pushing following right hemispheric brain damage. *Neuropsychological Rehabilitation, 17*(3), 374-396. doi: 10.1080/09602010601058854

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological Assessment* (4th ed.). New York, NY: Oxford University Press.

Luauté, J., Halligan P., Rode, J., Rossetti, Y., & Boisson, D. (2006). Visuo-spatial neglect: A systematic review of current interventions and their effectiveness. *Neuroscience & Biobehavioral Reviews, 30,* 961-982. doi: 10.1016/j.neubiorev.2006.03.001

Luauté, J., Schwartz, S., Rossetti, Y., Spiridon, M., Rode, G., Boisson, D., & Vuilleumier, P. (2009). Dynamic changes in brain activity during prism adaptation. *The Journal of Neuroscience, 29*(1), 169–178.

Milner, A.D., & McIntosh, R.D. (2005). The neurological basis of visual neglect. *Current Opinion in Neurology, 18,* 748-753.

Na, D.L., Adair, J.C., Williamson, D.J.G., Schwartz, R.L., Haws, B., & Heilman, K.M. (1998). Dissociation of sensory-attentional from motor-intentional neglect. *Journal of neurology, neurosurgery and psychiatry, 64*(3), 331-338.

Noel, J.P., Grivaz, P., Marmaroli, P., Lissek, H., Blanke, O., & Serino A. Full body action remapping of peripersonal space: the case of walking (2015). *Neuropsychologia*. 70: 375-84. doi: 10.1016/j.neuropsychologia.2014.08.030

Nys, G.M., Van Zandvoort, M.J., Van der Worp, H.B., Kappelle, L.J., & de Haan, E.H.F. (2006). Neuropsychological and neuroanatomical correlates of perseverative responses in subacute stroke. *Brain, 129,* 2148-2157. doi: 10.1093/brain/awl199

Paci, M., & Nannetti, L. (2005). The pusher syndrome in a patient with cerebellar infarction. *Physiotherapy Research International, 10*(3), 176-177. doi: 10.1002/pri.8

Pérennou, D. A., Mazibrada, G., Chauvineau, V., Greenwood, R., Rothwell, J., Gresty, M. A., & Bronstein, A. M. (2008). Lateropulsion, pushing and verticality perception in hemisphere stroke: a causal relationship? *Brain, 131*(9), 2401-2413. doi: 10.1093/brain/awn170

Plummer, P., Morris, M.E., & Dunai, J. (2003). Assessment of unilateral neglect. *Physical Therapy, 83*(8), 732-740.

Posner, M.I., Walker, J.A., Friedrich, F.J., & Rafal, R.D. (1984). Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience, 4*(7), 1863–1874.

Pouget, A., & Driver, J. (2000). Relating unilateral neglect to the neural coding of space. *Current Opinion in Neurobiology, 10,* 242-249. doi: 10.1016/S0959-4388(00)00077-5

Ringman, J.M., Saber, J.L., Woolson, R.F., Clarke, W.R., & Adams, H.P. (2004). Frequency, risk factors anatomy, and course of unilateral neglect in an acute stroke cohort. *Neurology, 63,* 468-474. doi: http://dx.doi.org/10.1212/01.WNL.0000133011.10689.CE

Robertson, I.H., & Halligan, J.C. (2000). *Spatial Neglect: A clinical handbook for diagnosis and treatment*. Hove, UK: Psychology Press.

Rode, G., Klos, T., Courtois-Jacquin, S., Rossetti, Y., & Pisella, L. (2006). Neglect and prism adaptation: a new therapeutic tool for spatial cognition disorders. *Restorative Neurology and Neuroscience, 24*(4-6), 347-356.

Ronchi, R., Algeri, L., Chiapella, L., Spada, M.S., & Vallar, G. (2012). Spatial neglect and perseveration in visuomotor exploration. *Neuropsychology, 26,* 588-603.

Ronchi, R., Posteraro, L., Fortis, P., Bricolo, E., & Vallar, G. (2009). Perseveration in left spatial neglect: drawing and cancellation tasks. *Cortex, 45*, 300-312.

Rossetti, Y., Rode, G., Pisella, L., Farnè, A., Ling, L., Boisson, D., & Perenin, M.T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature*, *395*, 166-169. doi: 10.1038/25988

Saj, A., Cojan, Y., Vocat, R., Luauté, J., & Vuilleumier, P. (2013). Prism adaptation enhances activity of intact fronto-parietal areas in both hemispheres in neglect patients. *Cortex, 49*, 107-119.

Saj, A., Honoré, J., Coello, Y., & Rousseaux, M. (2005). The visual vertical in the pusher syndrome - Influence of hemispace and body position. *Journal of Neurology, 252*(8), 885-891. doi: 10.1007/s00415-005-0716-0

Santos-Pontelli, T.E.G., Pontes-Neto, O.M., Colafemina, J.F., de Araujo, D.B., Santos, A., & Leite, J.P. (2004). Contraversive pushing in non-stroke patients. *Journal of Neurology, 251*(11), 1324-1328. doi: 10.1007/s00415-004-0532-y

Sarri, M., Greenwood, R., Kalra, L., & Driver, J. (2011). Prism adaptation does not change the rightward spatial preference bias found with ambiguous stimuli in unilateral neglect. *Cortex, 47*, 353-366.

Schendel, K.L., & Robertson, L.C. (2002). Using reaction times to assess patients with unilateral neglect and extinction. *Journal of Clinical and Experimental Neuropsychology, 24,* 942-950.

Serino, A. (in press). Variability in multisensory responses predicts the self-space. *Trends in Cognitive Sciences*. doi: http://dx.doi.org/10.1016/j.tics.2016.01.005

Serino, A., Angeli, V., Frassinetti, F., & Làdavas, E. (2006). Mechanisms underlying neglect recovery after prism adaptation. *Neuropsychologia, 44,* 1068-1078.

Serino, A., Noel, J.P., Galli, G., Canzoneri, E., Marmaroli, P., Lissek, H., Blanke, O. (2015). Body part-centered and full body-centered peripersonal space representations. *Scientific Reports, 5,* 18603. doi: 10.1038/srep18603

Sinnett, S., Juncadella, M., Rafal, R., Azañón, E., & Soto-Faraco, S. (2007). A dissociation between visual and auditory hemi-inattention: Evidence from temporal order judgements. *Neuropsychologia, 45*(3), 552-560. doi: 10.1016/j.neuropsychologia.2006.03.006

Stone, S.P., Halligan, P.W., Marshall, J.C., & Greenwood R.J. (1998). Unilateral neglect: a common but heterogeneous syndrome. *Neurology, 50,* 1902-1905.

Stone, S.P., Wilson, B., Wroot, A., Halligan, P.W., Lange, L.S., Marshall, J.C., & Greenwood, R.J. (1991). The assessment of visuo-spatial neglect after acute stroke. *Journal of Neurology, Neurosurgery and Psychiatry, 54*, 345-350.

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests. Administration, Norms, and Commentary*. New York, NY: Oxford University Press.

Striemer, C.L., & Danckert, J.A. (2010). Through a prism darkly: re-evaluating prisms and neglect. *Trends in Cognitive Sciences, 14*(7), 308-316.

Taylor , D. (2003). Measuring mild visual neglect: Do complex visual tests activate rightward attentional bias? *New Zealand Journal of Physiotherapy, 31*(2), 67-72.

Tatuene, J.K., Allali, G., Saj, A., Bernati, T., Sztajzel, R., Pollak, P., & Momjian-Mayor, I. (2016). Incidence, Risk Factors and Anatomy of Peripersonal Visuospatial Neglect in Acute Stroke. *European Neurology, 75*(3-4), 157-63. doi: 10.1159/000444709

Ticini, L. F., Klose, U., Nägele, T., & Karnath, H.O. (2009). Perfusion imaging in Pusher syndrome to investigate the neural substrates involved in controlling upright body position. *PloS ONE, 4*(5), e5737. doi: 10.1371/journal.pone.0005737

Vallar, G., Bottini, G., & Sterzi, R. (2003). Anosognosia for left-sided motor and sensory deficits, motor neglect, and sensory hemi-inattention: is there a relationship? *Progress in Brain Research, 142,* 289-301.

Ventre, J., Flandrin, J. M., & Jeannerod, M. (1984). In search for the egocentric reference. A neurophysiological hypothesis. *Neuropsychologia, 22*(6), 797-806. doi: 10.1016/0028-3932(84)90104-0

Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., & Vuilleumier, P. (2010). Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. *Brain, 133,* 880-894.

Vossel, S., Eschenbeck, P., Weiss, P.H., Weidner, R., Saliger, J., Karbe, H., & Fink, G.R. (2011). Visual extinction in relation to visuospatial neglect after right-hemispheric stroke: quantitative assessment and statistical lesion-symptom mapping. *Journal of Neurology, Neurosurgery, and Psychiatry, 82*(8), 862-868.

World Health Organization, regional office for the Eastern Mediterranean. (2016, September 1). Stroke, cerebrovascular accident. Retrieved from http://www.emro.who.int/health-topics/stroke-cerebrovascular-accident/index.html.

Chapter 2: Measuring Method in Spatial Neglect

2.1 Aim of the study

The SN syndrome is inherently multi-componential. Jehkonen, Laihosalo and Kettunen (2006) recommended that future research should assess various forms of neglect with a standardized test battery, rather than using a single test. Moreover, neglect patients' performances can be different and even dissociated in different types of tests. Therefore, we developed a digital Visuospatial Neglect Test Battery for administration on an electronic pen display, consisting of various types of tests. The battery fits well with the aim of measuring the lateralized attentional and exploration deficits in SN, in a clinical or experimental context. We employed the test battery for assessing treatment effects as described in Chapter 3, and some measures to map a behavioral difference between SN patients with and without CP, as explained in Chapter 4. The article below demonstrates the test properties and the advantages of the digital measurement method in SN. A case study is elaborated to illustrate the discourse. Furthermore, the article contains comparative analyses of the test performances of a neglect group and an age- and education-matched healthy control group.

2.2 Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes

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Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes

**Nathalie Vaes · Christophe Lafosse · Gudrun Nys ·
Hanne Schevernels · Lutgart Dereymaeker ·
Kristine Oostra · Dimitri Hemelsoet · Guy Vingerhoets**

Abstract

Computerized as well as paper-and-pencil tasks are applied in mapping visuospatial neglect in experimental research and clinical practice. This article presents a new kind of computer-based assessment method, using an electronic pen display and user-friendly software. The approach is tailored to specific spatial processes and highlights the usefulness of a pen display in neglect patients. The advantages of the introduced method are illustrated by a recently designed battery of classic as well as new types of tests. The development of the appropriate stimuli and assorted scoring system is addressed, as well as the resulting types of task implementation and data generation. The diagnostic value of the different visuospatial neglect tests is demonstrated by comparative analyses between a neglect group and a control group. Among the benefits of the proposed assessment method are the opportunity of standardized repeated measurements to quantify recovery, online performance monitoring, flexible employment, exact and little time-consuming data collection and the easy availability of more refined quantitative as well as interesting qualitative information, especially as compared to classic or paper-and-pencil tasks. To indicate that this method also lends itself well to measures for treatment procedures, an illustration is given with respect to specific measurements during prism adaptation. The tasks of the Visuospatial Neglect Test Battery and the prism adaptation measures are illustrated by a case study. The outlined applications are discussed with respect to experimental as well as clinical purposes.

Keywords

visuospatial neglect, peripersonal neglect, computer-based assessment, pen display, electronic test battery, digital measurements

Background on the Theoretical Concepts

Spatial or unilateral neglect is a disabling condition in which patients fail to orient, report or respond to stimuli in contralesional space (Heilman, Valenstein, & Watson, 1985). Next to the shortage of responses contralesionally, neglect patients may also show an excess of responses in ipsilesional space, such as perseverations (Nys, Van Zandvoort, Van der Worp, Kappelle, & de Haan, 2006; Ronchi, Algeri, Chiapella, Spada, & Vallar, 2012; Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009). Unilateral neglect is not caused by primary sensory or motor dysfunction, it is a higher order disorder (Heilman, Watson, & Valenstein, 1993). Neglect patients seem unaware of their contralesional side and seem to act as if it does not exist. Moreover, they often are not aware of this condition (Vallar, Bottini, & Sterzi, 2003), which makes compensating for it difficult. This contributes to the finding that neglect is a predictor of poor functional independence after stroke (Jehkonen et al., 2000; Jehkonen, Laihosalo, & Kettunen, 2006).

Spatial neglect is a heterogeneous disorder, manifesting itself in many different ways and degrees of severity (Heilman, Valenstein, & Watson, 1994; Robertson & Halligan, 2000; Stone, Halligan, Marshall, & Greenwood, 1998). Patients differ from each other in terms of the symptoms and their diverse combinations. Many symptoms can be dissociated from each other. Examples include hemineglect for personal (Guariglia & Antonucci, 1992), peripersonal and/or extrapersonal space (Aimola, Schindler, & Venneri, 2013; Halligan & Marshall, 1991), neglect with or without extinction (Cocchini, Cubelli, Della Sala, & Beschin, 1999; Vossel et al., 2011), contralesionally neglecting the visual, auditive (Sinnett, Juncadella, Rafal, Azanon, & Soto-Faraco, 2007) and tactile modality (Bisiach et al., 2004), and neglect for the imaginary (Beschin, Basso, & Della Sala, 2000; Coslett, 1997), sensory and/or the motor domain (Aimola et al., 2013; Na et al., 1998). Even within one of these listed modalities, patients can differ considerably from each other. Within the peripersonal visual dimension for instance, a patient’s test performances can be hemispatially distorted at one type of task, but not in another kind of task. For example, Binder, Marshall, Lazar, Benjamin and Mohr (1992), and Milner and McIntosh (2005) describe a double dissociation between the performances regarding cancellation and bisection.

Although different neglect symptoms can stand alone, spatial neglect mostly concerns a cluster of lateralized deficits encompassing a clinical syndrome. It can originate from damage to different neural mechanisms (Heilman et al., 1985; Stone et al., 1998). Neglect manifests itself more frequently and significantly after right hemisphere pathology (Bisiach, 1999; Halligan & Marshall, 1994). Up to two thirds of right hemispheric stroke patients are acutely affected by neglect (Stone et al., 1991).

In attempting to reduce neglect symptoms, many different interventions have been proposed. See Kerkhoff and Schenk (2012) and Luauté, Halligan, Rode, Rossetti and Boisson (2006) for reviews of neglect interventions and their effectiveness. A much discussed treatment procedure for spatial neglect is prism adaptation (Rossetti et al., 1998). During prism adaptation with a rightward visual displacement, an observer wears spectacles with prism lenses that shift the visual field to the right (mostly 10º). At the same time, he/she reaches for certain targets such as dots, starting from a central spot (e.g. at the trunk). At first the observer will reach too far to the right side. This pointing error is gradually reduced, known as “error reduction”. After reaching to targets for about five minutes, the prismatic glasses are removed, and an “after-effect” is observed in which he/she reaches too far to the left of a target. For a clear illustration, see Parton, Malhotra and Husain (2004). During prism adaptation in left-sided neglect, patients wear prism lenses with such a rightward visual displacement. Some authors suggest that the amount of after-effect corresponds to the neglect improvement after prism adaptation (e.g. Farnè, Rossetti, Toniolo, & Làdavas, 2002; Rossetti et al., 1998). On the contrary, others state that the level of error reduction corresponds to this improvement (Serino, Angeli, Frassinetti, & Làdavas, 2006).

Rationale and Introduction to the Method

This article demonstrates the benefits of employing an electronic pen display with specific software, in patients with visuospatial neglect. Computer-based testing can offer more advantages and a higher sensitivity compared to non-computerized tests (Deouell, Sacher, & Soroker, 2005; Schendel & Robertson, 2002). However, software to develop these tests is insufficiently known or has been unavailable so far (Bonato, 2012). We will describe user-friendly software and illustrate its use with diverse types of tests and measures, developed for administration on a pen display. An important contribution of this article is the development of a computer-based, repeatable test battery for spatial neglect and a digital system for the quantification of prism adaptation. Both tools deliver data of high quality and satisfactory signal-to-noise ratio. As far as we know, the resulting test battery is novel in its breadth of digitally capturing different modalities of spatial neglect on a tablet. It is applicable in any situation that requires mapping peripersonal neglect severity. Originally though, it was designed for administrations related to treatment. The battery consists of nine tasks. Their properties and advantages will be embodied in the second section below. Two tasks have a parallel version to minimize their test-retest sensitivity. To add a familiar part to the battery, two well-known tests are included, namely the Schenkenberg Line Bisection Test (Schenkenberg, Bradford, & Ajax, 1980) and the Bells Test (Gauthier, Dehaut, & Joanette, 1989, cited in Strauss, Sherman, & Spreen, 2006, and Lezak, Howieson, & Loring, 2004). As discussed above, neglect patients' performances on neglect tasks can be very diverse and even dissociated. This finding argues in favor of a battery that gauges various neglect modalities via different tests. However, the battery allows for flexible employment by selecting tests according to one's needs. Most studies using a test battery include up to seven different tests to capture spatial neglect in a differentiated way (Azouvi et al., 2006). The choice for which specific tests we should develop was based on multiple literature-based arguments. Cancellation, line bisection and figure copying are amongst the most frequently used neglect tests (Azouvi et al., 2002; Azouvi et al., 2006). We decided that they should be added to the battery because they have proven their usefulness since a long time and for reasons of comparability and replicability across studies. We wanted to develop a second cancellation and bisection task, based on findings that nourished experimental questions for future study, such as whether a more orderly cancellation task leads to less perseverations (Ronchi et al., 2012), and whether a second color could be noticed more frequently or reduce the bisection error after prism adaptation (Striemer & Danckert, 2010; Sarri, Greenwood, Kalra, & Driver, 2011). Azouvi et al. (2006) highlighted that an extinction test is lacking in most spatial neglect test batteries. Because of this lack and the relevance to detect an extinction phenomenon, especially in view of the possibility of a double dissociation between neglect and extinction (Vossel et al., 2011) and the independent influence of extinction on ADL (Vossel, Weiss, Eschenbeck, & Fink, 2013), we judged that an extinction test should be incorporated in our battery. The fact that it was unknown whether prism adaptation can remediate visual extinction, was an additional rationale. This same reason motivated us to develop a memory test and a search time test, since, to the best of our knowledge, no single study had demonstrated effects of prism adaptation on memory functions apart from representation or drawing, nor on visual search times. Besides, we wanted both tests in the battery for additional reasons. Lateralised search times can reveal neglect when untimed tasks cannot do that anymore (Laeng, Brennen, & Espeseth, 2002). Memory processes were found to be laterally distorted in spatial neglect (Moreh, Malkinson, Zohary, & Soroker, 2014), but a memory test for neglect in clinical practice did not seem to exist yet. Finally, a domain in the contemporary neglect literature that links egocentric space representation to subjective and objective postural characteristics (underpinned by the research groups of Honoré, Karnath, Lafosse, Pérennou, and others), encouraged us to conceive a peripersonal navigation test. A clinical visuospatial test linked to this domain did not seem to exist and can add an extra dimension to the conventional neglect assessment.

Of vital importance is that the tests adequately capture visuospatial neglect. The test performance of persons without neglect should not be deficient, in contrast to that of neglect patients. We administered the tests of the battery in the same order in a group of 20 healthy controls and an age- and education-matched group of 20 neglect patients. Based on their test performance, we investigated whether the tests disclosed visuospatial neglect in our patient group, but not in our non-neglect group. The digital system for prism adaptation is described as an illustration of the method in a treatment context. To reduce the scope of this article, the validation of this digital error reduction will be published elsewhere.

The article further consists of three sections. The first section describes the materials and method that were used to develop the Visuospatial Neglect Test Battery and measurement system for prism adaptation. The next section reports about the main results, with an overview of the tests in the battery and the digital prism measurements. Also in that section, the results are shown regarding the comparative analyses between the neglect patients and the controls without neglect. In the final section, we conclude with a discussion.

Materials and Method

Primary Equipment

Software

Aiming to develop a neglect test battery with sensitive and diverse types of measurements, we used Metrisquare DiagnoseIS (MDIS, www.diagnoseis.com). This software package enabled us to design every stimulus page and task, including the matching scoring system. The user-interface of the design module is shown as supplementary material (Fig. A1). To generate raw scores such as the position of a drawn line in millimeters or the number of hits, our finished stimuli are labeled with a millimeter field or coded fields (further illustrated below). For the specified presentation of stimulus pages (see infra, e.g. in our extinction task) or running calculations on the raw data, the program allows plug-in scripts. However, personalized support is offered on the accompanying platform too. To some tests we added specifications such as order tracing and time stamps, to extend qualitative information. The page with options for these additions is demonstrated as supplementary material (Fig. A2). Switching off the "electronic ink" (pen stripes) is another interesting option. Preventing patients from seeing in which display locations they already have been executing instructions might be required for certain research questions. We will show this with our prism adaptation example below. After task execution, the data are processed online, according to the coding system and scoring scripts. A report of choice presents the results, following an experimental or clinical lay-out (also adjusted following own preferences). The experimental report generates our created variables in a comma-separated-value file, facilitating subsequent data processing in SPSS® and Excel®. The clinical report is composed of images of the tasks, added comments and tables or charts representing the performances.

Minimal PC/laptop requirements for running MDIS are a dual core, i5 or i7 processor and 4 GB RAM, especially for experimental use. This is for instance not to slow down the "electronic ink", the display of stimulus pages and the registration of reaction times.

Electronic Pen Display

MDIS can be used with all kinds of monitors, but it seems to be especially well suited for pen displays and tablets. We used a DTU-2231 from Wacom, because of its active area of 47.70 x 26.82 cm (total screen size of 56.39 x 37.34 cm). It has a wide interactive field, which fits well with the aim of capturing the lateralized spatial exploration deficits in neglect. This kind of display can be used with practically every PC/laptop (Windows® 7, Vista or XP (32 and 64 bit) is minimally required, or OS X or v10.4 on a Macintosh® -next to a DVI or VGA connector and a USB port). It concerns a dual screen technology in which the participant uses the pen at the display surface, while the researcher can observe and designate those interim results at his/her own computer screen.

The pen mechanism is easy to employ because it is wireless and battery-free (based on electromagnetic resonance). The tablet registers the pen coordinates x, y and z, 133 times per second. The coordinate x is the position along the long side of the tablet, y the position along the short side and z the pressure while touching or the height while hovering above the tablet surface. The default tip of the pen can be replaced by a felt tip, giving more of a ‘pen on paper’ feeling. This feels more comfortable for patients who are not accustomed to electronic pen displays.

Pilot Testing

Developing a battery for administration on an electronic pen tablet, targeting the assessment of visuospatial processes, requires some pilot testing. First we wanted to ascertain whether stroke patients can comfortably work with the equipment. Several try-outs were conducted in Rehabilitation Hospital RevArte (Antwerp) and the Rehabilitation Center at the Ghent University Hospital (Rehabilitation Center UZ Gent). A large Wacom pen display was used, combined with some default exercises in MDIS. During the development process we also checked whether specific devised task elements were well suited for various patients and how to adapt them if necessary.

In order to obtain a situation comparable to other practice contexts and paper-and-pencil tasks, we presented the pen display horizontally to the patients. They executed the exercises on the tablet quite easily. Some of our observations and remarks from patients indicated that they were more amused by working with the tablet than with paper tasks, that some electronic stimuli can trigger patients' attention more easily to their neglected side and that some older people even were proud of working with this kind of material.

Auxiliary Equipment

Response Box

A response box was only employed to support the extinction task, one of the nine tests in the battery. We used a Cedrus Response Pad, model RB-530. Only its left and right keys were used during our extinction test, covered with a red and blue key top respectively. The central, non-used keys retained their white key tops.

Prismatic Glasses

During the digital measurements of the error reduction, participants wore prisms that induced a 10° optical shift to the right. These prismatic goggles were obtained from Optique Peter near Lyon (Lentilly, France; www.optiquepeter.com).

Participants

The study was approved by the two involved Committees on Medical Ethics, which were the ethics committee of the GasthuisZusters Hospitals Antwerp and the leading ethics committee of the University Hospital Ghent. Before taking part in the project, all participants signed an informed consent.

Control Group

Twenty right-handed non-patient controls took part in this project, consisting of nine men and eleven women. All of them were volunteers recruited from the authors' social environment. The inclusion criterion was a blanco neurological history according to their knowledge.

Exclusion criteria were a diagnosis of stroke, brain tumors, cerebral traumata or dementia, and significant oculomotor problems.

Patient Group

Twenty right-handed stroke patients participated in this study, consisting of twelve men and eight women. They were recruited in one of three participating centers, namely Rehabilitation Hospital RevArte (Antwerp) and the Rehabilitation Center UZ Gent and Neurology Department at the Ghent University Hospital. Inclusion criteria were a right hemispheric stroke and signs of left-sided spatial neglect according to two screening tasks from the Behavioral Inattention Test (Wilson, Cockburn, & Halligan, 1987): at least four more left-sided than right-sided omissions at Star Cancellation and/or at least 10% deviation to the right in Line Bisection. Exclusion criteria were cerebral tumors, traumatic brain injuries, dementia and significant oculomotor problems.

Case

The results of case G.L. are added to the first part of our discourse below, to illustrate the neglect tests and prism adaptation measures. G.L. is a relatively young woman with an average amount of educational training. She was diagnosed with left sided spatial neglect after a right hemispheric ischemic stroke, distributed across the middle and posterior cerebral artery territories.

Statistical Data Analysis

We conducted statistical tests as implemented in IBM SPSS Statistics, version 21. Adjustments for multiple testing according to Benjamini and Hochberg (1995) were calculated with the Stats-package in R 3.0.1.

Results

Results of the Tests and Measures Development Process: The Digital Visuospatial Neglect Test Battery and Prism Measurements

The Visuospatial Neglect Test Battery comprises nine tasks. Depending on which experimental or clinical research questions, one can select one or several different tests. An exercise page is added upfront, to give patients the opportunity to get familiarized with the electronic pen on the tablet. The battery consists of seven types of tasks: two Cancellation Tests, two Bisection Tests, a Drawing Test, a Search Time Test, an Extinction Test, a Spatial Memory Test and a Visuospatial Navigation Test. Most tasks take more or less five minutes (also depending considerably on a patient's execution times), the Maze and Line Bisection Tests take less time, and the Drawing Test usually takes some more time to complete. Parallel versions are provided for the Search Time Test and the Spatial Memory Test. As mentioned before, a widely used Bisection and Cancellation Test are included in the battery. We added another test of each type, to inspect for instance whether any situational or treatment results would be reproducible across the same familiar type of test commands (bisection and cancellation). We also wanted tasks related to drawing, search times, extinction, spatial memory and navigation to be part of the battery, to reveal extra information regarding peripersonal neglect patients. Each test measures multiple variables. The main variables and further rationale concerning the tasks are described below for each separate test.

To instruct participants in a standardized way, each test is preceded by an instruction page. The instructions are intended to be read aloud by the test leader. This prevents patients from only partly reading them because of neglect dyslexia. Most of the instruction pages (except the ones of the Drawing and Spatial Memory Tests) are followed by a brief exercise or demonstration, to completely clarify a test to the patient. In addition, this allows to assure oneself that the participant understood clearly how to execute the task, before starting it.

The different tests are described and depicted[1] below, always accompanied by a figure displaying the main results of the illustrative case G.L.

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[1] A thin written line may be noticed in the left upper corner of all task images. It displays some information such as test date and patient-ID. This is invisible to the patient. It is added to the images in the archive file of the researcher after task execution.

Two Cancellation Tests

The Bells Test. One classic way of demonstrating neglect is by administering cancellation tasks. The Bells Test from Gauthier et al. (1989, in Strauss et al., 2006, Lezak et al., 2004) is widely employed in clinical practice and experimental research. This test is incorporated in our battery to have a well known neglect task as a reference point (see Fig. 1).

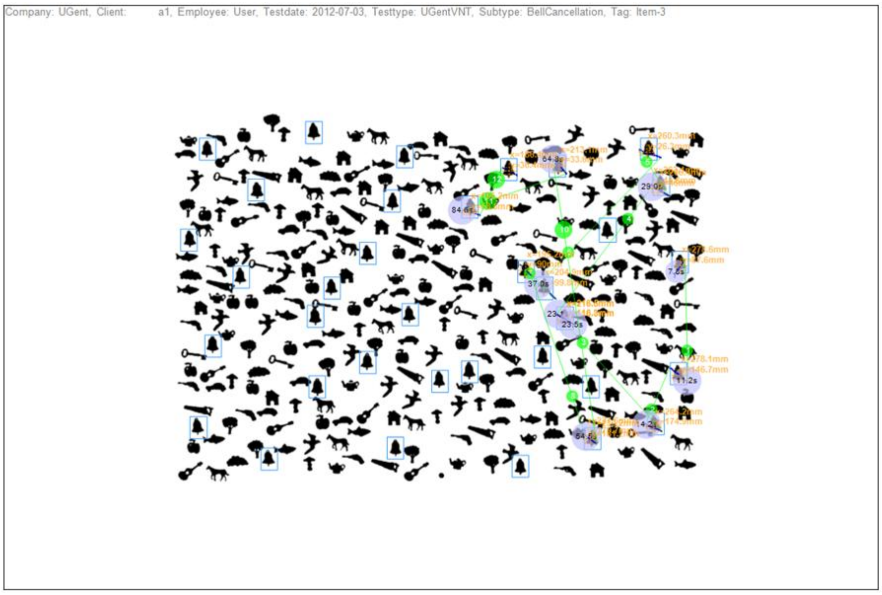
Diamond Cancellation. In the second cancellation task, we wanted to take advantage of the wide display length of the tablet, because of the lateral orienting bias in spatial neglect. We developed a task that encompasses the whole length of the display surface, in which one has to find and cancel the diamonds in between many other little line figures (see Fig. 2).

The variables that are automatically registered during both cancellation tasks are the numbers of hits and perseverations, globally and split out into equal column sections over the task surface. Moreover, the Center of Cancellation (CoC)-index was added, a meaningful measure first described by Binder et al. (1992). The CoC-index is operationalized and digitally provided by Rorden and Karnath (2010, see also www.cabiatl.com/CABI/resources/cancel). It is a continuous measure for neglect severity, ranging from -1 to 1, following the formula below,

$$CoC = \frac{2}{x_r - x_l}\left[\left(\frac{1}{m}\sum_{i=1}^{m} x_i\right) - \left(\frac{1}{n}\sum_{i=1}^{n} x_i\right)\right]$$

where x_r is the coordinate of the most rightward target on the X-axis, x_l the coordinate of the most leftward target on the X-axis, m the number of cancelled targets, n the number of all possible targets and x_i the coordinate of a certain target on the X-axis.

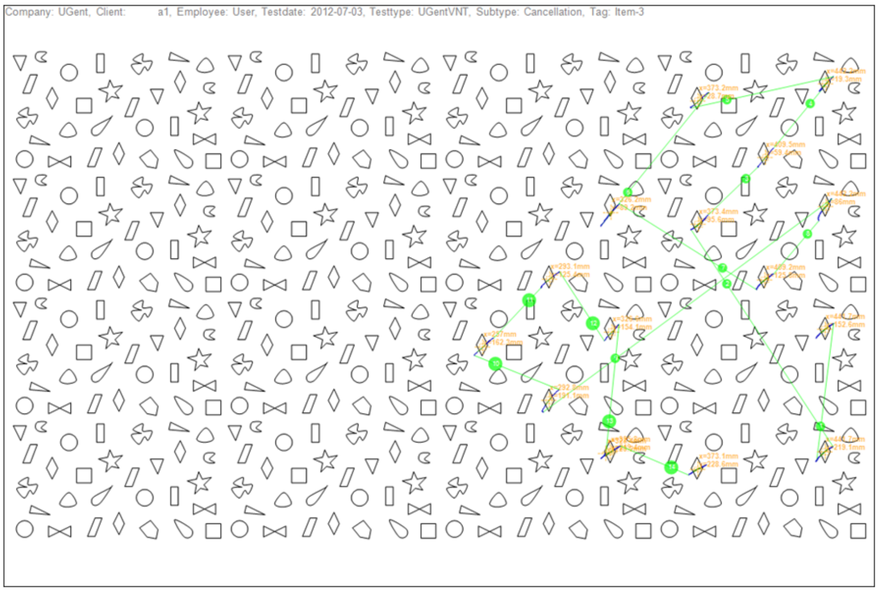
An obvious benefit of administering cancellation tasks on an electronic pen display with the proper software is the direct availability of the CoC-index. In the classic way, a patient's hits on the paper task are afterward transferred to a digital version by the investigator clicking on the corresponding stimuli. By coupling the coding fields to the target stimuli and writing a CoC-script for MDIS, participants' hits on the tablet are automatically registered and processed into the index. A second advantage of this digital method is the possibility of counting patients' perseverations while they cancel targets. Other interesting characteristics in electronic cancellation are 'order tracing' and 'timestamps'. By switching on 'order tracing' in MDIS, a participant's searching pattern can be reproduced. 'Timestamps' are added to show how long it takes someone to reach certain locations. All of those features are far less evident to record while a patient is executing a paper-and-pencil test.



Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: BellCancellation, Tag: Item-3

Bell cancellation	
CoC-index	0.61
Column 1	0/5
Column 2	0/5
Column 3	0/5
Column 4	1/5
Column 5	3/5
Column 6	3/5
Column 7	5/5

Figure 1. The Bells Test, performed by our case G.L. The accompanying table shows her CoC-index and hits per column. She did not perseverate. The time stamps, order traces and bell markings are only visible at the researcher's screen.



Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: Cancellation, Tag: Item-3

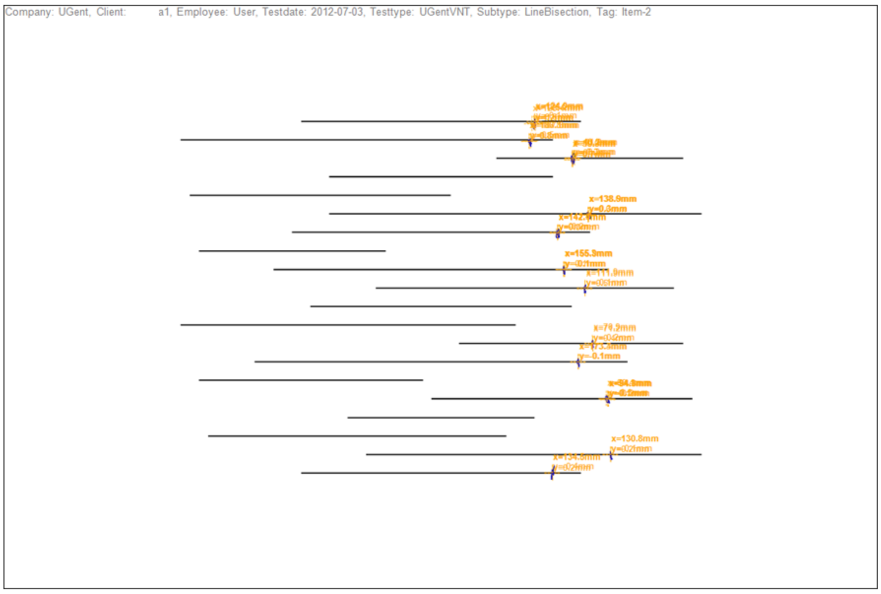
Diamond cancellation	
CoC-index	0.65
Column 1	0/12
Column 2	0/12
Column 3	6/12
Column 4	9/12

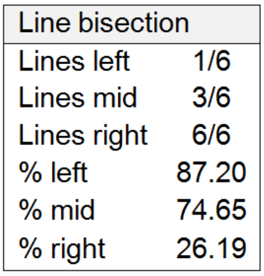
Figure 2. Diamond Cancellation by G.L. The accompanying table shows her CoC-index and hits per column. She didn't make perseverations. The order traces are only visible at the test leader's display.

Two Bisection Tests

The Schenkenberg Line Bisection Test. In addition to cancellation, line bisection is another well known and frequently used way of assessing neglect. That is why we also included a classic line bisection task in our battery, the Schenkenberg Line Bisection Test (Schenkenberg et al., 1980). Because we wanted to be able to compare the (longitudinal) results of the left and right lines, we modified it slightly. The lines of the same length in the right and left parts of the task now have their peripheral starting point at equal distances from the midline.

The automated registrations concern the number of bisected lines and the mean percentages of deviation (from the center of the lines) in the left, middle, right, and entire task sections. Figure 3 depicts the test and the matching table with the case results.


Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: LineBisection, Tag: Item-2

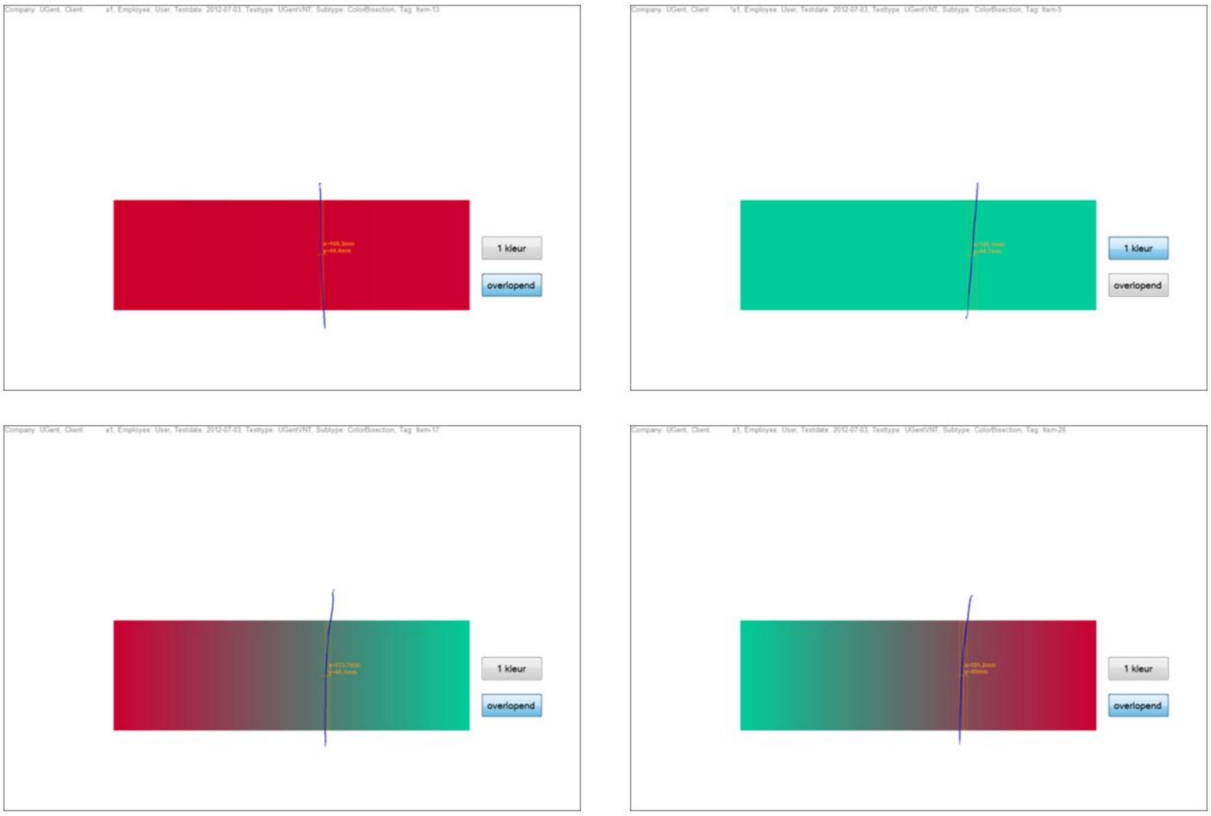


Line bisection	
Lines left	1/6
Lines mid	3/6
Lines right	6/6
% left	87.20
% mid	74.65
% right	26.19

Figure 3. The Schenkenberg Line Bisection Test, performed by G.L. The accompanying table shows her results: the number of bisected lines positioned on the left, central and right sides, as well as the mean percentages of deviation from the center of each line, for the left, central and right positioned lines. The bisection marks in millimeter are only displayed on the investigator's screen.

Colored Rectangles Bisection. For our second bisection test, we filled rectangles with single colors and with two colors that gradually merge in the middle. The task consists of 24 rectangles that are presented in randomly alternating high, middle, or low positions. They are horizontally centered on the display. In all, 12 different unicolored rectangles and 12 bicolored rectangles are shown. These last ones consist of the merging of the 12 unicolors, more specifically six plus six alike, with the left and right colors inverted (see Fig. 4). Participants are instructed to state whether the rectangle consists of one color or two merging colors and to bisect it. They only see the rectangle. On the test leader's screen, the answer "one" or "two merging colors" can be indicated.

The generated results comprise the mean percentages of deviation from the center of the rectangles, globally and for the uni- and bicolored rectangles. The numbers of rectangles judged to be one- or two-colored are also shown.


Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: ColorBisection, Tag: Item-13

Company: UGent, Client: 'a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: ColorBisection, Tag: Item-5

Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: ColorBisection, Tag: Item-17

Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: ColorBisection, Tag: Item-26

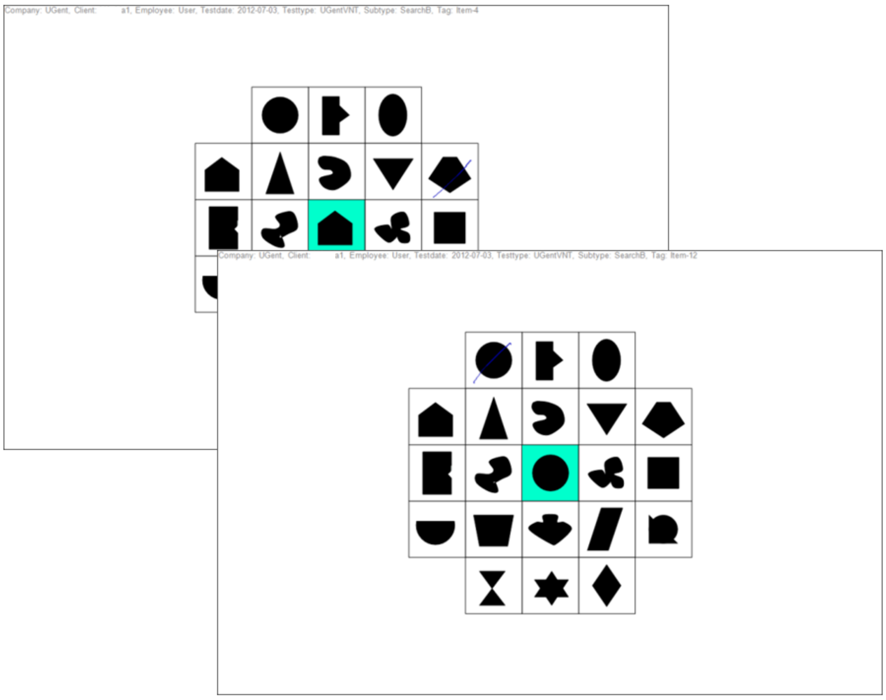
Figure 4. Stimulus examples of the Colored Rectangles Bisection. The mean percentage of deviation from the center of the unicolored rectangles for G.L. is 23.81 %, that of the bicolored rectangles 22.56 %. She judged eight rectangles as being one-colored and 16 as being two-colored. The indications of one color or merging colors are only visible at the test leader's display.

Search Time Test

A computerized visuospatial search task was developed for registering search times, because it is sensitive to the typical spatial dysfunctions in neglect patients (Erez, Katz, Ring, & Soroker, 2009). Each of the 16 test pages consists of a grid comprising 20 different stimuli, centered around one stimulus. This central one is always identical to one of the other stimuli. To facilitate the recognition of the central stimulus, it is placed in a green field. Four stimuli are located in the central column of the grid, next to eight right and eight left-sided stimuli. See Figure 5 for clarification. The parallel version consists of the same stimuli, but their locations are mirrored across the vertical midline. This means that the stimuli that are located on the right or, respectively, the left side of the original version are symmetrically positioned on the left or, respectively, the right side in the parallel version. The four stimuli in the central column stay in place and are not taken into account for the test results. They are used as examples in the original and parallel versions (two per version).

The participant is instructed to cross out the stimulus that is identical to the central stimulus as quickly as possible. Immediately afterward, the central stimulus changes into one of the other stimuli and in this way the task continues. Using the presented electronic method for a search time test optimizes the reliability of the registrations, in contrast to manual time registration.

The results show the number of errors and the total amount of search time in seconds for the left and right positioned stimuli. Whenever useful for certain research questions, the amount of errors and search time can be obtained for the upper and lower parts of the grid as well.



Visuospatial search	
Time left	210 s
Time right	35 s
Correct left	6/8
Correct right	8/8

Figure 5. Stimulus Examples of the Search Time Test. The accompanying table shows the case's search times in seconds and her correct responses regarding the left and right positioned targets.

Drawing Test

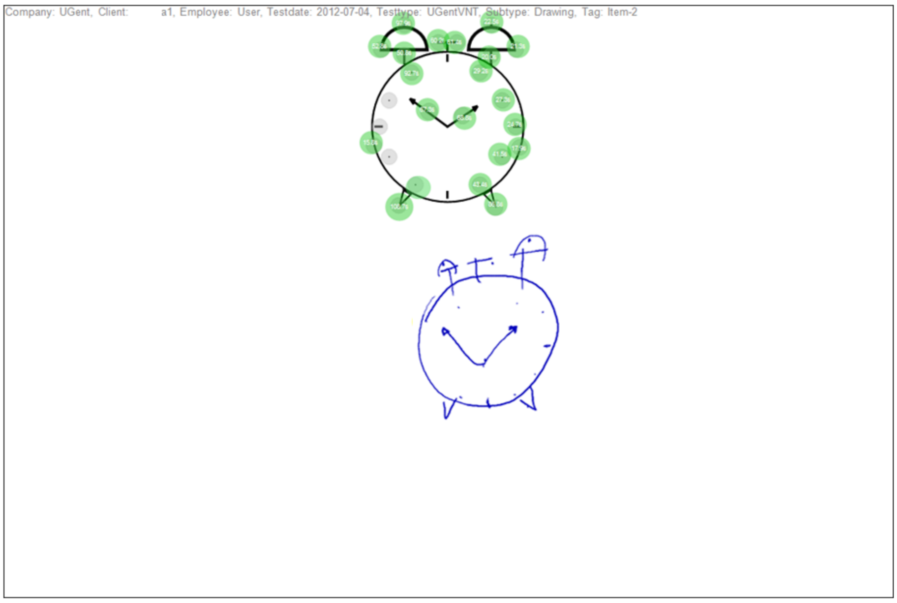
Two symmetrical line drawings were designed, differing in degree of difficulty by graphic design and amount of details. Part A of the Drawing Test is a relatively easy alarm clock (more encouraging to start a test with). Part B is a relatively complex butterfly. This second line drawing is added because it is more detailed, and therefore still a challenge for patients who copy the alarm clock without too much difficulty. The participant is instructed to copy the drawing beneath the example. On the researcher's screen, the details are coded with little gray circles, which are not shown on the patient's display. For each completed detail, the researcher needs to select the corresponding circle by a mouse click. This leaves a green circle in that place. Figure 6 demonstrates the coded gray and clicked green circles in the easy and complex line drawings.

Next to the amount of details completed by the patient on the left and right sides, the leftmost and rightmost points in millimeters are registered. The mean of the coordinates of each drawn pixel is inserted in MDIS to compute the center of gravity of a patient's drawing. We call this measure the "Center of Drawing-index" (CoD-index), calculated with the following simple formula,

$$CoD = \frac{1}{n}\sum_{i=1}^{n} x_i$$

where n is the number of pixels in the drawing and x_i the mm-coordinate on the X-axis with respect to the midline, of a pixel in the drawing. The CoD-index theoretically ranges between -237 and 237 mm.

The CoD-index makes the use of the pen tablet particularly useful, because it combines the positioning along the X-axis and the elaboration of the drawing. Besides, it would practically be impossible to calculate this index in a paper drawing test. The CoD-index is an especially interesting measure for neglect patients, since it can gauge their spatial visuomotor skills by the manner in which they handle space while drawing.



Drawing, part A	
CoD-index	18.11
Details left	9/12
Details right	12/12

Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-04, Testtype: UGentVNT, Subtype: Drawing, Tag: Item-3

Drawing, part B	
CoD-index	27.70
Details left	1/17
Details right	16/17

Figure 6. Parts A and B of the Drawing Test, executed by case G.L. The accompanying tables show her CoD-index (in mm from zero) and number of copied details from the left and right side of the example. The coded gray and clicked green circles are only visible on the test leader's screen.

Extinction Test

We judged that an extinction task could not be missed in our test battery, because of the reasons explained in the paragraph "Rationale and Introduction to the Method". The relationship between neglect and extinction is still largely debated (Vossel et al., 2011). Although double dissociations between neglect and extinction have been demonstrated (Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994; Vossel et al., 2011), they often appear together. Next to the aim of detecting extinction in the presence or absence of neglect, we also devised this extinction and neglect test in our quest for sufficiently sensitive tests, for instance to reaffirm treatment effects. In the remainder of this section it will become clear that such testing procedure is very unlikely in classic neglect and paper-and-pencil tests. We refer to a review by Bonato (2012) concerning computerized task demands that are more powerful for unveiling extinction and neglect than those in paper-and-pencil tests.

Figure 7 elucidates the subsequent description of our Extinction Test. Unlike the other tests, a participant needs to stay focused on the central spot of the tablet, located at the (230, 130) millimeter-coordinate of the display (230 mm on the X-axis, 130 mm on the Y-axis). In that spot, the digits zero, one and five are randomly presented. At the same time, one or two bilateral dots are displayed. Their possible positions are symmetric in the upper versus the lower part of the tablet surface and close versus far from fixation. Four single dots are positioned on the left side, four single dots on the right side, and the bilateral dots are presented on these same positions (hence four bilateral positions as well, see Fig. 8 for one example to scale). The X-axis, respectively Y-axis millimeter-coordinates of those locations on the display are (70,90), (150,90) and (70,170), (150,170) to the left and (310,90), (390,90) and (310,170), (390,170) to the right of the fixation point. Each of the 12 possible positions is shown four times, which equates to a total of 48 test trials. They are followed by time intervals of 3000, 4000 or 5000 ms during which the digits are presented without dots. Dots as well as digits are displayed for 750 ms each, to ensure that patients with slow information processing and/or reaction times can perform this test as well. The interstimulus intervals (ISIs) between digits and between digits and dots are consistently 250 ms. For other research purposes, the presentation times and ISIs can be shortened as needed. All presentations of dots, digits and time intervals are randomized, to avoid predictability.

A participant is instructed to focus at the digits in the center of the display and to mention “five” each time a five appears. The researcher directly registers this answer by pressing the space bar. Furthermore, the participant is asked to press the left or right key of a response box whenever a grey dot appears in his attention field, to the left or right of the central digit respectively. Finally, whenever he/she notices dots at the same time left and right from fixation, both response keys need to be pressed simultaneously.

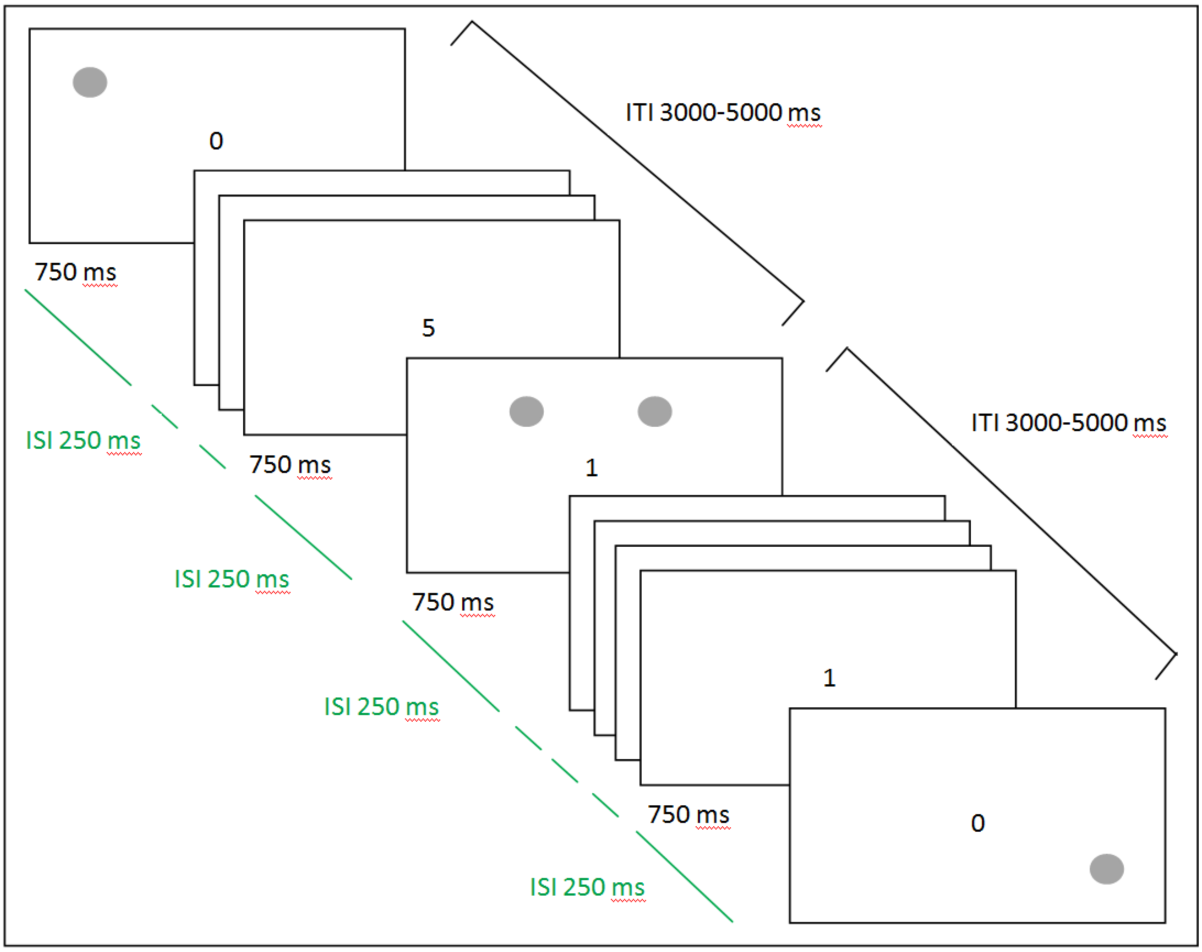
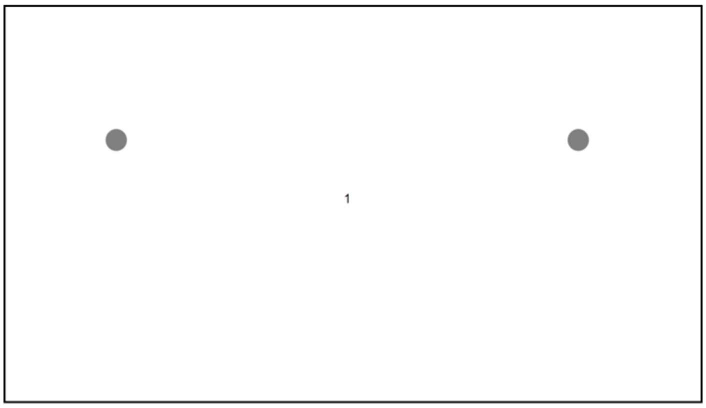
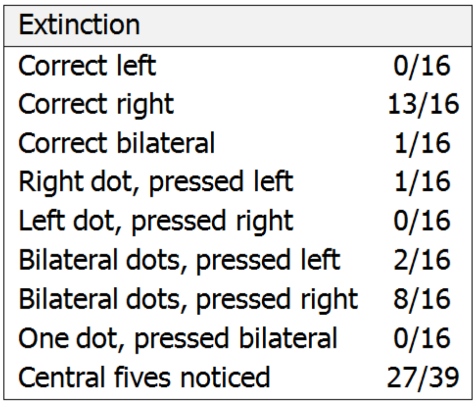


Figure 7. A sequence of stimulus pages from the Extinction Test (not depicted to scale). To facilitate the representation, the time intervals between dots are labeled ‘intertarget intervals’ (ITI), those between stimulus pages in general ‘interstimulus intervals’ (ISI).

The variables registered in the Extinction Test are the number of fives mentioned and the numbers of dots noticed on the left, the right, and both sides. Those amounts are split out over the dots’ positioning close or far from the fixation point. Concerning every variable, the number of errors is displayed, for instance the number of times pressed left instead of bilateral.





Extinction	
Correct left	0/16
Correct right	13/16
Correct bilateral	1/16
Right dot, pressed left	1/16
Left dot, pressed right	0/16
Bilateral dots, pressed left	2/16
Bilateral dots, pressed right	8/16
One dot, pressed bilateral	0/16
Central fives noticed	27/39

Figure 8. One stimulus page to scale of the Extinction Test pages. The accompanying table shows G.L.'s correct and wrong responses regarding the left, right and bilateral dots and the number of fives she noticed.

The following measures for this test give an idea of the degree of left- or right-sided extinction and neglect respectively: the Indices of Left- or Right-sided Extinction (I_{Ext_L} or I_{Ext_R}) and the Index of Neglect (I_{Neg}: negative in left-sided and positive in right-sided neglect), expressed as percentages.

$$I_{Ext\_L} = 100\left(\frac{errors\ \ right\ when\ bilateral}{16}\right)$$

$$I_{Ext\_R} = 100\left(\frac{errors\ \ left\ \ when\ bilateral}{16}\right)$$

$$I_{Neg} = 100\left(\frac{hits\ left}{16} - \frac{hits\ right}{16}\right)$$

'$Errors\ left\ when\ bilateral$' and '$errors\ right\ when\ bilateral$' represent the numbers of single left and right button presses, respectively, when bilateral dots were presented instead. '$Hits\ left$' and '$hits\ right$' are the numbers of correct responses to left and, respectively, right dots. The maximum amount of these four numerators is 16.

A combined Index that measures the Change in Performance Asymmetry due to a Bilateral stimulus (I_{CPAB}, expressed in percentages too) can be derived from the three measures above:

$$I_{CPAB} = I_{Neg} - (I_{Ext\_R} - I_{Ext\_L})$$

This measure is very similar to the one used by Vossel et al. (2011)[2]. Consequently, it is also suitable for research purposes in which patients with merely neglect or merely extinction need to be dissociated from each other. Someone with maximal left-sided extinction without neglect will obtain a score of 100, and someone with maximal left-sided neglect without extinction a score of -100 (change of sign for right-sided spatial dysfunction). Persons with maximal neglect as well as maximal extinction (or without either neglect or extinction) will obtain a zero score.

In our analysis below, we use the first three indices, not I_{CPAB}. Since we selected our patients for having neglect and because neglect and extinction often co-occur, the I_{IPAB} will regularly approach zero. This of course will also be the case in our control group without neglect or extinction.

Investigators might be interested in refining their research topic with respect to the left, right, and bilateral dots close versus far from fixation. In that case, the formulae above can be perfectly adapted to separate the positions close and far from the fixation point.

Spatial Memory Test

To explore the influence of neglect and treatment on the visuospatial memory functioning of neglect patients, we expanded the test battery with a spatial memory task. This test consists of six left and six right located pictural stimuli to remember. Specific black-and-white line drawings from Snodgrass and Vanderwart (1980) were used, to be able to assure that the left and right stimuli do not differ significantly from each other in terms of familiarity and name agreement.

In front of the memory task, a page is shown in which 12 red filled circles are presented (six left and six right, see Fig. 9). The participant is asked to cross out all of them. The collection that is discovered by him-/herself, gives the investigator an idea of the degree of spontaneous exploration and can be compared with the test results afterward. If a patient neglects red circles on this front page, he/she needs to be encouraged to find the others. The

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[2] because I_{CPAB} can be understood as $100\left(\left(\frac{hits\ left}{16} - \left(\frac{hits\ bilateral}{16} + \frac{errors\ left\ when\ bilateral}{16}\right)\right) - \left(\frac{hits\ right}{16} - \left(\frac{hits\ bilateral}{16} + \frac{errors\ right\ when\ bilateral}{16}\right)\right)\right)$

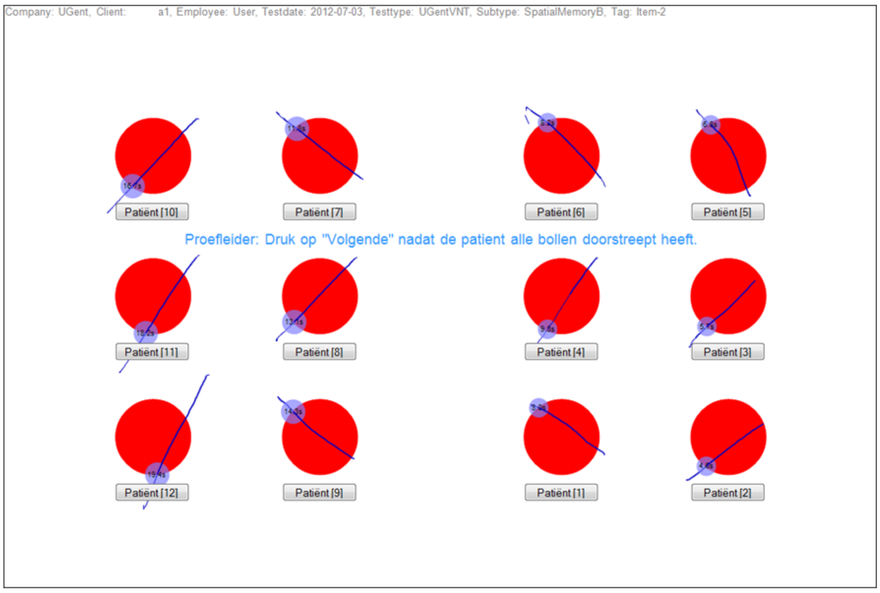
instruction page that follows states that the targets to memorize will appear separately at each of the preceding circles' location. So during the memory task itself, only one stimulus is presented at a time. To guarantee that patients will also discover the targets on their neglected side, the following strategy is used. A red line with little arrows leads the patient to every red filled circle. As soon as he/she crosses this circle out, the line drawing appears at the same spot -as if it is hidden behind the circle. See Figure 10 for further clarification. This strategy could not be implemented practically in a paper-and-pencil task, which illustrates another advantage of the method currently enunciated.

The memory test consists of an immediate recall, a delayed recall and a recognition part after about 20 minutes. During the recognition, the pictural stimuli are presented centrally on the display. They appear one by one and are randomly alternated with 15 other stimuli from Snodgrass and Vanderwart (1980). We also made sure that there were no significant differences between those 15 distracter items and the 12 target stimuli to memorize, in terms of familiarity and name agreement.

The parallel version of this test consists of 12 other targets in the memory part and 15 other distracters in the recognition part, also derived from Snodgrass and Vanderwart (1980). Any other information is identical to that of the original version. Regarding familiarity and name agreement, the parallel target line drawings, also the ones presented on the left and right sides separately, and the parallel recognition drawings, don't differ significantly from the same sets of stimuli in the original version.

In both the original and parallel spatial memory tasks, participants are instructed to remember as many of the line drawings as possible. After the presentation of all stimuli, a participant is asked to reproduce all of the remembered line drawings (immediate recall condition). It is not explicitly mentioned that this question will be repeated after 20 minutes (delayed recall condition). In the recognition part, one needs to say whether or not he/she saw the displayed line drawing during the preceding memory task. During each reproduction/recognition phase, the test leader indicates the answers via corresponding 'buttons' on his screen.

The results show the numbers of stimuli for the left and right sides separately, concerning the immediate reproduction, the delayed reproduction and the recognition.



Company: UGent, Client: a1, Employee: User, Testdate: 2012-07-03, Testtype: UGentVNT, Subtype: SpatialMemoryB, Tag: Item-2

Proefleider: Druk op "Volgende" nadat de patient alle bollen doorstreept heeft.

Spatial memory	
Imm. recall L	3/6
Imm. recall R	4/6
Del. recall L	3/6
Del. recall R	2/6
Recognition L	6/6
Recognition R	6/6

Figure 9. The page preceding the Spatial Memory Test depicts the 12 positions at which the separate targets to memorize will appear. It gives the researcher an idea of a patient's degree of spontaneous exploration since he/she is asked to cross out the red circles. Which red circles are spontaneously discovered by the patient, can be indicated below each circle. Those indications are invisible to the patient. Case G.L.'s results of the immediate and delayed recall and the recognition are presented in the table, for the left and right targets separately.

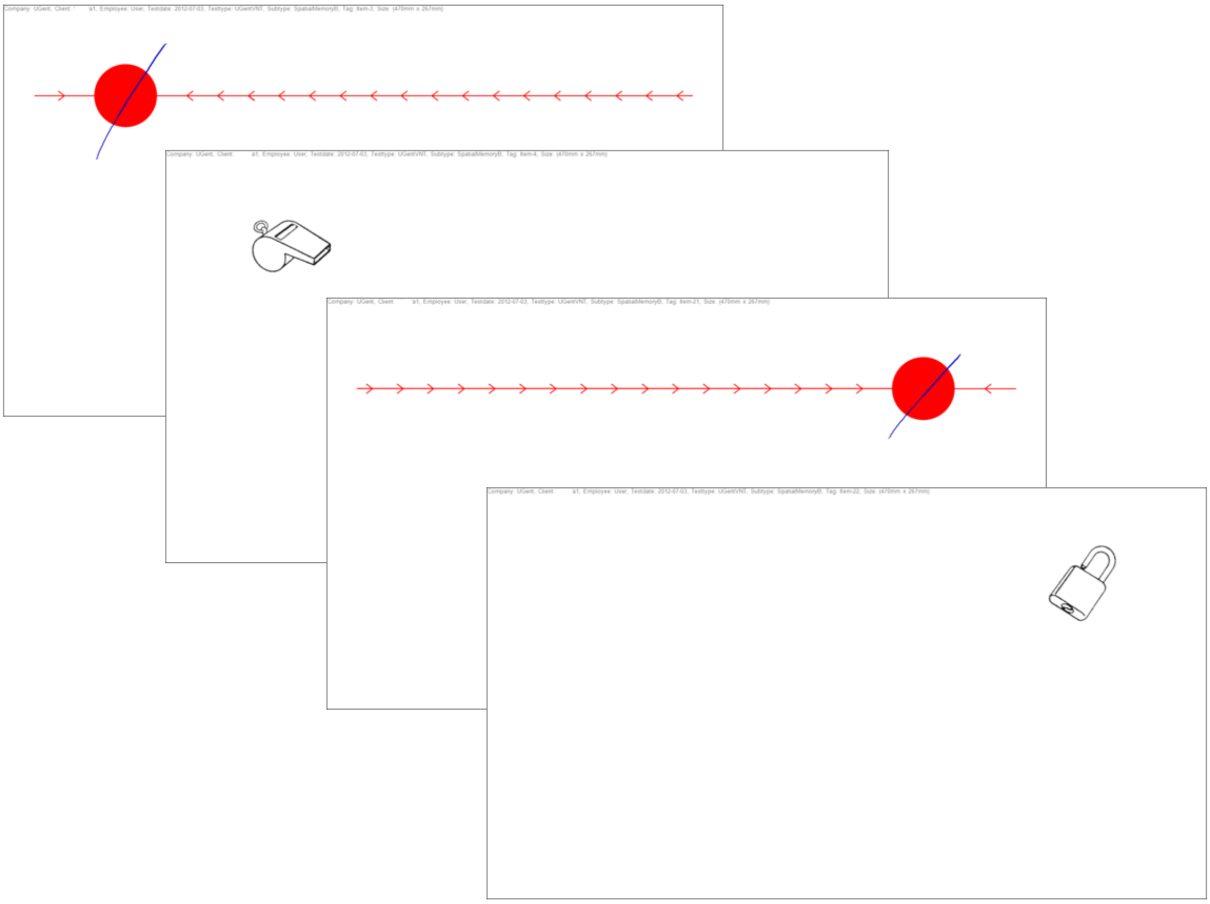


Figure 10. Illustration of some stimulus pages of the Spatial Memory Test. To guarantee that a participant will discover the targets on the neglected side, a red line with little arrows leads him/her to every red circle. As soon as the patient crosses the circle out, the line drawing appears at the same spot.

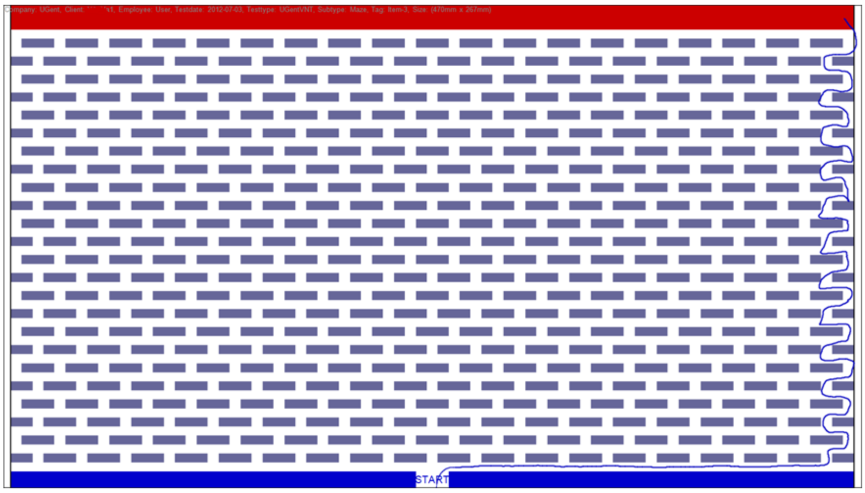
Visuospatial Navigation Test

In our opinion, classic neglect tests capture the spatial navigational dimension insufficiently or even not at all, while this seems to be an important characteristic in certain domains of the neglect syndrome. See Guariglia and Piccardi (2010) for a review concerning navigation in representational versus perceptual neglect, and Buxbaum et al. (2008) or Turton et al. (2009) regarding wheelchair navigation or walking. By pondering about a task in which visuospatial navigation could emerge freely within the limits of the pen display, we designed a kind of maze. This maze task thus incorporates a new test concept compared to common neglect tests: peripersonal spatial navigation. We took advantage of the wide length of the pen display as an opportunity for spatial deviation to emerge more freely. One can deviate as much to the left side as to the right side of the maze. The obstacles in the maze are very uniform and symmetric (see Fig. 11). The task has a central starting point at the bottom and a free end point at the top, anywhere between extreme left and extreme right. The instruction is to find one's way to the top via the shortest route.

The registrations concern the mean percentage of deviation from zero, the leftmost, rightmost, and end points in millimeters. All variables are computed starting from the second white line at the bottom of the maze. To calculate the mean percentage of lateral deviation, the center of gravity of the traced route across the X-axis is used. This "Center of Navigation-index" (CoN-index) demonstrates another benefit of working with a digital pen display in neglect patients. It would be practically infeasible to obtain this measure with a paper-and-pencil test. The CoN-index results from the formula below,

$$CoN = \frac{100}{x_e}\left(\frac{1}{n}\sum_{i=1}^{n} x_i\right)$$

where x_i represents the coordinate on the X-axis with respect to the midline, of a pixel at the route, x_e the absolute value of the most extreme coordinate that a pixel can have, and n the entire amount of pixels along the route. The higher the CoN percentage is, the more the rightward navigational deviation.



Visuospatial navigation	
CoN-index	94
Leftmost in mm	213
Rightmost in mm	233
End point in mm	229

Figure 11. The Visuospatial Navigation Test, performed by our case G.L. The accompanying table shows her CoN-index (% deviation from zero), the leftmost and rightmost mm of her traced route and the terminus in mm, all calculated upward from the second white line at the bottom of the maze.

Digital Prism Adaptation Measures

Using MDIS with a pen display, several applications for treatment can be thought of. Here we illustrate digital measures related to prism adaptation. For this measurement procedure, we turned the tablet 90°, so that its short side is near the patient's trunk instead of its long side.

Regarding the after-effect (reaching too much to the left of a target after removal of the prismatic glasses), manual measurements are easy to perform. In the pre- and post-exposure conditions (i.e. before and after wearing prisms), invisible pointing is performed to e.g. a central dot, after showing that dot to the participant. The after-effect is then calculated by subtracting the measured locations of pointing pre and post. The error reduction (the rightward pointing error while wearing prisms, which gradually reduces) is less easy to measure, because it is an 'online' correction. It takes place while the participant is observing and immediately correcting. So far, some authors measured the deviation with the naked eye and a kind of ruler invisible to the patient. In view of a more exact measurement, we asked patients to draw a line to targets on the display. However, this line was only visible on the researcher's screen. Similar to a classic prism procedure, the participants drew lines to a left or a right dot in the upper part of the tablet, starting from a central dot at the bottom. Figure 12 illustrates this for our case G.L. The dots are located 10° to the left and 10° to the right of the (imaginary) midline. To take baseline visuomotor performances into account, the patients drew lines randomly 10 times to the left and 10 times to the right dot, before wearing prisms. This enables the calculation of precise measures of error reduction, namely the 'mean angle' and the 'crossing angle', relative to the individual mean baseline performance:

Mean Angle ($\bar{\alpha}$). To capture patients' entire drawing curve in degrees, the mean of all pixel angles (to the central dot below) with the midline is computed (see Fig. 12),

$$\bar{\alpha} = \frac{1}{n}\sum_{i=1}^{n} \alpha_i$$

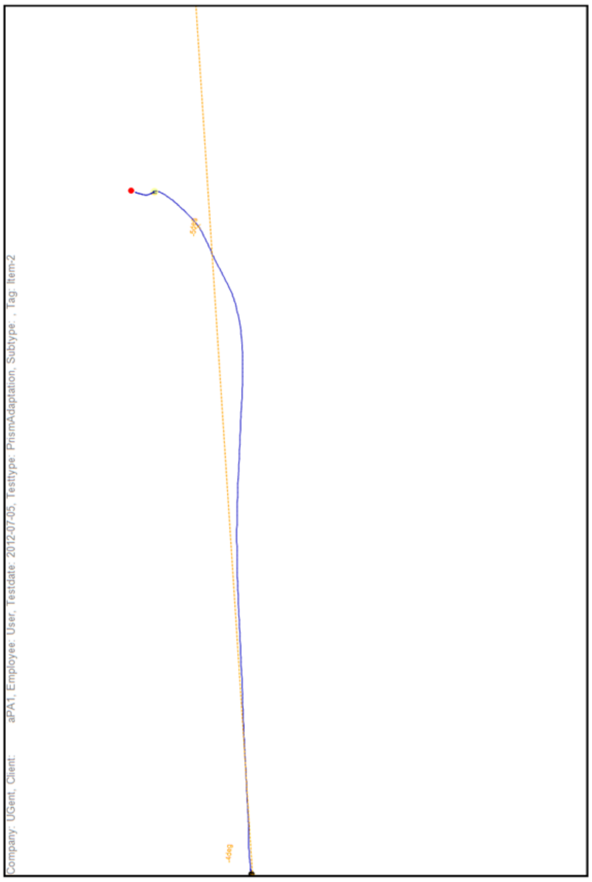
wherein α_i concerns the angle of every pixel on the drawing curve and n the entire amount of pixels on the curve.

Crossing Angle (α_C). Similar to the manual way of measuring the error reduction, an 'invisible ruler' is applied one cm in front of the upper left and right dots. When the patient crosses this line, the α_C is automatically calculated in degrees. It concerns the angle between the (imaginary) midline and the (imaginary) straight line through the patient's point of intersection at the ruler and the central dot below (see Fig. 12),

$$\alpha_C = \tan^{-1}\left(\frac{x_c}{y_c}\right)$$

where x_c is the coordinate on the X-axis, at which the patient's curve crosses the imaginary ruler, relative to the midline; y_c is the coordinate on the Y-axis, at which the patient's curve crosses the imaginary ruler, relative to the central dot below.

Table 1 reflects those measures, obtained from G.L.'s drawn baseline curves and her first curves while she was wearing the prismatic glasses.



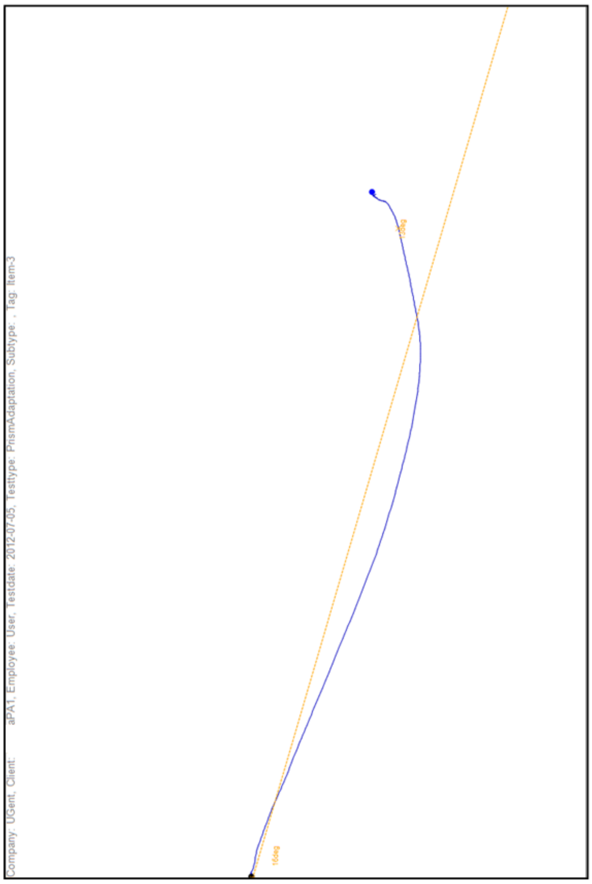


Figure 12. Case G.L.'s first drawn curves to the left and right dots, visualized on the test leader's screen. The thin orange line displays the $\bar{\alpha}$ and the small orange mark at one cm in front of the dot the α_C.

Table 1

Values of the drawn curves of case G.L., towards the left and right dots: the mean baselines and relative values towards the mean baseline, with regard to the mean angle and crossing angle. It took G.L. four curves to reach her baseline.

	Mean Angle		Crossing Angle	
	Left	Right	Left	Right
Mean baseline	- 10.96	9.00	- 9.83	10.02
Relative drawing curve 1	7.24	7.33	5.08	2.50
Relative drawing curve 2	2.45	3.32	0.87	1.82
Relative drawing curve 3	2.07	2.26	0.23	1.25
Relative drawing curve 4	- 0.33	0.75	- 0.11	0.76

Results of the Comparative Analysis between the Neglect Patients and Healthy Controls

Comparative Analysis of the Descriptive Characteristics

We found no evidence for a difference between the neglect group and non-neglect group in terms of age, years of education after the age of six (according to Kolmogorov-Smirnov tests) and sex (computed with a two-sided Fisher's Exact Test). See Table 2 for the mean age and years of education plus standard deviations of each group, next to the p-values.

Table 2

Concerning the neglect and control groups: means and standard deviations for age and years of education, p-values for the comparative analyses regarding age, education and sex

Characteristics	Mean		Standard Deviation		P-values
	Patients	Controls	Patients	Controls	
Age	61.65	61.45	9.85	9.37	0.978*
Education	13.40	13.70	2.76	2.45	1.000*
Sex					0.527†

* according to Kolmogorov-Smirnov Tests, † according to two-sided Fisher's Exact Test

Comparative Analysis of the Test Performances

With respect to the test performances of the neglect group and the matched control group, we inspected whether the variance between both groups was significantly larger than the variance within the groups. We defined a clear set of 26 test variables, based on the main registrations of each test. To facilitate interpretation, we transformed the numbers of correct responses and errors for each task into percentages (% in Table 3). Concerning the Search Time Task, the difference of the left- and right-sided errors was used and the ratio of the mean search time left and right. For the Drawing Test, we took the amount of drawn details on the right side minus those on the left side. The other test variables are delineated as in the descriptions of each task above. Table 3 gives the overview consisting of the main test variables, their medians in both groups, and the p-values in accordance with Mann-Whitney U tests. The adjusted p-values are added following Benjamini-Hochberg (1995), to take the false discovery rate into account.

Table 3

Main test variables with their medians in the neglect and control groups, next to the p-values from the comparative analyses and the corresponding adjusted p-values

Test Variables	Median Patients	Median Controls	P-value	Adj. p‡
Bells Test				
CoC-index	0.2	-0.01	<0.001	<0.002
Total perseverations	3	1	0.004	0.006
Diamond Cancellation				

CoC-index	0.27	0	<0.001	<0.002
Total perseverations	0	0	0.820	0.820
Schenkenberg Line Bisection				
% Number of left-sided lines	66.67	100	<0.001	<0.002
% Number of centered lines	100	100	0.030	0.037
% Number of right-sided lines	100	100	0.429	0.446
% Total deviation	15.54	0.4	<0.001	<0.002
Color Rectangles Bisection				
% Total deviation	12.1	-0.46	<0.001	<0.002
Search Time Test				
% Errors left minus right	12.5	0	0.020	0.026
Mean time left/mean time right	2.48	1.1	<0.001	<0.002
Drawing Test				
CoD in mm, A (alarm clock)	17.02	-1.53	<0.001	<0.002
CoD in mm, B (butterfly)	11.36	-0.1	0.011	0.016
% Details right minus left, A	8.33	0	<0.001	<0.002
% Details right minus left, B	20.59	0	<0.001	<0.002
Extinction Test				
% I_{Neg}	-37.5	0	<0.001	<0.002
% I_{Ext_L}	43.75	12.5	<0.001	<0.002
% I_{Ext_R}	6.25	12.5	0.009	0.014
Spatial Memory Test				
% Immediate recall left	50	66.67	<0.001	<0.002
% Immediate recall right	50	58.33	0.127	0.144
% Delayed recall left	33.33	66.67	<0.001	<0.002
% Delayed recall right	33.33	50	0.081	0.096
% Recognition left	83.33	100	0.013	0.018
% Recognition right	100	100	0.289	0.313
Visuospatial Navigation Test				
% CoN-index	44.53	1.34	<0.001	<0.002
End point in mm	160.75	7	<0.001	<0.002

‡ P-value adjusted according to Benjamini and Hochberg (1995)

We found that 21 out of the 26 test variables were significantly different between the neglect and non-neglect groups (adjusted p-values < 0.05 conform Mann-Whitney U tests after Benjamini-Hochberg correction). The CoC-index of both cancellation tests is clearly distinct in both groups. This is not the case for the number of perseverations, in which the between-group difference was only present in the Bells Test, not in the Diamond Cancellation. The total percentages of deviation are divergent between the neglect and control groups in both bisection tasks. The numbers of bisected lines in the Schenkenberg Line Bisection Test are different between groups for the left-sided and centered lines, not for the right-sided lines. Regarding the Search Time Test, the neglect patients make significantly more errors than the controls, when the target stimulus is positioned on their left side. Also their search time is clearly higher when the target is positioned on their left: about two and a half times as long as the search time for right-sided targets, compared to the controls with rather equal amounts of search time for left and right targets. In the Drawing Test as well, the CoD-indices and the amounts of details left versus right are obviously distinct between neglect and non-neglect participants. The same applies for the neglect and extinction indices of the Extinction Test. In the Spatial Memory Test, the numbers of items recalled and recognized are different between neglect patients and controls for the left positioned items, but not for the right-sided items. Finally, the CoN-index and terminus measure of the Visuospatial Navigation Test are clearly divergent between the groups.

Discussion

A digital method is presented, which is based on user-friendly software that is well-suited for pen displays[3]. It is designed for studying peripersonal visuospatial neglect processes. The method is elaborated with reference to a repeatable test battery and treatment measures,

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[3] Interested readers can obtain the software and the subtests of the Visuospatial Neglect Test Battery via the Metrisquare platform. The authors do not have any commercial interests or benefits and only ask to cite the present article correctly when subtests are used. Questions about the subtests can be addressed to the first author (nathalie.vaes@ugent.be, nathalie.vaes@revarte.be). For quotations on the software, test credits and tablets, an e-mail can be sent to info@metrisquare.com.

tailored to neglect patients. By means of a case study, these digital neglect and prism measurements are illustrated.

The Visuospatial Neglect Test Battery consists of nine tests (two Cancellation Tests, two Bisection Tests, a Drawing Test, a Search Time Test, an Extinction Test, a Spatial Memory Test and a Visuospatial Navigation Test). The discriminant validity of the tests is demonstrated by means of comparative analyses between a control group of 20 healthy participants and an age-, sex- and education-matched group of 20 neglect patients. Taken all tests together, 21 out of 26 test variables differed significantly between both groups (see Table 3). Practically all variables of the classic and new types of tests show clear performance differences between neglect patients and persons without neglect. As such, they adequately capture the diverse visuospatial neglect processes. One of the five non-significantly different variables was the number of perseverations in the Diamond Cancellation Test. However, the number of perseverations in the Bells Test (Gauthier et al., 1989, in Strauss et al., 2006, Lezak et al., 2004) did differ significantly between groups. This contradiction could be explained by the manner in which the targets are structured within the task (see Ronchi et al., 2012). Indeed, in our Diamond Cancellation, the stimuli are presented in a rather orderly fashion. On the contrary, the presentation of stimuli in the Bells Test is more scattered. The second non-significantly different variable was the number of bisected right-positioned lines (adjusted p-value 0.446) in the Schenkenberg Line Bisection Test (Schenkenberg et al., 1980). Yet, the numbers of bisected centered lines (adjusted p-value 0.037) and left-positioned lines (adjusted p-value <0.002) did differ significantly. This mirrors the performance gradient in spatial neglect, with a systematic decrement in target detection from left to right (Butler, Eskes, & Vandorpe, 2004; Marshall & Halligan, 1989; Small, Cowey, & Ellis, 1994). The last three non-significantly different variables were the numbers of remembered right-sided items in the three conditions of the Spatial Memory Test (immediate and delayed recall, and recognition). In contrast, the same three conditions were significantly different regarding the left-sided items. These results emerge exactly as expected in neglect patients compared with controls. We also want to highlight that the I_{Ext_L} and I_{Ext_R} of the Extinction Test differed significantly between groups, but in opposite directions. This means that the controls had equally small extinction indices for the left and right sides. The neglect patients however, had a large left-sided extinction index relative to the controls, but an even smaller right-sided extinction index than controls. In bilateral stimulus conditions, they were inclined to respond to the right stimuli, but barely to left stimuli, whereas the controls responded in equally small numbers to left and right stimuli.

Next to the comparison of neglect patients and healthy controls to inspect the discriminant validity of the neglect tests, other objects of investigation are worth being mentioned, such as the more specific comparison between comparable right hemisphere patients with neglect on the one hand and without neglect on the other, the comparison between neglect patients' test results on the digital battery versus those on conventional neglect tests, and repeated subtest administrations in the same group of neglect patients, without any specific intervention in between. The tests' validity, reliability, sensitivity, specificity, minimal detectable change, and clinical important difference need to be examined, since such information is relevant to optimize diagnostic and impact assessments. Certain related information is available regarding the conventional paper-and-pencil cancellation and line bisection tasks (although they are digitally incorporated into our test battery). Both types of tests have a marginal to fairly good convergent validity and test-retest reliability. The reported sensitivity depends on the cut-offs used, and cancellation is found to be more reliable and sensitive than line bisection (Azouvi et al., 2002; Chen Sea & Henderson, 1994; Ferber & Karnath, 2001; Lezak et al., 2004; Plummer et al., 2003; Rorden & Karnath, 2010; Salter et al., 2013; Strauss et al., 2006; Vanier et al., 1990). For the tests that are available in or allow for a paper version (such as cancellation and line bisection), it will also be useful to investigate whether there are SN performance differences between the tablet or paper versions of tests.

An advantage of the reported method is the online performance monitoring thanks to the dual-screen technology. At the own computer screen, the investigator can observe and designate the interim results of a participant working at the pen display. Related to data-collection, the experimental benefits of exact and less time-consuming measurements because of automated scoring and calculation are self-explanatory. Additionally, important measures are directly available via Metrisquare DiagnoseIS combined with an electronic pen display, such as the CoN-, CoD-, and CoC-indices, the number of perseverations and the 'mean angle' and 'crossing angle'. These are not directly within reach of classic or paper-and-pencil tasks. Reliable and sensitive gauging of extinction and lateralized search or reaction times is of clinical relevance as well. It even can be vitally important, for instance with respect to advice on driving capabilities. Collecting qualitative information thanks to digital characteristics such as order tracing and time stamps is an extra advantage of the discussed method.

Moreover, informing patients underpinned by digital visualizations of their task performance might be more “eye-opening”. It is easier to increase the salience of their results by magnifying, visually stressing or displacing them while explaining. This might be helpful for proper rehabilitation, for example by creating awareness of a patient’s difficulties.

Besides the benefits described here, it is important not to forget about the drawbacks. Of course the peripersonal dimension of the pen display is only one domain of the heterogeneous syndrome that spatial neglect can be. The loss of freedom of movement by using the pen on the tablet surface might be a disadvantage too, for instance with respect to prism adaptation. Activating the ‘register hover’ option in MDIS might be an alternative. With this option, the pen does not need to touch the display, because the registrations are saved while the pen hovers above its surface. Although we have chosen for a large pen display (cf. advantage regarding spatial exploration), this can be impractical. In some research contexts, a fixed location to install and leave the equipment is not available. In the case of multicenter research for instance, it needs to be transferred from one department or patient clinic to another. From a clinical perspective, an important drawback is the lack of functional measures in the test battery. Therefore, we advise to combine the battery with an ecologically valid neglect-specific functional assessment. The Catherine Bergego Scale is an excellent example in this respect (Chen, Hreha, Fortis, Goedert, & Barrett, 2012).

In conclusion, the usefulness of an electronic method for visuospatial neglect assessment was demonstrated. We did this on the basis of various test properties in a newly developed test battery, and based on the measurement procedure for the error reduction during prism adaptation. However, the outlined software combined with a digital pen tablet will also lend itself well to other testing or training purposes. Examples include precise measures of specific visuomotor or attention-related skills in children with different developmental disorders, and cognitive training modules for neurological patients. Advantages in this respect are the ability to design individually tailored exercises and the flexible adaptation of stimuli or tasks in light of gradually increasing training difficulty. The method described in this article might thus be of interest to other domains of investigation, but surely appears to be a valuable one for experimental, as well as clinical objectives in peripersonal visuospatial neglect.

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The authors declare that they have no conflicts of interest.

References

Aimola, L., Schindler, I., & Venneri, A. (2013). Task- and response related dissociations between neglect in near and far space: A morphometric case study. *Behavioural Neurology, 27* (3), 245–257.

Azouvi, P., Bartolomeo, P., Beis, J., Perennou, D., Pradat-Diehl, P., & Rousseaux, M. (2006). A battery of tests for the quantitative assessment of unilateral neglect. *Restorative neurology and neuroscience*, *24*(4-6), 273-285.

Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J.M., ..., Rousseaux, M. (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *J Neurol Neurosurg Psychiatry, 73,* 160–166.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the false discovery rate: A practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society, Series B, 57*, 289–300.

Beschin, N., Basso, A., & Della Sala, S. (2000). Perceiving left and imagining right: dissociation in neglect. *Cortex, 36* (3), 401–414.

Binder, J., Marshall, R., Lazar, R., Benjamin, J., & Mohr, J.P. (1992). Distinct syndromes of hemineglect. *Archives of Neurology, 49,* 1187–1194.

Bisiach, E. (1999). Unilateral neglect and related disorders. In G. Denes & L. Pizzamiglio (Eds.), *Handbook of Clinical and Experimental Neuropsychology* (pp. 479–495). London, UK: Psychology Press.

Bisiach, E., McIntosh, R.D., Dijkerman, H.C., McClements, K.I., Colombo, M., & Milner, A.D. (2004). Visual and tactile length matching in spatial neglect. *Cortex, 40* (4-5), 651–657.

Bonato, M. (2012). Neglect and extinction depend greatly on task demands: a review. *Frontiers in Human Neuroscience, 6* (195). doi:10.3389/fnhum.2012.00195

Butler, B.C., Eskes, G.A., & Vandorpe, R.A. (2004). Gradients of detection in neglect: comparison of peripersonal and extrapersonal space. *Neuropsychologia, 42,* 346–358.

Buxbaum, L.J., Palermo, M.A., Mastrogiovanni, D., Schmidt Read, M., Rosenberg-Pitonyak, E., Rizzo, A.A., & Branch Coslett, H. (2008). Assessment of spatial attention and neglect with a virtual wheelchair navigation task. *Journal of Clinical and Experimental Neuropsychology, 30* (6), 650–660.

Chen Sea, M.J., & Henderson, A. (1994). The reliability and validity of visuospatial inattention tests with stroke patients. Occupational Therapy International, 1, 36–48.

Chen, P., Hreha, K., Fortis, P., Goedert, K.M., & Barrett, A.M. (2012). Functional assessment of spatial neglect: a review of the Catherine Bergego Scale and an introduction of the Kessler Foundation Neglect Assessment Process. *Top Stroke Rehabilitation, 19*(5), 423–435.

Cocchini, G., Cubelli, R., Della Sala, S., & Beschin, N. (1999). Neglect without extinction. *Cortex, 35* (3), 285–313.

Coslett, H.B. (1997). Neglect in vision and visual imagery: a double dissociation. *Brain, 120,* 1163–1171.

Deouell, L.Y., Sacher, Y., & Soroker, N. (2005). Assessment of spatial attention after brain damage with a dynamic reaction time test. *Journal of the International Neuropsychological Society, 11,* 697–707.

Erez, A.B., Katz, N., Ring, H., & Soroker, N. (2009). Assessment of spatial neglect using computerised feature and conjunction visual search tasks. *Neuropsychological Rehabilitation, 19* (5), 677–695.

Farnè, A., Rossetti, Y., Toniolo, S., & Làdavas, E. (2002). Ameliorating neglect with prism adaptation: Visuo-manual and visuo-verbal measures. *Neuropsychologia*, *40*, 718–729.

Ferber, S., & Karnath, H.O. (2001). How to assess spatial neglect - Line bisection or cancellation tasks? *Journal of Clinical and Experimental Neuropsychology*, *23*(5), 599-607.

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology*, *11*, 49–54.

Guariglia, C., & Antonucci, G. (1992). Personal and extrapersonal space - a case of neglect dissociation. *Neuropsychologia*, *30* (11), 1001–1009.

Guariglia, C., & Piccardi, L. (2010). Environmental orientation and navigation in different types of unilateral neglect. *Experimental Brain Research, 206,* 163–169.

Halligan, P.W., & Marshall, J.C. (1991). Left neglect for near but not far space in man. *Nature*, *350* (6318), 498–500.

Halligan, P.W., & Marshall, J.C. (1994). Toward a principled explanation of unilateral neglect. *Cognitive Neuropsychology, 11* (2), 167–206.

Heilman, K.M., Valenstein, I.E., & Watson, R.I. (1985). The neglect syndrome. In: P.J. Vinken, G.W. Bruyn & H.L. Klawans (Eds), *Handbook of Clinical Neurology* (Vol. 45) (pp. 152–183). Amsterdam, The Netherlands: Elsevier Science Publishers.

Heilman, K.M., Valenstein E., & Watson, R.T. (1994). The what and the how of neglect. In P.W. Halligan & J.C. Marshall (Eds.). *Spatial neglect: position papers on theory and practice* (pp. 133–141). Hove, UK: Lawrence Erlbaum.

Heilman, K.M., Watson, R.T., & Valenstein, E. (1993). Neglect and related disorders. In K.M. Heilman & E. Valenstein (Eds.). *Clinical Neuropsychology* (pp. 279–346). New York, NY: Oxford University Press.

Jehkonen, M., Ahonen, J.P., Dastidar, P., Koivisto, A.M., Laippala, P., Vilkki, J., & Molnar, G. (2000). Visual neglect as a predictor of functional outcome one year after stroke. *Acta Neurologica Scandinavica, 101,* 195–201.

Jehkonen, M., Laihosalo, M., & Kettunen, J.E. (2006). Impact of neglect on functional outcome after stroke – a review of methodological issues and recent research findings. *Restorative Neurology and Neuroscience, 24,* 209–215.

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: an update. *Neuropsychologia*, 50 (6), 1072-1079.

Laeng, B., Brennen, T., & Espeseth, T. (2002). Fast responses to neglected targets in visual search reflect pre-attentive processes: An exploration of response times in visual neglect. *Neuropsychologia, 40*, 1622-1636.

Lezak, M.D., Howieson, D.B., & Loring, D.W. (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Luauté, J., Halligan P., Rode, J., Rossetti, Y., & Boisson, D. (2006). Visuo-spatial neglect: A systematic review of current interventions and their effectiveness. *Neuroscience & Biobehavioral Reviews, 30,* 961–982. doi:10.1016/j.neubiorev.2006.03.001

Marshall, J.C., & Halligan, P.W. (1989). Does the midsagittal plane play any privileged role in “left” neglect? *Cognitive Neuropsychology, 6* (4), 403–422.

Milner, A.D., & McIntosh, R.D. (2005). The neurological basis of visual neglect. *Current Opinion in Neurology, 18,* 748–753.

Moreh, E., Malkinson, T.S., Zohary, E., & Soroker, N. (2014). Visual memory in unilateral spatial neglect: immediate recall versus delayed recognition. *Journal of Cognitive Neuroscience, 26,* 2155-2170.

Na, D.L., Adair, J.C., Williamson, D.J.G., Schwartz, R.L., Haws, B., & Heilman, K.M. (1998). Dissociation of sensory-attentional from motor-intentional neglect. *Journal of neurology, neurosurgery and psychiatry, 64* (3), 331–338.

Nys, G.M., Van Zandvoort, M.J., Van der Worp, H.B., Kappelle, L.J., & de Haan, E.H.F. (2006). Neuropsychological and neuroanatomical correlates of perseverative responses in subacute stroke. *Brain, 129,* 2148–2157.

Parton, A., Malhotra, P., & Husain, M. (2004). Hemispatial neglect. *Journal of Neurology, Neurosurgery and Psychiatry, 75,* 13–21.

Plummer, P., Morris, M.E., & Dunai, J. (2003). Assessment of unilateral neglect. *Physical Therapy, 83*(8), 732-740.

Robertson, I.H., & Halligan, J.C. (2000). *Spatial Neglect: A clinical handbook for diagnosis and treatment*. Hove, UK: Psychology Press.

Ronchi, R., Algeri, L., Chiapella, L., Spada, M.S., & Vallar, G. (2012). Spatial neglect and perseveration in visuomotor exploration. *Neuropsychology, 26,* 588–603.

Ronchi, R., Posteraro, L., Fortis, P., Bricolo, E., & Vallar, G. (2009). Perseveration in left spatial neglect: drawing and cancellation tasks. *Cortex, 45,* 300–312.

Rorden, C., & Karnath, H.O. (2010). A simple measure of neglect severity. *Neuropsychologia, 48,* 2758–2763.

Rossetti, Y., Rode, G., Pisella, L., Farnè, A., Ling, L., Boisson, D., & Perenin, M.T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature, 395,* 166–169.

Salter, K., Campbell, N., Richardson, M., Mehta, S., Jutai, J., Zettler, L., ..., & Teasell, R. (2013). Outcome Measures in Stroke Rehabilitation. In: R. Teasell (Ed.), *Evidence-Based Review of Stroke Rehabilitation* (1-144). Available at www.ebrsr.com.

Sarri, M., Greenwood, R., Kalra, L., & Driver, J. (2011). Prism adaptation does not change the rightward spatial preference bias found with ambiguous stimuli in unilateral neglect. *Cortex, 47,* 353-366.

Schendel, K.L., & Robertson, L.C. (2002). Using reaction times to assess patients with unilateral neglect and extinction. *Journal of Clinical and Experimental Neuropsychology, 24,* 942–950.

Schenkenberg, T., Bradford, D.C., & Ajax, E.T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30,* 509–517.

Serino, A., Angeli, V., Frassinetti, F., & Làdavas, E. (2006). Mechanisms underlying neglect recovery after prism adaptation. *Neuropsychologia, 44,* 1068–1078.

Sinnett, S., Juncadella, M., Rafal, R., Azanon, E., & Soto-Faraco, S. (2007). A dissociation between visual and auditory hemi-inattention: Evidence from temporal order judgements. *Neuropsychologia, 45* (3), 552–560. doi:10.1016/j.neuropsychologia.2006.03.006

Small, M., Cowey, A., & Ellis, S. (1994). How lateralised is visuospatial neglect? *Neuropsychologia, 32* (4), 449–464.

Snodgrass, J.G., & Vanderwart, M. (1980). A Standardized Set of 260 Pictures: Norms for Name Agreement, Image Agreement, Familiarity, and Visual Complexity. *Journal of Experimental Psychology: Human Learning and Memory, 6* (2), 174–215.

Stone, S.P., Halligan, P.W., Marshall, J.C., & Greenwood R.J. (1998). Unilateral neglect: a common but heterogeneous syndrome. *Neurology, 50,* 1902–1905.

Stone, S.P., Wilson, B., Wroot, A., Halligan, P.W., Lange, L.S., Marshall, J.C., & Greenwood, R.J. (1991). The assessment of visuo-spatial neglect after acute stroke. *Journal of Neurology, Neurosurgery and Psychiatry, 54,* 345–350.

Strauss, E., Sherman, E.M.S., & Spreen, O. (2006). *A Compendium of Neuropsychological Tests. Administration, Norms, and Commentary*. New York, NY: Oxford University Press.

Striemer, C.L., & Danckert, J.A. (2010). Through a prism darkly: re-evaluating prisms and neglect. *Trends in Cognitive Sciences, 14*(7), 308-316.

Turton, A.J., Dewar, S.J., Lievesley, A., O'Leary, K., Gabb, J., & Gilchrist, I.D. (2009). Walking and wheelchair navigation in patients with left visual neglect. *Neuropsychological Rehabilitation, 19* (2), 274–290.

Vallar, G., Bottini, G., & Sterzi, R. (2003). Anosognosia for left-sided motor and sensory deficits, motor neglect, and sensory hemi-inattention: is there a relationship? *Progress in Brain Research, 142,* 289–301.

Vallar, G., Rusconi, M.L., Bignamini, L., Geminiani, G., & Perani, D. (1994). Anatomical correlates of visual and tactile extinction in humans: A clinical CT scan study. *Journal of Neurology, Neurosurgery and Psychiatry, 57,* 464–470.

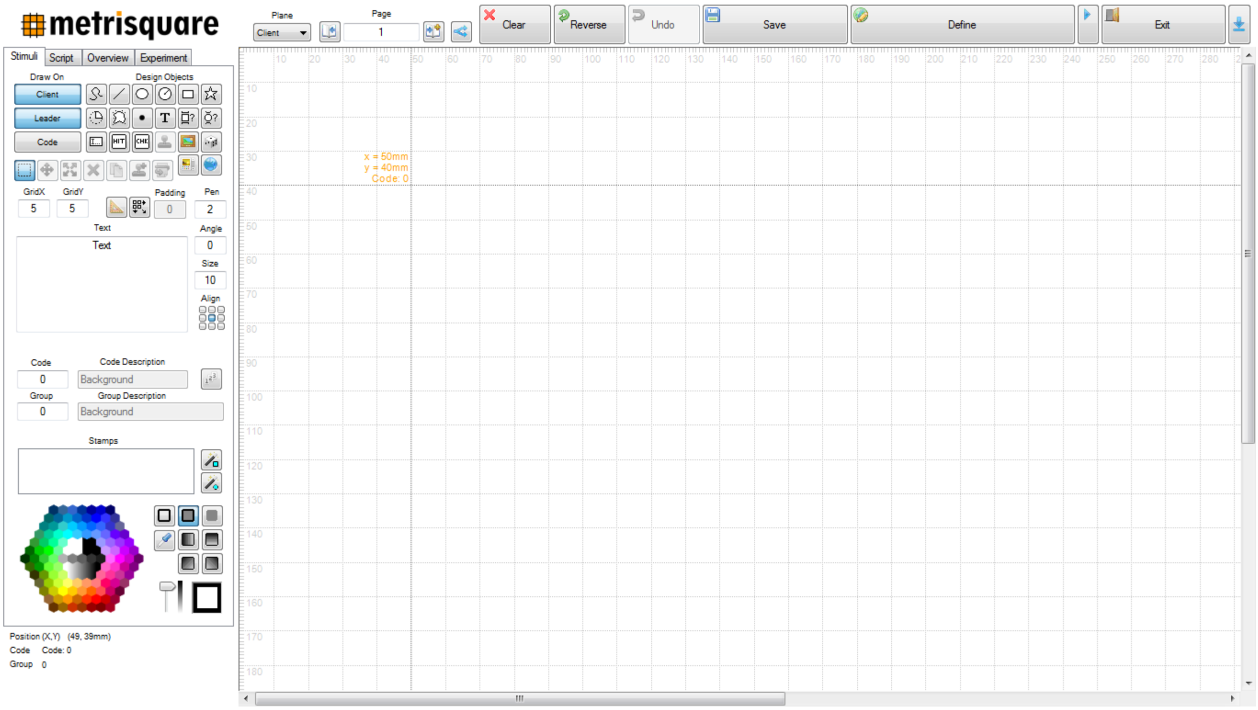
Vanier, M., Gauthier, L., Lambert, J., Pepin, E.P., Robillard, A., Dubouloz, C.J., Gagnon, R., & Yoannette, Y. (1990). Evaluation of left visuospatial neglect: norms and discrimination power of two tests. *Neuropsychology, 4,* 87–96.

Vossel, S., Eschenbeck, P., Weiss, P.H., Weidner, R., Saliger, J., Karbe, H., & Fink, G.R. (2011). Visual extinction in relation to visuospatial neglect after right-hemispheric stroke: quantitative assessment and statistical lesion-symptom mapping. *Journal of Neurology, Neurosurgery, and Psychiatry, 82* (8), 862–868.

Vossel, S., Weiss, P.H., Eschenbeck, P., & Fink, G.R. (2013). Anosognosia, neglect, extinction and lesion site predict impairment of daily living after right-hemispheric stroke. *Cortex, 49,* 1782-1789.

Wilson, B., Cockburn, J., & Halligan, P.W. (1987). *The Behavioural Inattention Test*. Bury St. Edmunds, UK: Thames Valley Test Company.

Supplementary Material



Plane Client

Page 1

GridX 5

GridY 5

Padding 0

Pen 2

Text

Angle 0

Size 10

Code 0

Code Description Background

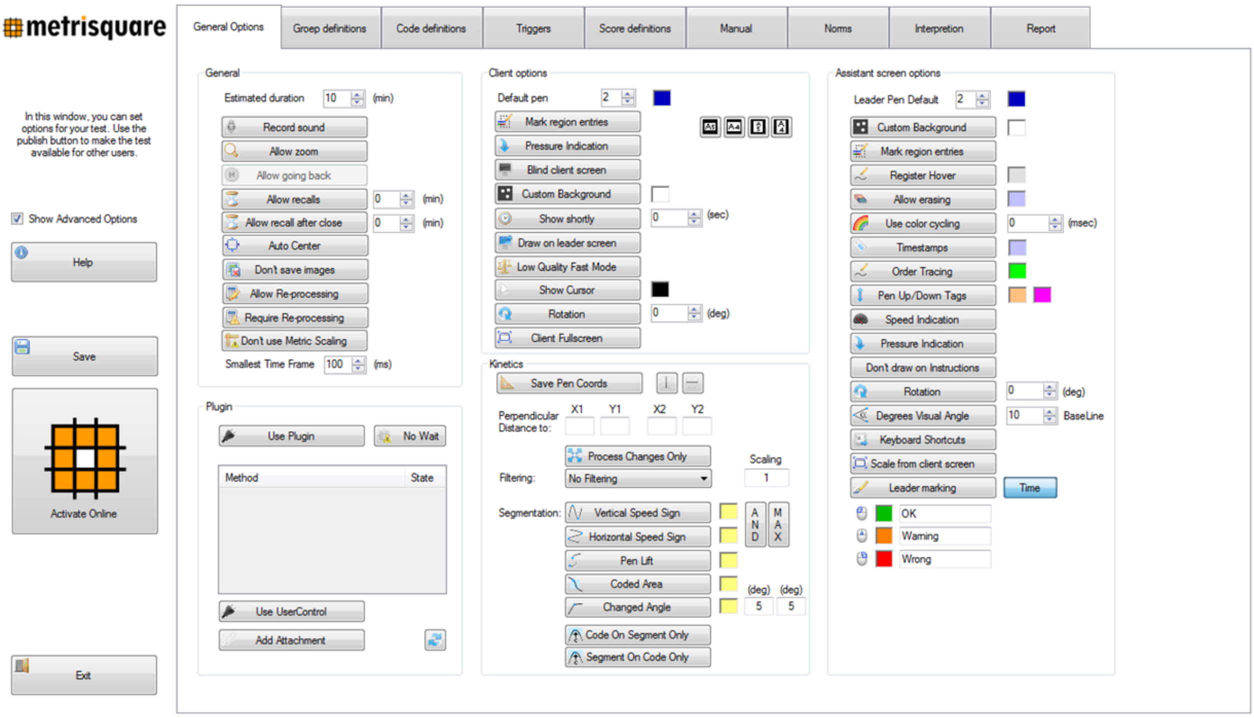
Group 0

Group Description Background

x = 50mm
y = 40mm
Code: 0

Position (X,Y) (49, 39mm)
Code Code: 0
Group 0

Figure A1. The user-interface of the design module in MDIS.



In this window, you can set options for your test. Use the publish button to make the test available for other users.

☑ Show Advanced Options

Estimated duration 10 (min)

Allow recalls 0 (min)

Allow recall after close 0 (min)

Smallest Time Frame 100 (ms)

Default pen 2

Show shortly 0 (sec)

Rotation 0 (deg)

Filtering: No Filtering

Scaling 1

(deg) 5 (deg) 5

Leader Pen Default 2

Use color cycling 0 (msec)

Rotation 0 (deg)

Degrees Visual Angle 10 BaseLine

Figure A2. The MDIS page with optional specifications to add to a designed test, to extend qualitative information or quantitative measures (e.g. order tracing, saving registrations while hovering, showing time stamps).

Chapter 3: Prism Training in Spatial Neglect

3.1 Aim of the study

The amount of PA sessions in a training schedule differs notably between different authors. Jacquin-Courtois and coworkers (2013) mentioned that the ideal treatment regime for routine application requires further research. We included right-hemispheric stroke patients with neglect in an RCT and implemented short-term repetitive PA of 7 sessions in a practically feasible regime. This enabled us to explore whether it would be beneficial in practice to offer PA during short hospitalization periods, for instance in a stroke unit. The optimal post-stroke delay for PA also remains to be defined (Jacquin-Courtois et al., 2013). First, we question if PA effects can be found in a SN population with very diverse post-stroke delays, after a short assessment interval. Secondarily, we explore if PA effects differ between acute, subacute and chronic subgroups of patients. Third, we investigate the extent to which potential PA effects are maintained in the long term.

As mentioned above, we used the digital VNTB of Vaes and colleagues (2015). This includes tests on processes that are conventionally investigated in neglect assessment (cancellation, bisection and drawing) and novel tests on peripersonal navigation, visual extinction, anterograde memory apart from drawing, and lateralized search times. To our knowledge, PA influences on these latter visuospatial processes have not been previously reported, especially not in a RCT with more patients than in most other PA studies on SN. From a theoretical point of view it is also relevant to inspect whether PA influences only test performances that require an intentional-motor component, or other cognitive processes as well. Our post-tests were conducted within 2 to 24 hours after the last prism session and after 3 months to monitor potential long-term effects.

3.2 Rehabilitation of visuospatial neglect by prism Adaptation: Effects of a mild treatment regime - a randomized controlled trial

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Rehabilitation of visuospatial neglect by prism adaptation: effects of a mild treatment regime. A randomised controlled trial

Nathalie Vaes[a,b], Gudrun Nys[c], Christophe Lafosse[a,d], Lutgart Dereymaeker[e], Kristine Oostra[f], Dimitri Hemelsoet[g] and Guy Vingerhoets[a]

[a]Department of Experimental Psychology, Ghent University, Ghent, Belgium; [b]Scientific Unit Rehabilitation Hospital RevArte, Antwerp, Belgium; [c]Rehabilitation Center Overleie, Kortrijk, Belgium; [d]KU Leuven Department of Psychology, University of Leuven, Leuven, Belgium; [e]Medical Department Rehabilitation Hospital RevArte, Antwerp, Belgium; [f]Department of Physical & Rehabilitation Medicine, Ghent University Hospital, Ghent, Belgium; [g]Department of Neurology, Ghent University Hospital, Ghent, Belgium

Abstract

Closely examining the effects, optimal regime and time window of prism adaptation (PA) promotes guidelines for effective rehabilitation practice. The effects of short-term repetitive PA on spatial neglect manifestations were evaluated in patients with heterogeneous post-stroke delays, using a digital Visuospatial Neglect Test Battery. Secondarily, potential differences in PA effects between acute, subacute or chronic neglect were explored. A multicenter randomized controlled trial (RCT) was conducted in 43 right-hemispheric neglect patients. They were treated in a mild PA regime: seven sessions of experimental or placebo prism training over 7 to 12 days. The outcome measures were diverse neglect variables related to peripersonal navigation, visual extinction, visuospatial memory, bisection, cancellation, drawing and visual search. The treatment effects were assessed after a short and a long time interval. Two to 24 hours after PA, conventional effects were found for drawing and centered bisection, and novel effects for peripersonal visuospatial navigation, visual extinction, and non-motor memory (with caution). No effects were found for visual search times and cancellation. The assessments after 3 months were still indicative of PA benefits for navigational, drawing and memory functions. PA did not yet prove to be more effective in acute, subacute or chronic patients. The extension of effects is theoretically framed within the debate about the levels of cognitive processing that are impacted by PA. Clinical suggestions are formulated regarding PA implementation in neglect treatment.

Keywords

hemineglect, short-term repetitive prism training, computer-based navigation, visual extinction, memory

Introduction

Spatial neglect (SN)[4] is a neurologic condition in which patients fail to orient, report or respond to stimuli in contralesional space (Heilman, Watson, & Valenstein, 1993). Neglect patients often are not aware of this condition (Vallar, Bottini, & Sterzi, 2003), which makes compensating for it difficult. SN is frequently associated with an important overall disability and is a predictor of poor functional performance after stroke (Jehkonen, Laihosalo, & Kettunen, 2006; Katz, Hartman-Maeir, Ring, & Soroker, 1999). It adversely affects patients' progress and length of stay in rehabilitation (Gillen, Tennen, & McKee, 2005). Although different neglect symptoms can stand alone, SN mostly concerns a cluster of lateralized deficits encompassing a heterogeneous clinical syndrome (Robertson & Halligan, 2000; Stone, Halligan, Marshall, & Greenwood, 1998; Striemer & Danckert, 2010). Typically, patients also exhibit non-lateralized deficits that modulate or aggravate their lateralized symptoms, for instance impaired sustained attention and working memory (Robertson et al., 1997; Van Vleet & DeGutis, 2013, and Ferber & Danckert, 2006; Husain et al., 2001; Malhotra, Mannan, Driver, & Husain, 2004; Wojciulik, Husain, Clarke, & Driver, 2001).

SN can originate from damage to different neural mechanisms (Stone et al., 1998), but manifests more frequently and significantly after right hemisphere pathology (Halligan & Marshall, 1994). Which area is indicated as critical depends on the diagnostic definition adopted for neglect, but the damage is mostly situated around the parieto-temporal junction

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[4] Overview of the abbreviations used: CG control group; EG experimental group; PA prism adaptation; RCT randomized controlled trial; SLBT Schenkenberg Line Bisection Test; SN spatial neglect; T0 baseline measurements; T1 effect measurements within 2 to 24 hours after the last PA session; T2 effect measurements 3 months after PA

(Milner & McIntosh, 2005). Karnath and Rorden (2012) premise egocentric deficits as the core of SN, as opposed to allocentric deficits. They associate them with the perisylvian network, consisting of the superior/middle temporal, inferior parietal and ventrolateral frontal cortices. Verdon, Schwartz, Lövblad, Hauert and Vuilleumier (2010) combined a factorial analysis of symptoms with voxel-based lesion-symptom mapping to allocate cerebral substrates to different components of the SN syndrome. The allocentric component was associated with deep temporal lobe regions, the visuospatial perceptual one with the right inferior parietal lobule, and the visuomotor explorative component with the right dorsolateral prefrontal cortex.

Meanwhile, sensorimotor realignment by prisms (PA) is a well-known rehabilitation method for SN. It produces a shift in the proprioceptive reference frame to the neglected side by stimulating sensorimotor reorganization (Jacquin-Courtois et al., 2013; Rossetti et al., 1998). An enormous advantage of PA in neglect rehabilitation is that it is a bottom-up strategy (Jacquin-Courtois et al., 2013). Consequently, patients’ frequently impaired awareness of their lateralized symptoms cannot hinder the prism training. The mechanism of action behind PA is still debated. Certain researchers theorize that PA activates cerebral functions related to multisensory integration and higher spatial representations (Jacquin-Courtois et al., 2010; Rode, Klos, Courtois-Jacquin, Rossetti, & Pisella, 2006). Following their point of view, PA can affect spatial cognitive processes in the attentional-perceptual as well as the intentional-motor/explorative domain, even apart from the modalities that are trained during PA (visual, proprioceptive, motor). Other authors state that PA affects components of the brain network related to spatial action planning and execution (intentional-motor) and not to isolated attentional-perceptual biases (Fortis, Chen, Goedert, & Barrett, 2011; Goedert, Chen, Boston, Foundas, & Barrett, 2014). Striemer and Danckert (2010) propose that PA influences attention and visuomotor behaviors that are controlled by the dorsal visual stream, and barely the perceptual biases relying on the ventral stream (see also Ferber, Danckert, Joanisse, Goltz and Goodale (2003) and Sarri, Greenwood, Kalra and Driver (2011)).

The following event-related fMRI studies in healthy participants demonstrate the involvement of a cortical cerebro-cerebellar network in the sensorimotor realignment in PA. Danckert, Ferber and Goodale (2008) showed that monitoring and correcting pointing movements were associated with activity changes in the anterior cingulate and anterior intraparietal cortices, and in a medial region of the right cerebellum. Similar results were found by Luauté et al. (2009). The anterior intraparietal and the parieto-occipital sulci were associated with error detection and correction respectively, during the earliest phase of prism exposure. Cerebellar activity increased progressively in accordance with the spatial realignment during PA. The authors suggest that the cerebellum promotes neural changes in the superior temporal cortex, which was selectively activated during the later phase of prism exposure and could mediate the PA effects on higher spatial representations. Patient fMRI data showed increased activation in bilateral parietal, frontal, and occipital cortices after PA, suggesting a transfer from the short-term plastic changes induced by PA to a longer-term reorganization in fronto-parietal networks regulating internal spatial representations (Jacquin-Courtois et al., 2013; Saj, Cojan, Vocat, Luauté, & Vuilleumier, 2013).

The amount of PA sessions in a training schedule differs notably between different authors. An overview is given in the review of Jacquin-Courtois and coworkers (2013). These authors mention that the ideal treatment regime for routine application requires further research. We have chosen 7 PA sessions in a liberal regime to promote compliance despite a short length of stay or clinical and practical constraints. This enabled us to explore whether it would be beneficial in practice to offer PA during short hospitalization periods, for instance in a stroke unit. The optimal post-stroke delay for PA also remains to be defined (Jacquin-Courtois et al., 2013). First, we question if PA effects can be found in a SN population with very diverse post-stroke delays, after a short assessment interval. Secondarily, we explore if PA effects differ between acute, subacute and chronic subgroups of patients. Third, we investigate the extent to which potential PA effects are maintained in the long term.

Because of the multi-component nature of the neglect syndrome, we use the digital Visuospatial Neglect Test Battery of Vaes and colleagues (2015). This includes tests on processes that are conventionally investigated in clinical neglect assessment (cancellation, bisection and drawing) and newly designed tests on peripersonal navigation, visual extinction, anterograde memory apart from drawing, and lateralized search times. To our knowledge, PA research in SN did not yet demonstrate effects on these latter visuospatial processes, especially not in a RCT with more patients than in most other PA studies on SN (for an overview, please see the Tables in Jacquin-Courtois et al. (2013) and Striemer & Danckert (2010)). Since SN is incapacitating, it is meaningful to examine whether PA can affect multiple components of the syndrome. Jehkonen et al. (2006) recommended that future research should assess various forms of neglect with a standardized test battery, rather than using a single test. Improvements in diverse neglect measures are important, because deficits in these measures are associated with poorer performance in rehabilitation outcomes and functionality (Gillen et al., 2005; Jehkonen et al., 2006; Katz et al., 1999).

Most studies using a test battery include up to seven different tests to capture SN in a differentiated way (Azouvi et al., 2006). The decision about which specific test variables we should use was based on several arguments. Cancellation, line bisection and figure copying are amongst the most frequently used SN tests (Azouvi et al., 2002; Azouvi et al., 2006). We included variables based on these tests because they have proven their usefulness since a long time and for reasons of comparability and replicability across studies. We judged that an extinction variable should also be incorporated because of the independent influence of extinction on ADL (Vossel, Weiss, Eschenbeck, & Fink, 2013), and because it is unknown whether PA can remediate visual extinction. This last reason motivated us to include variables related to memory and search times as well. Although search times and memory processes were found to be laterally distorted in SN (Laeng, Brennen, & Espeseth, 2002; Moreh, Malkinson, Zohary, & Soroker, 2014), to our knowledge, no single study has demonstrated effects of PA on memory functions apart from representation or drawing, nor on visual search times. Furthermore, a domain in the contemporary SN literature that links egocentric space representation to subjective and objective postural characteristics (underpinned by the research groups of Honoré, Karnath, Lafosse, Pérennou, and others), encouraged us to inspect whether PA could influences variables related to peripersonal visuospatial navigation. Finally, from a theoretical point of view it is relevant to inspect whether or not PA influences only test performances that require an intentional-motor component, as introduced above in the debate between different authors (Fortis et al., 2011; Goedert et al., 2014; Jacquin-Courtois et al., 2010; Rode et al., 2006). Our extinction and memory variables can be used to answer this question.

Because several authors report that effects hold for at least two hours after PA (Farnè, Rossetti, Toniolo, & Làdavas, 2002; Rode et al., 2006; Rossetti et al., 1998; Saevarsson, Kristjansson, Hildebrandt, & Halsband, 2009), we conducted our post-tests within 2 to 24 hours after the last prism session and after 3 months to monitor potential long-term effects.

In sum, we list the main aims of this study. We question whether a mild treatment regime of 7 PA sessions can improve SN processes in hospitalized patients with heterogeneous post-stroke delays. We use multiple visuospatial measures and examine which specific SN processes are influenced. The assessments are conducted after a short and long time interval. An explorative research question is formulated about the potential differences in PA effects between acute, subacute and chronic subgroups of patients. We consider this as an initial research impetus because of its clinical importance. In the Method section, the research questions are systematically listed once more. In the Results section, the questions about the short- and long-term PA effects are answered. However, the answer to the potential differences in PA effects related to the post-stroke phase (acute, subacute, chronic) is formulated in the Appendix, because of its exploratory nature. The results are discussed in the final section, which ends with a conclusion that summarizes the main messages of this PA study in SN patients.

Method

Research Design

A multicenter, placebo-controlled study was conducted to assess the effects of short-term repetitive PA on diverse SN manifestations in right-hemispheric (sub)acute and chronic stroke patients. Patients were randomly assigned to an experimental group (EG) and a control group (CG), stratified by the number of days post stroke. Unlike the assessor, the patients were blinded to their experimental or placebo treatment following the same procedure as described below. An oral inquiry after the prism sessions confirmed that they remained unaware of their EG or CG assignment.

Digital neglect measurements were performed at baseline (T0) and within 2 to 24 hours after the last PA session (short time interval, T1). In the patients who were still supervised in the hospitals after 3 months, the effect measurements were repeated (long time interval, T2). The study was approved by the Committee on Medical Ethics of the GasthuisZusters Hospitals Antwerp and the leading Ethical Committee of the University Hospital Ghent.

Patients

Patients were recruited from the Neurology Department and the Rehabilitation Center UZ Gent at the Ghent University Hospital and at Rehabilitation Hospital RevArte (Antwerp). From each center, patients were referred to us by leading physicians, when they detected signs of SN after a right-hemispheric stroke. We then screened the patients for inclusion by means of the Star Cancellation Test (Halligan, Wilson, & Cockburn, 1990) and a 3-lined bisection task. Patients were included when they had at least 4 more left-sided than right-sided omissions at cancellation or a mean of 10 % rightward bisection deviation. In addition, they needed to agree to participate by providing informed consent.

Exclusion criteria were cerebral tumors, traumatic brain injuries, dementia, premorbid mental deterioration or significant oculomotor problems, and not demonstrating a PA aftereffect of at least 3° (cf. infra), medical complications or neurologic deterioration after inclusion. We set the minimum sample-size at 40 included patients to achieve at least as many inclusions as reported in most of the previous studies on PA in SN patients (Jacquin-Courtois et al., 2013; Striemer & Danckert, 2010).

Prism Procedure

As in most of the studies on PA in SN, and as explained in Jacquin-Courtois et al. (2013), we implemented the 3 steps associated with a PA procedure: the pre-exposure baseline measurement of pointing, the exposure to prismatic displacement to elicit sensorimotor adaptation and the post-exposure after-effect measurement. For these 3 steps, we used 10 pointing movements pre-exposure, 80 during exposure, and one post-exposure after every PA session. Seven PA sessions were conducted as much as possible between 7 and 12 days. Due to clinical and practical constraints, finishing the PA sessions took more days in 2 patients (1 in each group) and less days in 3 patients (1 in the EG and 2 in the CG). Our liberal treatment regime stipulated a maximum of 2 PA sessions per day and a maximum of 2 days without PA between 2 sessions. In accordance with the pioneering work of Rossetti and colleagues (1998), our patients wore wedge prisms inducing a rightward optical shift of 10° (EG) or placebo prisms (0° shift, CG). Meanwhile, they pointed randomly at a rather fast but comfortable speed to a left and a right dot positioned at 10° from the body midline. This took place for 5 to 8 minutes depending on the pointing speed and fatigability of each patient. The pre- and post-exposure conditions consisted of open-loop pointing movements to a dot hidden beneath the extendable top surface of a wooden box placed in front of the patient. This box was also used during the exposure to enable individually tailored terminal PA, visualizing only the end of the pointing movements, as explained in Làdavas, Bonifazi, Catena and Serino (2011). Inspired by Nys, de Haan, Kunneman, de Kort and Dijkerman (2008) and based on previous studies (Serino, Angeli, Frassinetti, & Làdavas, 2006), we decided that patients should be excluded from the study if they did not reach an after-effect of at least 3°. Hence this after-effect, computed as the difference between the post- and pre-exposure open-loop pointing conditions, reflects the proper adaptation (Jacquin-Courtois et al., 2013). Inspection of those data revealed that none of the patients needed to be excluded.

Descriptive and Outcome Measures

In addition to the conventional demographic descriptors and the amount of neglect in both screening tasks, we assessed the degree of head and gaze deviation, the presence of homonymous hemianopia, the functional status and 3 PA-related time variables. The outcome measures are the 12 most informative variables derived from 9 tests in a digital format[5], as thoroughly explained and depicted in an article about electronic visuospatial measurements (Vaes et al., 2015). Their discriminative value in the assessment of neglect processes is demonstrated by statistically underpinned, clearly lateralized performance differences between neglect patients and healthy participants. More specifically, the test variables contain cancelling diamonds and bells, bisecting rectangles and lines, searching as fast as possible for the stimulus identical to the alternating central one, copying a clock and butterfly drawing, paying attention to dots at one and both sides of a fixation point, memorizing 12 visually presented images (6 left and 6 right, separately presented in random order), and navigating upwards by the shortest route and ending at the top of the maze. The test battery was presented on a large pen display positioned horizontally in front of the participants. We refer to the Appendix for more details about the descriptive and outcome measures.

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[5] The tests run on the DiagnoseIS software platform, Metrisquare BV, www.metrisquare.com, www.diagnoseis.com.

Research Questions and Statistical Evaluations

We used non-parametric statistics for all the analyses, because our variables are bounded and results of SN patients are typically skewed. The missing data described in the Appendix were handled as exclusions on a test-by-test basis. The statistical tests were implemented in IBM SPSS Statistics version 22, except for the sensitivity analyses that were implemented in the Npsm-package version 0.5 in R 3.0.2. All of the *P*-values were adjusted for multiple tests according to protocol in Benjamini and Hochberg (1995). This method does not control the familywise error rate like the Bonferroni correction, but instead controls the false discovery rate. The adjustments were calculated with the Stats-package in R 3.0.2. The effects were considered to be significant with adjusted *p*-values smaller than .05.

Conforming to the CONSORT statement (Moher et al., 2012; Schulz, Altman, & Moher, 2011), the effect sizes were inspected for the various descriptors in the EG and CG. Hodges-Lehmann median differences were computed for the multi-valued variables and odds ratios for the dichotomous variables.

Our primary aim was to investigate at T1 whether the EG and CG, both with heterogeneous post-stroke delays, differed on the 12 visuospatial variables within 2 to 24 hours after the PA treatment. Two-sided Mann-Whitney U Tests were conducted on the individual subtraction scores of the test results at T0 and T1.

Secondarily, we explored whether PA would be more effective in the acute, subacute or chronic subgroup of the EG. We termed this part of the study exploratory because the smaller patient numbers in the subgroups reduces the power of the statistical tests. For the same reason, we describe this exploration in the Appendix.

As a third aim, we examined potential long-term PA effects on the 12 variables at T2, in a reduced sample of EG and CG patients who were still supervised in the hospitals 3 months after T1. Two-sided Mann-Whitney U Tests were performed on the subtraction scores of the T0 and T2 results.

We also investigated the dependence of the study's findings on the analysis approach, as recommended in Thabane et al. (2013). Despite stratified randomization, baseline imbalances may occur by chance (Altman, 1985). Such imbalances may confound analyses that are based on difference scores. Therefore, in case of observed treatment effects, sensitivity analyses with non-parametric ANCOVAs were performed to verify whether the effects are still significant when conditioned on the T0 scores (Thabane et al., 2013). Please see the Appendix for details. Effects will be called "marginally significant" if they would be significant according to a somewhat different analysis approach (e.g. taking the baseline values into account, using one-sided instead of two-sided tests, or using 0.1 as cut-off for adjusted p-values), although not supported by our primary analyses. Such results cannot be seen as proven facts –we formulate them in cautious terms, but they nevertheless warrant special attention and further research in our opinion.

Results

Patient Flow and Characteristics

The clinical trial could be completed in 43 of the 94 referred patients. Of these 43 patients, 28 were still followed up in the participating hospitals after 3 months. See Figure 1 for the patient flow diagram following the CONSORT 2010 statement (Moher et al., 2012; Schulz et al., 2011).

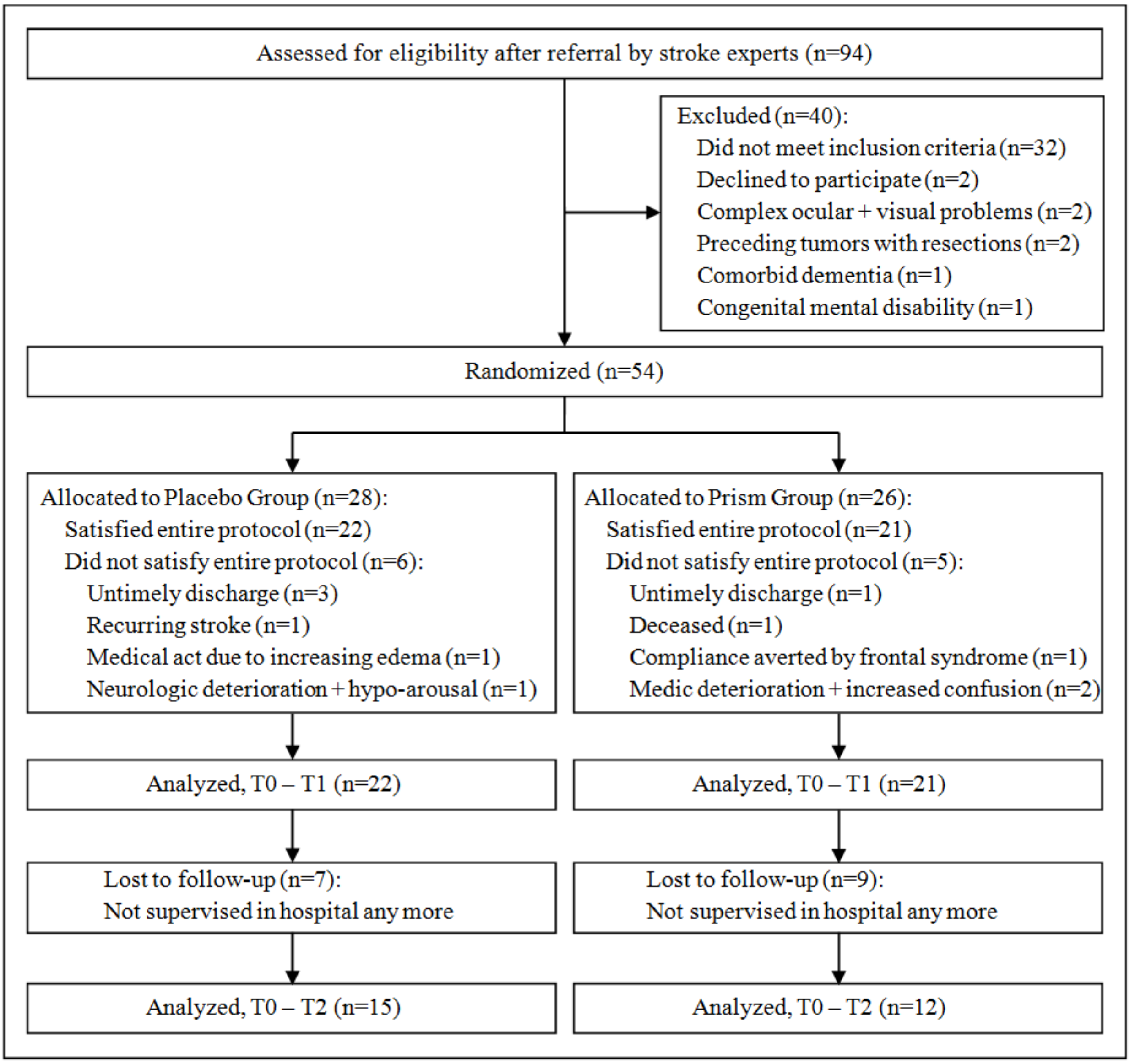

Figure 1. Diagram of the patient flow through the phases of the RCT, as recommended by CONSORT. The consecutive phases are the enrollment, intervention allocation, primary analysis (T0-T1), follow-up and long-term analysis (T0-T2). Information is provided on the counts and excluded patients.

Based on the estimated effect sizes, no essential median intergroup differences were observed regarding the descriptive characteristics listed in Table 1.

Table 1

Descriptive Characteristics

Characteristics	Placebo (CG)[*]	Prism (EG)[*]	Effect Size Estimates[†]
	n = 22	n = 21	
Male/female	14/8	14/7	1.14 [.32-4.01]
Handedness L/R	3/19	2/19	.67 [.10-4.45]
Hemianopia +/-	8/14	7/14	.88 [.25-3.07]
Age	67.50 [60.25-75.50]	59.00 [52.50-74.00]	5.00 [-4.00-12.00]
Educational years	12.00 [8.75-15.00]	12.00 [11.00-15.00]	.00 [-3.00-1.00]
FIM	62.00 [46.75-85.50]	75.00 [48.50-102.00]	-9.00 [-27.00-8.00]
Head and gaze deviation	1.00 [1.00-2.00]	1.00 [.75-1.50]	.00 [.00-.50]
Omissions L – R star cancel	11.00 [6.00-17.50]	10.00 [6.00-13.50]	1.00 [-3.00-5.00]
Mean % deviation line bisect	15.92 [7.68-38.25]	13.92 [11.60-21.02]	-1.00 [-7.45-9.57]
Days from stroke to PA1	48.50 [31.50-103.00]	52.00 [22.50-172.00]	-1.50 [-45.00-24.00]
Days from prism session 1 to 7	8.50 [7.00-10.25]	8.00 [7.00-9.00]	.00 [-1.00-1.00]
Minutes between PA7 and T1	205.20 [160.00-1249.20]	222.10 [117.80-1336.40]	14.94 [-115.64-89.23]

Abbreviations: FIM, Functional Independence Measure.

[*] Values of the multi-valued variables represent medians with [lower-upper quartiles].

[†] Values of the dichotomous variables represent odds ratios and of the other variables Hodges-Lehmann median differences, all with a [95% confidence interval].

The results of the intergroup analyses with respect to the effect measurements at T1 are presented in the left section of Table 2 and in Figure 2. We clearly found significant differences in 6 visuospatial variables, namely, complex drawing, the neglect and extinction indices (confirmation of results without hemianopiacs is in the Appendix), the 2 variables of visuospatial navigation and the composite memory score of the left items. We inspected whether PA mainly affected immediate recall, delayed recall or recognition from the composite memory score. The respective *p*-values after implementing the Mann-Whitney U Tests were .044, .084 and .034.

The percentage of deviation in rectangle bisection was marginally significant between the EG and the CG (adjusted $p = .051$). However, the percentage of line bisection deviation did not differ between the groups (adjusted $p = .144$). Because of this discrepancy between both bisection tasks and because 6 lines are positioned to the left, 6 centrally and 6 to the right in the Schenkenberg Line Bisection Test (SLBT, Schenkenberg, Bradford, & Ajax, 1980) whereas all 24 rectangles are positioned centrally in the Rectangles Bisection Test, we investigated whether the effect could be influenced by position. We conducted extra Mann-Whitney U Tests on the left, centrally and right SLBT lines, which produced *p*-values of .265, .046 and .331, respectively.

Finally, significant differences were not found concerning easy drawing, the CoC-indices of either cancellation task or lateralized search times.

Table 2

Comparisons of Outcome Measures between Control and Experimental Groups

Visuospatial Variables	T0-T1 Subtractions				T0-T2 Subtractions			
	Medians[*] CG/EG n=22/n=21	Effect Size Estimates[†]	*p*[‡]	Adj. *p*	Medians[*] CG/EG n=15/n=12	Effect Size Estimates[†]	*p*[‡]	Adj. *p*
CoC-index bells	.08/.12	-.05 [-.17-.08]	.382	.382	.04/.25	-.09 [-.29-.14]	.456	.658
CoC-index diamonds	.07/.19	-.12 [-.28-.03]	.092	.138	.13/.20	-.07 [-.21-.18]	.323	.554
% SLBT§	.77/5.11	-6.16 [-13.05-1.60]	.120	.144	6.03/12.01	-4.60 [-14.38-5.52]	.548	.658
% Rectangles bisection[§]	.29/2.10	-3.68 [-9.72--.43]	**.030**	**.051**	6.92/8.26	-1.91 [-12.28-9.83]	.648	.707
Search times L/R	-0.18/0.5	-.80 [-2.01-.46]	.220	.240	-0.18/0.53	-1.36 [-3.78-.22]	.093	.223
% Drawing A, R-L	.00/.00	-8.33 [-25.00-.00]	.110	.144	8.33/.00	.00 [-16.67-16.67]	.905	.905
% Drawing B, R-L	-14.71/5.88	-23.53 [-41.18--5.88]	**.015**	**.034**	-5.88/17.65	-35.29 [-64.70-.00]	**.032**	**.092**
Index neglect	3.12/-21.88	25.00 [6.25-50.00]	**.007**	**.034**	.00/-12.50	18.75 [-12.50-37.50]	.247	.494
Index extinction L	-6.25/15.62	-25.00 [-56.25--6.25]	**.017**	**.034**	.00/3.12	-6.25 [-37.50-18.75]	.503	.658
% Memory items L	16.67/-25.00	41.67 [.00-66.67]	**.015**	**.034**	-8.33/-75.00	66.67 [16.67-116.67]	**.006**	**.072**
Mm Navigation end	-4.8/55.4	-70.82 [-120.90--31.05]	**.002**	**.024**	-1.95/118.98	-95.98 [-191.30--21.80]	**.014**	**.076**
CoN-index	-1.26/17.4	-18.82 [-37.60--4.90]	**.010**	**.034**	3.78/45.28	-31.65 [-57.06--6.38]	**.019**	**.076**

Abbreviations: T0, baseline tests; T1, 2-24 hours post-tests; T2, 3 months post-tests; CG, control group; EG, experimental group; CoC, Center of Cancellation; SLBT, Schenkenberg Line Bisection Test; CoN, Center of Navigation.

[*] The higher the medians, the greater the improvement, with the exception of '% Memory items L' and 'Index neglect' where the relation is

reversed.

[†] Hodges-Lehmann median differences with [95% confidence interval].

[‡] *p*-values according to Mann-Whitney U Tests, adjusted *p*-values according to Benjamini-Hochberg multiple tests correction.

[§] Mean percentages of bisection deviation.

The sensitivity analyses demonstrated that our results at T1 are robust for 5 out of 7 variables when taking the T0 scores into account (see Appendix Table 2). For the ‘CoN-index’ and ‘% Memory items L’, the adjusted *p*-values were insignificant.

Effects of Short-term Repetitive Prism Adaptation after 3 Months

The output of the intergroup analyses regarding the effect assessments at T2 is displayed in the right section of Table 2. Figure 2 gives an overview of the results by depicting the effects after the short and long time intervals next to each other. Of the 6 significantly different T1 effects, 4 exhibited a trend towards remaining significantly distinct in the long term despite the reduced EG and CG sizes. The 4 corresponding variables are the composite memory score, complex drawing and the 2 variables from visuospatial navigation. Their adjusted *p*-values, situated between .05 and .1, are rather marginally significant. However, in all of the analyses, we adhered to a conservative approach and implemented two-sided tests, even though one-sided testing would be justified to verify improvement by treatment.

As for the T1 assessment, we inspected with the same tests at T2 whether the PA effect on the composite memory score could be mainly attributed to immediate recall, delayed recall or recognition. The respective *p*-values were .016, .041 and .041.

The sensitivity analyses demonstrated that the results at T2 are robust for all 4 marginally significant variables, when taking the T0 scores into account (see Appendix Table 2). Notably, even the significances of ‘CoN-index’ and ‘% Memory items L’ that were not confirmed by the sensitivity analyses at T1, were now confirmed at T2.

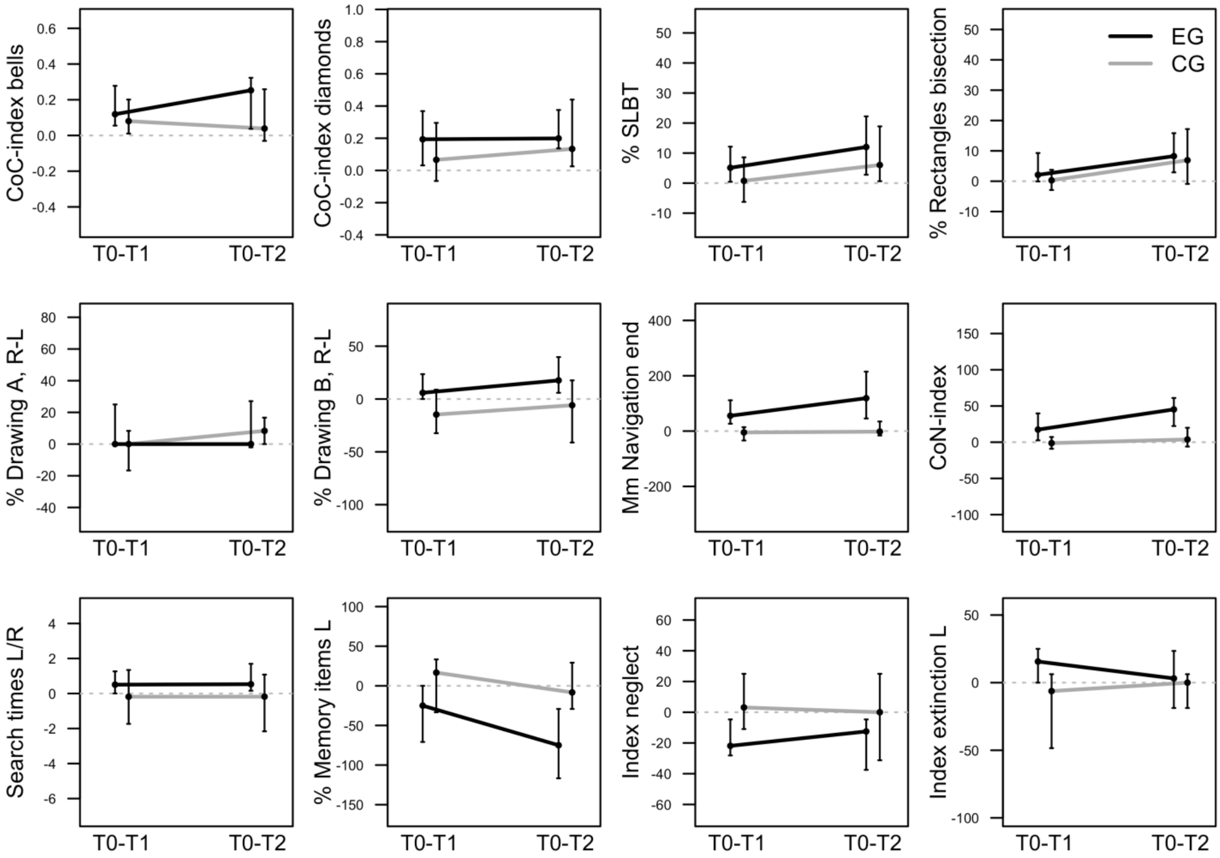

Figure 2. Results from the EG (black) and CG (grey) for each of the 12 peripersonal visuospatial variables. The corresponding evolution along the trial is depicted by connecting the PA effects after the short (T0-T1) and the long (T0-T2) time interval with each other. The lower and upper quartiles are plotted next to the medians. The higher the medians, the greater the improvement, with the exception of '% Memory items L' and 'Index neglect' where the relation is reversed.

Discussion

The present RCT demonstrates that short-term repetitive PA improves certain visuospatial deficits in SN patients with heterogeneous post-stroke delays. In addition to partial conventional effects on drawing and bisection, novel visuospatial PA effects were uncovered on computer-based navigation, anterograde memory (apart from drawing from memory as demonstrated by Rode, Rossetti and Boisson (2001) and Rossetti et al. (1998)) and visual extinction (next to auditory and tactile extinction as evinced by Jacquin-Courtois et al. (2010), and Maravita et al. (2003), Serino, Bonifazi, Pierfederici and Làdavas (2007)). This applies to a short assessment interval after the last prism session (2 to 24 hours). We are cautious about the effects on visuospatial memory and 1 navigational variable (CoN-index) because the outcomes of the primary analyses were not supported by the sensitivity analyses. However, pessimism is not necessary as both variables were still affected by PA at the long assessment interval (3 months after PA), significantly in the sensitivity analyses and to a lesser degree in the primary analyses. The same applies to the other navigational variable (navigation terminus) and complex drawing. It is at least noteworthy that 4 out of 7 variables with a better EG performance at T1 still demonstrated this tendency in the long term, because we used a liberal treatment regime and only 7 sessions of PA. Yet the treatment scheme was insufficient to maintain the PA benefit for centered bisection and both variables of the extinction task.

The results concerning memory and visual extinction are particularly interesting. Unlike the PA training, their assessments did not require arm or ocular movements. The expansion of PA effects to processes that differ from the modalities exposed during PA is important because it demonstrates the PA impact at higher levels of cognitive functioning (Jacquin-Courtois et al., 2013). Moreover, in the debate that was introduced earlier, these results provide support for the view that PA affects not only intentional-motor cerebral functions, but also attentional and non-motor memory functions. Although we add evidence to the existing literature on the beneficial effects of PA on visuospatial attention (see for instance Nijboer, McIntosh, Nys, Dijkerman, & Milner, 2008; Schindler et al., 2009; Striemer & Danckert, 2007), we are not positioned here to comment on the disconfirmation of PA effects on perceptual judgments (as discussed in Ferber & Murray, 2005; Striemer & Danckert, 2010), which requires answers to further, more specific research questions. The improved visuospatial memory performance (immediate recall, delayed recall (not at T1) and recognition) after PA is a remarkable result, but the reasons for this also need further study. One reason can be an improvement in representational neglect because this component has been proven to be influenced by PA (Rode et al., 2001; Rossetti et al., 2004). An alternative explanation is that the left-sided items could be consolidated or retrieved with a higher degree of efficiency. Thirdly, one could imagine that patients were able to pay more attention to the left items after PA, leading to deeper memory processing. However, a special memory test method was used, enabling patients to perceive and attend thoroughly to the right as well as the left items (Vaes et al., 2015). The complex drawing B was affected after the short and long time interval as well, whereas the easy drawing A was not. A ceiling effect inherent to the easy part and a relatively high sensitivity inherent to the complex part appears to cause this discrepancy. Cancellation and the lateralized visual search times were not influenced by

PA. A first potential explanation is the short-term repetitive PA of 7 sessions combined with the mild treatment regime. A recent review of the PA literature concludes that 10 to 20 sessions, at a frequency of 2 per week to 2 per day, appears to produce positive results (Jacquin-Courtois et al., 2013). A second potential reason is that the effects were assessed immediately after PA in various studies (Angeli, Benassi, & Làdavas, 2004; Nys et al., 2008; Watanabe & Amimoto, 2010), in contrast to our post-tests which were performed after 2 to 24 hours and after 3 months. In third place, as suggested by a reviewer and in Striemer and Danckert (2010), it is possible that PA influences spatial attention and perception in impoverished environments, but not in complex environments with more distraction, and in easy tasks with unlimited time or with target detection, but not in tasks with speeded target discrimination. It is just when search is more effortful (higher cognitive load) by enhanced visual complexity (for instance more distracters or combining target features) that SN patients' visual field asymmetry and attentional priority for ipsilesional information increase (Fellrath, Blanche-Durbec, Schnider, Jacquemoud, & Ptak, 2012). PA might not be powerful enough to counter this ipsilesional bias in demanding visual environments. The suggestion of abolished PA-effects in visual search tasks that are speeded or have a higher cognitive load was confirmed in the studies of Morris et al. (2003) and Saevarsson, et al. (2009).

PA induced a leftward bisection shift in centrally presented rectangles and in centered SLBT lines, not in left or right positioned lines. Although the bisection of an object pertains to allocentric neglect, one can hypothesize that those findings result from the shift in the egocentric reference frame because the center of the stimuli was aligned with the body-midline. It would be tempting to investigate whether distinct positions are differentially influenced by PA, with a faster PA effect on stimuli aligned with the body-midline and/or a faster decrease in effect on stimuli positioned elsewhere. Another intriguing research question can be formulated concerning different types of navigation. Two fascinating studies reported PA effects on wheelchair driving (Jacquin-Courtois, Rode, Pisella, Boisson, & Rossetti, 2008; Watanabe & Amimoto, 2010). It is valuable to examine to what degree the Visuospatial Navigation Test results correlate with assessment parameters in wheelchair driving or with postural characteristics that are crucial for spatial navigation. The influence of PA on postural imbalance, for instance, is documented by Tilikete and colleagues (2001).

The exploratory analyses of the acute, subacute and chronic grouping in the EG and CG did not indicate more PA effects in one subgroup or another. However, care should be taken when interpreting these results because of the small subgroup sizes. Currently, the results suggest to not withhold PA from SN patients in a certain post-stroke phase. Meanwhile, future research aimed at unraveling the quest for the optimal phase remains important. This is especially true for RCT’s with large groups above all in Solomon four-group designs (Dimitrov & Rumrill, 2003; Solomon, 1949). Ideally, more answers will be formulated about the best time window for optimal enhancement of cerebral plasticity by PA, and about the best PA regime depending on SN patients’ post-stroke phase.

Despite the heterogeneous post-stroke delays in our SN patients, a mild PA regime can ameliorate visuospatial processes in peripersonal navigation, extinction, centered bisection, drawing and memory. This is of clinical relevance because several authors found that deficits in such neglect measures are associated with lower performances in rehabilitation outcomes, functionality and daily activities (Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001; Gillen et al., 2005; Jehkonen et al., 2006; Katz et al., 1999). If patients’ length of stay is extensive, long-term repetitive PA is preferred to maximize the benefits. However, even during short hospitalization episodes, SN patients can benefit from short-term repetitive PA. We encourage future studies to include appropriate measures of activities of daily living (ADL) and to inspect which domains are affected after which PA intensity and frequency. Valid and sensitive measures should be used. Hence patients might for instance still need help for housekeeping (a typical item of an instrumental ADL scale) because of their hemiplegia, while they are able to read again and bump less into obstacles, items that are typically not included in ADL scales (Kerkhoff and Schenk, 2012).

We conclude with the main messages of this study. A mild treatment regime of 7 PA sessions affects certain SN processes in hospitalized patients, assessed after a short time interval. Conventional visuospatial effects were found on drawing and centered bisection, and novel ones on peripersonal navigation, anterograde memory (with caution) and visual extinction. Despite the mild regime, a trend towards better performance in navigation, drawing and memory was seen in the long term. The effects on visual extinction and memory did not depend on an intentional-motor component, suggesting that PA also influences other levels of cognitive processing. To enhance the probability of extending and consolidating PA effects, we encourage clinicians and researchers to offer PA daily and over an extended time period. However, when patients’ stay is short, they can still benefit from short-term repetitive PA. In addition, when the implementation of treatment sessions is practically constrained, a mild regime with a maximum of 2 days between sessions can still be beneficial. We did not observe different PA influences in the acute, subacute or chronic subgroups yet, but strongly encourage larger investigations about the ideal post-stroke phase for PA in SN.

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References

Altman, D.G. (1985). Comparability of randomised groups. *Statistician, 34,* 125-136.

Angeli, V., Benassi, M.G., & Làdavas, E. (2004). Recovery of oculo-motor bias in neglect patients after prism adaptation. *Neuropsychologia, 42*(9), 1223-1234.

Azouvi, P., Bartolomeo, P., Beis, J., Perennou, D., Pradat-Diehl, P., & Rousseaux, M. (2006). A battery of tests for the quantitative assessment of unilateral neglect. *Restorative neurology and neuroscience, 24*(4-6), 273-285.

Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J.M., ..., Rousseaux, M. (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *J Neurol Neurosurg Psychiatry, 73,* 160–166.

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate - a Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society, Series B Methodological, 57*(1), 289-300.

Cherney, L.R., Halper, A.S., Kwasnica, C.M., Harvey, R.L., & Zhang, M. (2001). Recovery of functional status after right hemisphere stroke: Relationship with unilateral neglect. *Archives of Physical Medicine and Rehabilitation, 82*(3)*,* 322-328.

Danckert, J., Ferber, S., & Goodale, M.A. (2008). Direct effects of prismatic lenses on visuomotor control: an event-related fMRI study. *European Journal of Neuroscience, 28,* 1696-1704.

Dimitrov, D.M., & Rumrill, P.D. Jr. (2003). Pretest-posttest designs and measurement of change. *Work, 20*(2), 159-165.

Farnè, A., Rossetti, Y., Toniolo, S., & Làdavas, E. (2002). Ameliorating neglect with prism adaptation: visuo-manual and visuo-verbal measures. *Neuropsychologia, 40,* 718–729.

Fellrath, J., Blanche-Durbec, V., Schnider, A., Jacquemoud, A.S., & Ptak, R. (2012). Visual search in spatial neglect studied with a preview paradigm. *Frontiers in Human Neuroscience, 6*(93). doi: 10.3389/fnhum.2012.00093

Ferber, S., & Danckert, J. (2006). Lost in space--the fate of memory representations for non-neglected stimuli. *Neuropsychologia, 44*(2), 320-325.

Ferber, S., Danckert, J., Joanisse, M., Goltz, H.C., & Goodale, M.A. (2003). Eye movements tell only half the story. *Neurology, 60,* 1826–1829.

Ferber, S., & Murray, L.J. (2005). Are perceptual judgments dissociated from motor processes?--A prism adaptation study. *Cognitive Brain Research, 23*(2-3), 453-456.

Fortis, P., Chen, P., Goedert, K.M., & Barrett, A.M. (2011). Effects of prism adaptation on motor-intentional spatial bias in neglect. *Neuroreport, 22*(14), 700-705.

Gillen, R., Tennen, H., & McKee, T. (2005). Unilateral spatial neglect: Relation to rehabilitation outcomes in patients with right hemisphere stroke. *Archives of Physical Medicine and Rehabilitation, 86*(4), 763-767.

Goedert, K.M., Chen, P., Boston, R.C., Foundas, A.L., & Barrett, A.M. (2014). Presence of motor-intentional aiming deficit predicts functional improvement of spatial neglect with prism adaptation. *Neurorehabilitation and Neural Repair, 28,* 483-493.

Halligan, P.W., & Marshall, J.C. (1994). Toward a principled explanation of unilateral neglect. *Cognitive Neuropsychology, 11*(2), 167-206.

Halligan, P., Wilson, B., & Cockburn, J. (1990). A short screening test for visual neglect in stroke patients. *International Disability Studies, 12*(3), 95-99.

Heilman, K.M., Watson, R.T., & Valenstein, E. (1993). Neglect and related disorders. In K.M. Heilman & E. Valenstein (Eds.). *Clinical Neuropsychology* (pp. 279-336). New York: Oxford University Press.

Husain, M., Mannan, S., Hodgson, T., Wojciulik, E., Driver, J., & Kennard, C. (2001). Impaired spatial working memory across saccades contributes to abnormal search in parietal neglect. *Brain, 124*, 941-952.

Jacquin-Courtois, S., O'Shea, J., Luaute, J., Pisella, L., Revol, P., Mizuno, K., …, Rossetti, Y. (2013). Rehabilitation of spatial neglect by prism adaptation. A peculiar expansion of sensorimotor after-effects to spatial cognition. *Neuroscience and Biobehavioral Reviews, 37*(4), 594-609.

Jacquin-Courtois, S., Rode, G., Pavani, F., O'Shea, J., Giard, M.H., Boisson, D., & Rossetti, Y. (2010). Effect of prism adaptation on left dichotic listening deficit in neglect patients: glasses to hear better? *Brain, 133,* 895-908.

Jacquin-Courtois, S., Rode, G., Pisella, L., Boisson, D., & Rossetti, Y. (2008). Wheel-chair driving improvement following visuo-manual prism adaptation. *Cortex, 44*(1), 90-96.

Jehkonen, M., Laihosalo, M., & Kettunen, J.E. (2006). Impact of neglect on functional outcome after stroke – a review of methodological issues and recent research findings. *Restorative Neurology and Neuroscience, 24*(4-6), 209-215.

Karnath, H.O., & Rorden, C. (2012). The anatomy of spatial neglect. *Neuropsychologia, 50*(6), 1010-1017.

Katz, N., Hartman-Maeir, A., Ring, H., Soroker, N. (1999). Functional disability and rehabilitation outcome in right hemisphere damaged patients with and without unilateral spatial neglect. *Archives of Physical Medicine and Rehabilitation, 80*(4), 379-384.

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: an update. *Neuropsychologia*, 50(6), 1072-1079.

Laeng, B., Brennen, T., & Espeseth, T. (2002). Fast responses to neglected targets in visual search reflect pre-attentive processes: An exploration of response times in visual neglect. *Neuropsychologia, 40,* 1622-1636.

Làdavas, E., Bonifazi, S., Catena, L., & Serino, A. (2011). Neglect rehabilitation by prism adaptation: Different procedures have different impacts. *Neuropsychologia, 49,* 1136-1145.

Luauté, J., Schwartz, S., Rossetti, Y., Spiridon, M., Rode, G., Boisson, D., & Vuilleumier, P. (2009). Dynamic changes in brain activity during prism adaptation. *The Journal of Neuroscience, 29*(1), 169–178.

Malhotra, P., Mannan, S., Driver, J., & Husain, M. (2004). Impaired spatial working memory: one component of the visual neglect syndrome? *Cortex, 40*(4-5), 667-676.

Maravita, A., McNeil, J., Malhotra, P., Greenwood, R., Husain, M., & Driver, J. (2003). Prism adaptation can improve contralesional tactile perception in neglect. *Neurology, 60*(11), 1829-1831.

Milner, A.D., & McIntosh, R.D. (2005). The neurological basis of visual neglect. *Current Opinion in Neurology, 18*(6), 748-753.

Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Götzsche, P.C., Devereaux, P.J., …, Altman, D.G. (2012). CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery, 10*(1), 28-55.

Moreh, E., Malkinson, T.S., Zohary, E., & Soroker, N. (2014). Visual memory in unilateral spatial neglect: immediate recall versus delayed recognition. *Journal of Cognitive Neuroscience, 26,* 2155-2170.

Morris, A.P., Kritikos, A., Berberovic, N., Pisella, L., Chambers, C.D., Mattingley, J.B. (2004). Prism adaptation and spatial attention: A study of visual search in normals and patients with unilateral neglect. *Cortex, 40,* 703-721.

Nijboer, T.C., McIntosh, R.D., Nys, G.M., Dijkerman, H.C., & Milner, A.D. (2008). Prism adaptation improves voluntary but not automatic orienting in neglect. *Neuroreport, 19*(3), 293-298.

Nys, G.M.S., de Haan, E.H.F., Kunneman, A., de Kort, P.L.M., & Dijkerman, H.C. (2008). Acute neglect rehabilitation using repetitive prism adaptation: A randomized placebo-controlled trial. *Restorative Neurology and Neuroscience, 26*, 1-12.

Robertson, I.H., & Halligan, J.C. (2000). *Spatial Neglect: A clinical handbook for diagnosis and treatment*. Hove, UK: Psychology Press.

Robertson, I.H., Manly, T., Beschin, N., Daini, R., Haeske-Dewick, H., Hömberg, V., …, Weber, E. (1997). Auditory sustained attention is a marker of unilateral spatial neglect. *Neuropsychologia, 35*(12), 1527-1532.

Rode, G., Klos, T., Courtois-Jacquin, S., Rossetti, Y., & Pisella, L. (2006). Neglect and prism adaptation: a new therapeutic tool for spatial cognition disorders. *Restorative Neurology and Neuroscience, 24*(4-6), 347-356.

Rode, G., Rossetti, Y., & Boisson, D. (2001). Prism adaptation improves representational neglect. *Neuropsychologia, 39*(11), 1250-1254.

Rossetti, Y., Jacquin-Courtois, S., Rode, G., Ota, H., Michel, C., & Boisson, D. (2004). Does action make the link between number and space representation? Visuo-manual adaptation improves number bisection in unilateral neglect. *Psycholocial Science, 15*(6), 426-430.

Rossetti, Y., Rode, G., Pisella, L., Farnè, A., Ling, L., Boisson, D., & Perenin, M.T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature*, *395*(6698), 166-169.

Saevarsson, S., Kristjansson, A., Hildebrandt, H., & Halsband, U. (2009). Prism adaptation improves visual search in hemispatial neglect. *Neuropsychologia*, *47*, 717-725.

Saj, A., Cojan, Y., Vocat, R., Luauté, J., & Vuilleumier, P. (2013). Prism adaptation enhances activity of intact fronto-parietal areas in both hemispheres in neglect patients. *Cortex, 49*, 107-119.

Sarri, M., Greenwood, R., Kalra, L., & Driver, J. (2011). Prism adaptation does not change the rightward spatial preference bias found with ambiguous stimuli in unilateral neglect. *Cortex, 47*, 353-366.

Serino, A., Angeli, V., Frassinetti, F., & Làdavas, E. (2006). Mechanisms underlying neglect recovery after prism adaptation. *Neuropsychologia, 44*(7), 1068-1078.

Serino, A., Bonifazi, S., Pierfederici, L., & Làdavas, E. (2007). Neglect treatment by prism adaptation: What recovers and for how long. *Neuropsychological Rehabilitation, 17*(6), 657-687.

Schenkenberg, T., Bradford, D.C., Ajax, E.T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30*(5), 509-517.

Schindler, I., McIntosh, R.D., Cassidy, T.P., Birchall, D., Benson, V., Ietswaart, M., & Milner, A.D. (2009). The disengage deficit in hemispatial neglect is restricted to between-object shifts and is abolished by prism adaptation. *Experimental Brain Research, 192*(3), 499-510.

Schulz, K.F., Altman, D.G., & Moher, D. (2011). CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. *International Journal of Surgery*, 9(8), 672-677.

Solomon, R.L. (1949). An extension of control group design. *Psychological Bulletin, 46*(2), 137-150.

Stone, S.P., Halligan, P.W., Marshall, J.C., & Greenwood R.J. (1998). Unilateral neglect: a common but heterogeneous syndrome. *Neurology, 50*(6), 1902-1905.

Striemer, C., & Danckert, J. (2007). Prism adaptation reduces the disengage deficit in right brain damage patients. *Neuroreport, 18*(1), 99-103.

Striemer, C.L., & Danckert, J.A. (2010). Through a prism darkly: re-evaluating prisms and neglect. *Trends in Cognitive Sciences, 14*(7), 308-316.

Thabane, L., Mbuagbaw, L., Zhang, S., Samaan, Z., Marcucci, M., Ye, C., …, Goldsmith, C.H. (2013). A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. *BMC Medical Research Methodology, 13,* 92.

Tilikete, C., Rode, G., Rossetti, Y., Pichon, J., Li, L., & Boisson D. (2001). Prism adaptation to rightward optical deviation improves postural imbalance in left-hemiparetic patients. *Current Biology, 11*(7), 524-528.

Vaes, N., Lafosse, C., Nys, G., Schevernels, H., Dereymaeker, L., Oostra, K., …, Vingerhoets, G. (2015). Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes. *Behavior Research Methods, 47*(1), 27-44.

Vallar, G., Bottini, G., & Sterzi, R. (2003). Anosognosia for left-sided motor and sensory deficits, motor neglect, and sensory hemi-inattention: is there a relationship? *Progress in Brain Research, 142,* 289-301.

Van Vleet, T.M., DeGutis, J.M. (2013). Cross-training in hemispatial neglect: auditory sustained attention training ameliorates visual attention deficits. *Cortex, 49*(3), 679-690.

Verdon, V., Schwartz, S., Lovblad, K.O., Hauert, C.A., & Vuilleumier, P. (2010). Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. *Brain, 133,* 880-894.

Vossel, S., Weiss, P.H., Eschenbeck, P., & Fink, G.R. (2013). Anosognosia, neglect, extinction and lesion site predict impairment of daily living after right-hemispheric stroke. *Cortex, 49*, 1782-1789.

Watanabe, S., & Amimoto, K. (2010). Generalization of Prism Adaptation for Wheelchair Driving Task in Patients With Unilateral Spatial Neglect. *Archives of Physical Medicine and Rehabilitation, 91*(3), 443-447.

Wojciulik, E., Husain, M., Clarke, K., & Driver, J. (2001). Spatial working memory deficit in unilateral neglect. *Neuropsychologia*, *39*(4), 390–396.

Appendix

Method

Descriptive and Outcome Measures

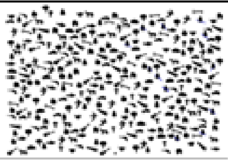
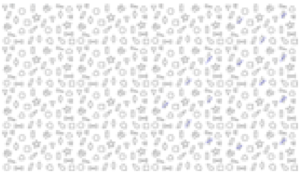
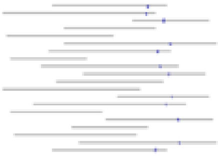
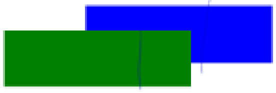
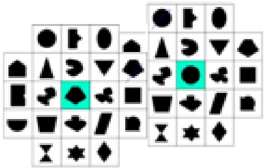
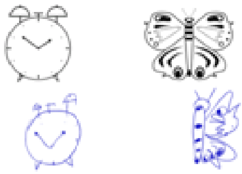
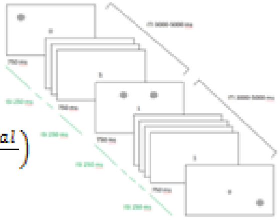
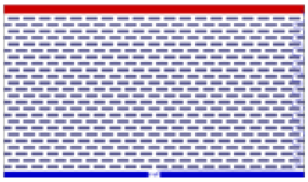
In addition to the conventional demographic characteristics and the amount of neglect in both screening tasks, we assessed the degree of head and gaze deviation, the presence of homonymous hemianopia, the functional status and 3 PA-related time variables. The degree of head and gaze deviation was measured by a four level scale ranging from no deviation to a deviation that cannot be reduced after verbal instruction (Rode, Mauguière, Fischer, & Boisson (1995) in Azouvi et al. (2002) and Rousseaux et al. (2001)). Hemianopia is difficult to measure reliably in SN (Walker, Findlay, Young, & Welch, 1991), but we considered patients as hemianopiacs only if this diagnosis was set in the initial neurological report and was still confirmed after inclusion by combined visual field confrontation testing as described in other studies (Johnson & Baloh, 1991; Kerr, Chew, Eady, Gamble, & Danesh-Meyer, 2010). The functional status was rated by means of the Functional Independence Measure (Center for Functional Assessment Research, 1990). Its score ranges from 18 to 126 by assessing self-care, sphincter control, transfers, locomotion, communication and social cognition. The 3 time variables were the post-stroke delay to the first PA session, the delay between the first and the last prism session and the number of minutes between the last PA session and the T1 effect measurements.

The outcome measures were the 12 most informative variables derived from 9 tests in a digital format. Two well known tests were included for comparability, namely, the Schenkenberg Line Bisection Test (SLBT, Schenkenberg, Bradford, & Ajax, 1980) and The Bells Test (Gauthier, Dehaut, & Joanette, 1989). Each of the seven other tests are thoroughly explained and depicted in an article about a digital method to measure visuospatial processes (Vaes et al., 2015). To clarify them here concisely with the 12 accompanying dependent variables, they are summarized in Table 1. The test battery was presented on an electronic pen display (a Wacom DTU-2231) with a wide interactive field (48 to 27 cm, width to height), well suited for assessing lateralized spatial dysfunctions. The patients performed the tests in the same order. Because of the dual-screen technology, the researcher could observe and mark the interim results at his own computer while the patient used the pen on the display surface.

To capture PA effects in a more unbiased manner in variables that are sensitive to test-retest bias, at T1 we used the parallel versions of the Search Time and Spatial Memory Test as described in Vaes et al. (2015). The Extinction Test is complex compared to the other 8 tests. It was only administered in patients who understood the instructions and could implement them during the subsequent example, which included 30 of the 43 patients. In 1 patient, the baseline data of 4 tests were not saved due to a technical defect (Rectangle Bisection, Diamond Cancellation, Search Time and Navigation Test). With respect to all other T0, T1 and T2 measurements of the 9 tests in all 43 patients, 1 test was not saved or incompletely saved due to human or technical error on 5 occasions. This applies to the Search Time Test (once at T1), the Memory Test (once at T0, T1 and T2) and the Navigation Test (once at T0).

Some clarification is needed regarding the '% memory items L' variable of the Spatial Memory Test. Theoretically, this variable is not a meaningful measure of lateralization. However, it is practically a measure of lateralization because the comparative analysis between right-hemispheric stroke patients with left neglect and healthy controls differed significantly on the '% memory items L', and not on the '% memory items R' (Vaes et al., 2015). The authors deliberately did not use right to left subtraction scores here (6 to 6 items), as opposed to in Drawing A (12 to 12 items) and Drawing B (17 to 17 items). For in the case of a few items, the measurement error could be large and subtraction scores could further decrease the test sensitivity by increasing the error variation.

Table 1 *Clarification of the Computer-based Outcome Measures*

Neglect Test	Visuospatial Variable	Brief Description*	Thumbnail of Test/Test Part
Bells Test Gauthier	Center of Cancellation-index bells	$CoC = \frac{2}{x_r - x_l}\left[\left(\frac{1}{m}\sum_{i=1}^{m} x_i\right) - \left(\frac{1}{n}\sum_{i=1}^{n} x_i\right)\right]$ result ranges from -1 to 1	
Diamond Cancellation	Center of Cancellation-index diamonds	$CoC = \frac{2}{x_r - x_l}\left[\left(\frac{1}{m}\sum_{i=1}^{m} x_i\right) - \left(\frac{1}{n}\sum_{i=1}^{n} x_i\right)\right]$ result ranges from -1 to 1	
Schenkenberg Line Bisection Test	% SLBT	mean % of deviation of 18 lines, result ranges from -100 to 100	
Colored Rectangle Bisection	% rectangles bisection	mean % deviation of 24 rectangles, result ranges from -100 to 100	
Search Time Test	Search times L/R	ratio of left-to-right search times	
Drawing Test A & B	% drawing A, R-L % drawing B, R-L	easy part (alarm clock) complex part (butterfly) % of left-minus-right omissions, result ranges from -100 to 100	
Extinction Test	Index of Neglect Index of Extinction L	$I_{Neg} = 100\left(\frac{hits\ left}{16} - \frac{hits\ right}{16}\right)$ result ranges from -100 to 100 $I_{Ext\_L} = 100\left(\frac{errors\ right\ when\ bilateral}{16}\right)$ result ranges from 0 to 100	
Spatial Memory Test	% memory items L	composite score of immediate + delayed reproduction, and recognition of the left items, result ranges from 0 to 300	
Visuospatial Navigation Test	Mm navigation end Center of Navigation-Index	terminus at the top in mm (Instruction: "Navigate upwards by the shortest route.") result ranges from -233 to 233 $CoN = \frac{100}{x_g}\left(\frac{1}{n}\sum_{i=1}^{n} x_i\right)$ result ranges from -100 to 100	

Abbreviations: CoC, Center of Cancellation; SLBT, Schenkenberg Line Bisection Test; I_{Neg}, Index of Neglect; I_{Ext_L}, Index of left-sided extinction; CoN, Center of Navigation.

[*] Symbols: x_r, coordinate of the most rightward target on the x-axis; x_l, coordinate of the most leftward target on the x-axis; m, number of cancelled targets; n, number of all possible targets (CoC) or of all pen coordinates along the route (CoN); x_i, coordinate on the x-axis (with respect to the midline) of a target (CoC) or a pen coordinate at the route (CoN); x_e, the most extreme absolute value a coordinate can have on the x-axis. We refer to Vaes et al. (2015) for extensive clarification of the variables.

Research Questions and Statistical Evaluations

Sensitivity analyses were conducted to verify whether the observed treatment effects were still significant when conditioned on the patients' T0 scores. They were performed with non-parametric ANCOVAs as implemented in the R-package npsm v0.5 (Kloke & McKean, 2014). Homogenous slopes were assumed to avoid over-fitting of the ANCOVA model on the datasets. As for the primary analyses, *p*-values were adjusted for multiple tests with the Benjamini-Hochberg correction.

In the secondary, exploratory part of our study, we questioned whether PA would be more effective in the acute, subacute or chronic subgroup of the EG. This was done for the CG as well. If one only examines the subgroups in the EG and no effect is found, one would risk overlooking hidden effects of PA in a subgroup. For instance, this could be the case when spontaneous recovery causes a faster improvement in acute patients than in subacute patients in the CG, and PA would neutralize this in the EG by stimulating a faster recovery in the subacute subgroup relative to the acute one. The T0-T1 subtraction scores and Kruskall-Wallis Tests were used because the dependent variables are bounded, and the test results of SN patients are typically skewed.

Results

Effects of Short-term Repetitive Prism Adaptation after 2 to 24 Hours and after 3 Months

We used the outcome of the sensitivity analyses (displayed in Table 2) to judge the impact of T0 baseline imbalances on our T1 and T2 results.

Table 2

Sensitivity Analyses

Visuospatial Variables	Effect	T0-T1*		T0-T2*	
		p	Adj. *p*	*p*	Adj. *p*
% Rectangles bisection	PA treatment	**.033**	**.047**		
	Covariate T0	**.001**			
% Drawing B, R-L	PA treatment	**.031**	**.047**	**.011**	**.024**
	Covariate T0	**.007**			
Index neglect	PA treatment	**.025**	**.047**		
	Covariate T0	.158			
Index extinction L	PA treatment	**.018**	**.047**		
	Covariate T0	.170			
% Memory items L	PA treatment	.508	.508	**.050**†	**.050**†
	Covariate T0	**<.001**			
Mm Navigation end	PA treatment	**.015**	**.047**	**.027**	**.036**
	Covariate T0	**.009**			
CoN-index	PA treatment	.114	.133	**.012**	**.024**
	Covariate T0	**.003**			

Abbreviations: T0, baseline tests; T1, 2-24 hours post-tests; T2, 3 months post-tests; PA, prism adaptation; CoN, Center of Navigation.

**p*-values according to non-parametric ANCOVAs, adjusted *p*-values according to Benjamini-Hochberg multiple test correction.

†Rounded from .0497.

Verification of the Results of the Extinction Test, Excluding Patients with Hemianopia

We repeated the analyses for both variables of the Extinction Test after excluding hemianopiacs (n = 8 in CG, n = 7 in EG) because this test requires central fixation. The results remained significant with *p*-values .038 for the Index of Neglect and .025 for the Index of Extinction L.

Comparison between Acute, Subacute and Chronic Neglect

The means and standard deviations of the number of days post stroke to the first PA session in the acute, subacute and chronic subgroups for the EG were 20.43 ± 3.31, 58.14 ± 21.54 and 702 ± 672.14, respectively, and for the CG were 21 ± 8.88, 57.27 ± 19.43 and 470.40 ± 413.70, respectively. Table 3 displays the results of the comparative intersubgroup analyses of the T0-T1 subtraction scores of the 12 visuospatial variables. There weren’t any intersubgroup differences in the EG or in the CG.

Table 3

Comparisons of T0-T1 Subtractions between Acute, Subacute and Chronic Neglect[*]

Visuospatial Variables	Control Group			Experimental Group		
	Medians[†]	*p*	Adj.*p*	Medians[†]	*p*	Adj.*p*
	Acute/Subacute/Chronic			Acute/Subacute/Chronic		
	n = 6 / n = 11 / n = 5			n = 7 / n = 7 / n = 7		
CoC-index bells	.20/.10/-.01	**.037**	**.422**	.12/.16/-.04	.382	.819
CoC-index diamonds	.21/.04/-.02	.297	.466	.37/.06/.19	.318	.819
% SLBT[ε]	8.50/.74/-.92	.353	.471	11.39/5.11/4.24	.925	.966
% Rectangles bisection[‡]	.76/-1.25/.34	.921	.921	6.74/2.57/1.46	.953	.966
Search times L/R	1.06/.25/-1.73	.150	.422	1.76/.38/.17	.108	.819
% Drawing A, R-L	4.17/-16.67/16.67	.123	.422	.00/16.67/.00	.478	.819
% Drawing B, R-L	-17.65/-5.88/-17.65	.513	.616	5.88/23.53/5.88	.569	.854
Index neglect	-18.75/6.25/18.75	.123	.422	-25.00/-6.25/-25.00	.251	.819
Index extinction L	6.25/-25.00/-12.50	.176	.422	25.00/3.12/12.50	.456	.819
% Memory items L	-16.67/16.67/16.67	.825	.900	.00/-50.00/-25.00	.966	.966
Mm Navigation end	4.90/-22.80/-22.80	.287	.466	55.40/39.30/98.10	.911	.966
CoN-index	17.97/-4.34/.19	.311	.466	17.41/36.34/2.53	.393	.819

Abbreviations: T0, baseline tests; T1, 2-24 hours post-tests; CoC, Center of Cancellation; SLBT, Schenkenberg Line Bisection Test; CoN, Center of Navigation.

[*] *p*-values according to Kruskal-Wallis Tests, adjusted *p*-values according to Benjamini-Hochberg multiple test correction.

[†] The higher the medians, the greater the improvement, with the exception of '% Memory items L' and 'Index neglect' where the relation is reversed.

[‡] Mean percentages of bisection deviation.

References of Appendix

Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J. M., . . . Rousseaux, M. (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *Journal of Neurology Neurosurgery and Psychiatry, 73*(2), 160-166.

Center for Functional Assessment Research (1990). *Data Management Service of the Uniform Data System for Medical Rehabilitation: Guide for Use of the Uniform Data Set for Medical Rehabilitation Including the Functional Independence Measure (FIM), Version 3.0.* Buffalo, NY: State University of New York.

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology, 11*(2), 49-54.

Johnson, L.N., & Baloh, F.G. (1991). The accuracy of confrontation visual field test in comparison with automated perimetry. *Journal of the National Medical Association, 83*(10), 895-898.

Kerr, N. M., Chew, S. S. L., Eady, E. K., Gamble, G. D., & Danesh-Meyer, H. V. (2010). Diagnostic accuracy of confrontation visual field tests. *Neurology, 74*(15), 1184-1190.

Kloke, J., & McKean, J.W. (2014). *Nonparametric statistical methods using R*. Boca Raton, FL: Chapman-Hall.

Rode, G., Mauguière, F., Fischer, C., & Boisson, D. (1995). Lésions hémisphériques droites et négligence unilatérale; La part de la déafférentation. *Annales de Réadaptation et de Médecine Physique, 38*, 324.

Rousseaux, M., Beis, J. M., Pradat-Diehl, P., Martin, Y., Bartolomeo, P., Bernati, T., . . . Azouvi, P. (2001). Présentation d'une batterie de dépistage de la négligence spatiale. Normes et effets de l'âge, du niveau d'éducation, du sexe, de la main et de la latéralité. *Revue Neurologique, 157*, 1385-1400.

Schenkenberg, T., Bradford, D.C., Ajax, E.T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30*(5), 509-517.

Vaes, N., Lafosse, C., Nys, G., Schevernels, H., Dereymaeker, L., Oostra, K., …, Vingerhoets, G. (2015). Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes. *Behavior Research Methods, 47*(1), 27-44.

Walker, R., Findlay, J. M., Young, A. W., & Welch, J. (1991). Disentangling neglect and hemianopia. *Neuropsychologia, 29*(10), 1019-1027.

Chapter 4: Posture-related Theory in Spatial Neglect

4.1 Aim of the study

Based on two lines of evidence, we wanted to investigate whether right-hemispheric patients' visuospatial orienting and behavior manifest itself differently in SN patients with versus without CP. First, Honoré, Saj, Bernati and Rousseaux (2009) found a significant contralesional shift in the subjective straight ahead in SN patients with CP, as opposed to the ipsilesional shift in SN patients without CP. They concluded that the pusher syndrome reverses the ipsilesional orienting bias in SN. Second, Richard, Honoré, Bernati and Rousseaux (2004) evinced a significant correlation between long line bisection error and subjective straight ahead position in right-hemispheric SN patients. The combination of both findings led us to the research question about a contralesionally directed shift in visuospatial functioning, including line bisection, in SN patients with CP ("contraversive neglect"), compared with SN patients without CP. To be able to monitor whether or not this is the case, we conceived a digital task which allows for quasi unrestricted lateral visuomotor deviation (within the limits of the task surface). This means that patients' responses were not directed towards or triggered by certain stimuli at the left, central or right part, but free to move in a navigation task with complete uniform stimuli across its surface. In addition, we wanted to inspect whether a contralesional instead of ipsilesional deviation (cross-over) in long line bisection actually is a phenomenon characterizing SN patients with CP, as opposed to SN patients without CP. The navigation and line bisection tasks are part of the digital VNTB that is described in Chapter 2 (Vaes et al., 2015).

4.2 Contraversive neglect? A modulation of visuospatial neglect in association with contraversive pushing

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Contraversive Neglect? A Modulation of Visuospatial Neglect in Association With Contraversive Pushing

Nathalie Vaes
Ghent University and Rehabilitation Hospital RevArte, Antwerp, Belgium

Christophe Lafosse
Rehabilitation Hospital RevArte, Antwerp, Belgium and University of Leuven

Dimitri Hemelsoet
Ghent University Hospital

Els Van Tichelt
Rehabilitation Hospital RevArte, Antwerp, Belgium

Kristine Oostra
Ghent University Hospital

Guy Vingerhoets
Ghent University

Abstract

Objective: Contraversive pushing (CP) is a neurologic disorder characterized by a lateral postural imbalance. Pusher patients actively push towards their contralesional side due to a misperception of the body's orientation in relation to gravity. Although not every patient with CP suffers from spatial neglect (SN), both phenomena are highly correlated in right-hemispheric patients. The present study investigates whether peripersonal visuospatial functioning differs in neglect patients with versus without CP (NP^+ versus NP^- patients). ***Method:*** Eighteen right-hemispheric stroke patients with SN were included, of which 17 in a double-blind case-control study and one single case with posterior pushing to supplement the discourse. A computer-based visuospatial navigation task, in which lateralized deviation can freely emerge, was used to quantify visuospatial behavior. In addition, visuospatial orienting was monitored using line bisection. ***Results:*** Significant intergroup differences were found. The NP^+ patients demonstrated a smaller ipsilesional navigational deviation and more cross-over (contralesional instead of ipsilesional deviation) in long line bisection. As such, they demonstrated a contraversive (contralesionally directed) shift in comparison with the NP^- patients. ***Conclusions:*** These findings highlight the similarity between two systems of space representation. They are consistent with a coherence between the neural processing system which mainly provides for postural control, and the one responsible for non-predominantly postural, visuospatial behavior.

Keywords

visuospatial neglect, contraversive pushing, spatial shift, cross-over, posterior pusher syndrome

Introduction and Rationale

Patients with CP demonstrate a ‘pusher syndrome’, encompassing a contralesionally tilted posture with severe imbalance, an active pushing away from the ipsilesional side with the non-paretic limbs, and resistance to external attempts to correct their posture (Davies, 1985). We refer to Karnath (2007) for a recapitulatory review of this less known phenomenon. CP mainly is reported after stroke, but other cerebral etiologies are possible too (Santos-Pontelli et al., 2004). The critical neural substrates reported so far, are the posterolateral thalamus (Karnath, Ferber, & Dichgans, 2000a; Karnath, Johannsen, Broetz, & Kuker, 2005), the insula and postcentral gyrus (Johannsen, Broetz, Naegele, & Karnath, 2006) (lesion sites) and the inferior frontal gyrus, middle temporal gyrus, precentral gyrus and inferior parietal lobule (Ticini, Klose, Nagele, & Karnath, 2009) (structurally intact but malperfused). Cases with CP are also described after cerebellar and anterior cerebral artery infarctions, though (Karnath, Suchan, & Johannsen, 2008; Paci & Nannetti, 2005). Most authors observed that CP occurs more frequently after right than after left hemisphere lesions (Davies, 2000; Karnath et al., 2000a; Lafosse et al., 2005). In right-hemispheric patients, CP often is allied with SN (Bateman & Riddoch, 1996; Davies, 2000; Lafosse et al., 2005; Saj, Honoré, Coello, & Rousseaux, 2005). According to Karnath (1994) and hypothesized by Ventre, Flandrin, and Jeannerod (1984), the central transformation of sensory input coordinates to a body centered reference frame is disturbed in SN patients. This induces a horizontal deviation of the spatial reference frame, with a corresponding ipsilesional displacement of the subjective body orientation in the axial plane. In line with this, SN patients’ body axis is tilted towards the ipsilesional side, in contrast to the contralesionally tilted body axis in CP patients. Counterintuitively however, Karnath, Ferber, and Dichgans (2000b) found that CP patients’ subjective postural vertical was not displaced contralesionally, but distinctly tilted by 18° towards the ipsilesional side. Other findings exist as well, see Pérennou et al. (2008) concerning a contralesionally perceived vertical in CP. It is suggested that the pusher syndrome stems from a severe misperception of body orientation in relation to gravity, in the coronal plane. Apparently as a pathological compensation mechanism for this misperception, CP patients push their body *contraversively* (towards the contralesional side) (Karnath, 2007; Karnath et al., 2000b), transferring their center of mass to the contralesional side. On the contrary, the body axis and center of mass of SN patients, reside ipsilesionally (Lafosse, Kerckhofs, Troch, Santens, & Vandenbussche, 2004). In a way of extending this theoretical framework, pushing posteriorly co-occurs in some patients with CP. This peculiar behavior has already been identified early (Davies, 1985). The term “posterior pusher syndrome” was only recently proposed though, denoting a disorder of body orientation in the sagittal plane, characterized by a posterior tilt, pushing the trunk backward, backward falling and active resistance to corrective attempts to pull the body forward (Cardoen & Santens, 2010). Based on two case studies, these authors suggest that posterior pushing (PP) occurs on the occasion of progressive, aspecific encephalopathy. However, a casus with PP after a right-hemispheric stroke has been described as well (Mikolajewska, 2012). Interestingly, Santos-Pontelli, Pontes-Neto, and Leite (2011) question whether the PP syndrome is a newly reported neurological entity, or a severe postural reaction to the geriatric ‘psychomotor disadaptation syndrome’, which is characterized by postural impairments including retropulsion, backward disequilibrium, axial and limb rigidity (Pfitzenmeyer, Mourey, Tavernier, & Camus, 1999). Backward disequilibrium is associated with a posteriorly positioned center of mass (Mourey, Manckoundia, Martin-Arveux, Tavernier-Vidal, & Pfitzenmeyer, 2004). Furthermore, a posterior trunk orientation might also be related to a shift in the perception of verticality in the sagittal plane, observed by Utz et al. (2011) in many SN patients.

Given the disturbance in the sensory based central neurologic generation of the body-centered reference frame in SN, Karnath, Christ, and Hartje (1993) manipulated the proprioceptive input (the head-on-trunk signal) in right-hemispheric SN patients. They observed that SN decreases by turning the trunk 15° to the left (real lengthening of the posterior neck muscles) or by vibrating the left posterior neck muscles (apparent lengthening). These results were hypothetically interpreted in line with a contralesional shift in two components necessary for visuomotor coordination and space exploration, namely the subjective midplane localization and the egocentric coordinate system. The trunk midline constitutes the physical anchor for the generation of the egocentric reference frame, allowing the determination of body position with respect to visual space. Hence the spatial orientation of the trunk seems to be determinant for neglecting the contralesional part of space, by dividing space perception into an egocentric “left” and “right” sector (Karnath, Schenkel, & Fischer, 1991). Intrigued by these studies and the distinct postural characteristics of patients with SN on the one hand and CP on the other, the question sets in about the possibility of a correspondingly distinct pattern of visuospatial functioning in these two patient groups. In 2008-2009 we conducted an exploratory investigation (unpublished academic thesis), that nourished the implementation of the current case-control study. It was suggestive of a cross-over phenomenon at long line bisection, in NP^+ patients. Furthermore, evidence of Honoré, Saj, Bernati, and Rousseaux (2009) thoroughly encouraged more solid research in this respect. Regarding the subjective straight ahead, these authors found a significant contralesional shift in NP^+ patients, as opposed to the ipsilesional shift in NP^- patients. They concluded that the pusher syndrome reverses the ipsilesional orienting bias in SN. To be able to monitor whether right-hemispheric patients' visuospatial orienting and behavior manifest itself differently in NP^+ versus NP^-, we conceived a digital task which allows for quasi unrestricted lateral visuomotor deviation (within the limits of the task surface). This means that patients' responses were not directed towards or triggered by certain stimuli at the left, central or right part, but free to move in a navigation task with complete uniform stimuli across its surface (Vaes et al., 2015). In addition, we wanted to inspect by means of this study, whether cross-over in long line bisection actually is a phenomenon characterizing NP^+ as opposed to NP^-. This should be expected based on the research of Honoré et al. (2009, cf. supra) and Richard and colleagues (Richard, Honoré, Bernati, & Rousseaux, 2004), the latter of which evinced a significant correlation between long line bisection error and subjective straight ahead position in right-hemispheric SN patients. Indeed, combining both lines of evidence, a reversed long line bisection error –contraversive cross-over– should be observed in association with a reversed subjective straight ahead position in right-hemispheric NP^+ patients. In place here, is a short demarcation of the cross-over phenomenon in long line bisection hypothesized here, from the one in short line bisection. SN patients can demonstrate cross-over in lines of 2 to 2.5 cm (Halligan & Marshall, 1988). Several reasons are advanced for this phenomenon in short lines, such as representational overextension (Ishiai et al., 2004), confabulation released by desinhibition (Chatterjee, 1995; Monaghan & Shillcock, 1998) and hemianopia (Doricchi et al., 2005). Interesting discussions on hemianopic contralesional line bisection error in longer lines, however, can be found in Kerkhoff and Schenk (2011) and Kuhn et al. (2012a, 2012b). Concerning long line bisection, a spatial performance difference is documented, with less ipsilesional deviation in right, compared to left positioned lines (Heilman & Valenstein, 1979; Nichelli, Rinaldi, & Cubelli, 1989). This performance difference fits well with the theory of egocentric space representation anchored to the trunk midline, leading to SN in case of a disturbance in this representational system (Bisiach, Capitani, & Porta, 1985; Karnath et al., 1991).

Method

Research Design

A multicenter double-blind case-control study was conducted to assess visuospatial functioning in right-hemispheric SN patients with versus without CP. Whenever a patient qualified for inclusion, the Scale for Contraversive Pushing[6] (SCP, Karnath, Brotz, & Gotz, 2001; Karnath et al., 2000b) intended for that patient, was given to the collaborating physiotherapist and the visuospatial measurements were administered by the test leader. At the time of testing, patient nor test leader knew whether the patient would be in the NP^+ or NP^- group, and the physiotherapist did not know the patient's visuospatial performance. Patients were only assigned to the NP^+ group in case of a clinically experienced pusher syndrome by the treating stroke physiotherapist, plus a pusher profile on the SCP, administered by a stroke physiotherapist trained in the use of the SCP. The scale was employed with the detailed instructions published in an update, to enhance its reliability and validity (Karnath & Brotz, 2007). We adhered to the modified SCP-cutoff criterion of Baccini and coworkers (Baccini, Paci, Nannetti, Biricolti, & Rinaldi, 2008), being a score > 0 in each of the three sections of the scale, because of its excellent correspondence with the clinical diagnosis. To avoid confounds due to overlap in features of the SCP, we only included patients in the NP^- group if they obtained a zero SCP-score.

The study was approved by the two Committees on Medical Ethics involved, being the ethical committee of the GasthuisZusters Hospitals Antwerp and the leading ethical committee of the University Hospital Ghent.

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[6] The SCP is based on Davies criteria (Davies, 1985) and assesses the symmetry of the spontaneous posture (related to the contraversive tilt), the extension of the arm or leg to enlarge physical contact with the surface, and the resistance to passive correction of posture, all in the sitting and standing position.

Patients

For this study, we drew data from the baseline measurements of a recently conducted randomized placebo-controlled trial (results submitted elsewhere). Patients were recruited from the stroke unit (Neurology Department) and the Rehabilitation Center UZ Gent at the Ghent University Hospital, and from Rehabilitation Hospital RevArte (Antwerp). From each center, right-hemispheric stroke patients were considered for trial inclusion after detection of SN signs by the leading neurologist or neurorehabilitation physician, confirmed by a quick screening by means of the Star Cancellation Test (Halligan, Wilson, & Cockburn, 1990) and a short three-lined bisection task. Upon inclusion, they needed to agree with participation by signing an informed consent. To ascertain a manifest SN in the patients of the NP^+ and NP^- groups, preventing confounding influences of negligible SN on our depending variables, we opted for secure inclusion criteria based on prior studies: a Center of Cancellation (CoC, Binder, Marshall, Lazar, Benjamin, & Mohr, 1992) > .081 (Rorden & Karnath, 2010) on the Bells Test (Gauthier, Dehaut, & Joanette, 1989), and a mean percentage of deviation of ≥ 14% (Ferber & Karnath, 2001) on the Schenkenberg Line Bisection Test (SLBT, Schenkenberg, Bradford, & Ajax, 1980). Patients were excluded based on the following criteria: declining to participate, significant visual problems, cerebral tumors, traumatic brain injuries, hydrocephalus, comorbid dementia, premorbid mental deterioration, a > 0 score in only one or two of the three sections of the SCP and not meeting our CoC- or SLBT-criterion. Inferred from previously reported patient numbers in related studies (Honoré et al., 2009; Karnath et al., 2000b; Richard et al., 2004), we deemed a minimum sample size of 15 to 18 included patients to be acceptable, balanced between both groups.

The NP^+ and NP^- groups were comparable in age, sex, handedness, years of education after the age of six, days post-stroke, the presence of hemianopia, and the amount of SN as quantified by the CoC index at the Bells Test and the mean deviation percentage in the SLBT. Furthermore, their levels of head and gaze deviation, muscle tone at the affected hemi-body, upper extremity impairment and gait independence were similar, suggesting that the severity of their physical post-stroke condition was controlled for too (see the results section 3.1.).

Descriptive and Outcome Measures

Next to the conventional demographic characteristics, we assessed a number of descriptives that are informative for the amount of stroke related impairment. They are clarified consecutively. Hemianopia is difficult to objectify in SN (Walker, Findlay, Young, & Welch, 1991). Besides, the sensitivity of confrontation visual field testing for mild to moderate visual field defects is low. It improves by combining confrontation tests and is rather satisfactory for severe visual defects such as homonymous hemianopia (Kerr, Chew, Eady, Gamble, & Danesh-Meyer, 2010; Lenworth & Frank, 1991). Our patients' visual fields were examined by their neurologists and after inclusion by clinical confrontation tests administered by the neuropsychologist, to reduce uncertainty about the presence of hemianopia. The degree of head and gaze deviation was measured by a four level scale ranging from no deviation to a deviation that even cannot be reduced after verbal instruction (Azouvi et al., 2002; Rode, Mauguière, Fischer, & Boisson, 1995; Rousseaux et al., 2001). For the evaluation of rigidity during passive extension and flexion of the affected fingers, wrist, elbow, knee and ankle, the Ashworth Scale (AS) was used (Ashworth, 1964), a five level scale ranging from no to a severely increased muscle tone. The upper limb motor function was assessed by means of the Utrecht Arm/Hand Test (UAT, Kruitwagen-van Reenen, Post, Mulder-Bouwens, & Visser-Meily, 2009), an eight level ordinal scale based on the following stages of recovery: a-functional arm, flexion-synergy, first distal selectivity, wrist dorsal flexion, hook grip, cylinder grasp, tweezers grasp and clumsy hand (Brunnstrom, 1966; Twitchell, 1951). To rate the degree of assistance needed while walking, the six ordinal items of the Functional Ambulation Categories (FAC) were employed, ranging from an afunctional gait to independent walking on any surface (Holden, Gill, Magliozzi, Nathan, & Piehlbaker, 1984).

The outcome measures are twofold. First, we used the navigational terminus and the Center of Navigation (CoN) index of the digital Visuospatial Navigation Test (VNT) of Vaes et al. (2015). Conceived for the use on a wide pen display and existing of symmetrically ordered uniform obstacles (see Figure 1), this test allows for quasi free lateral spatial deviation. The employed pen display has an interactive field of circa 48 to 27 cm (width to height) and was positioned horizontally in front of the patients. Patients were instructed to start centrally at the bottom of the maze and to find their way (between the obstacles) to the top (the red bar) *by the shortest route*. The navigational terminus is the end point along the red bar at the top, quantified in mm counted from zero, with a maximum value of 233. With regard to the X-axis of the task, zero is located in the middle. The CoN index[7] is the mean percentage of navigational deviation with respect to zero, of all registered pen coordinates at the navigational route, along the X-axis. It is calculated starting from the second white line at the bottom of the maze.

Second, the amount of cross-over in long line bisection was counted, more specifically the number of times that a patient bisected a line left instead of right of its midpoint. The SLBT (Schenkenberg et al., 1980) was used, presented on the same pen display as the one employed for the VNT. Eighteen horizontal lines were taken into account, interlacingly positioned within a left, middle and right test section. Each section contains six lines, always with lengths of 100, 120, 140, 160, 180 and 200 mm. The midpoints of the left and right lines of the same lengths were located at equal distances of the centered line midpoints in the middle section.

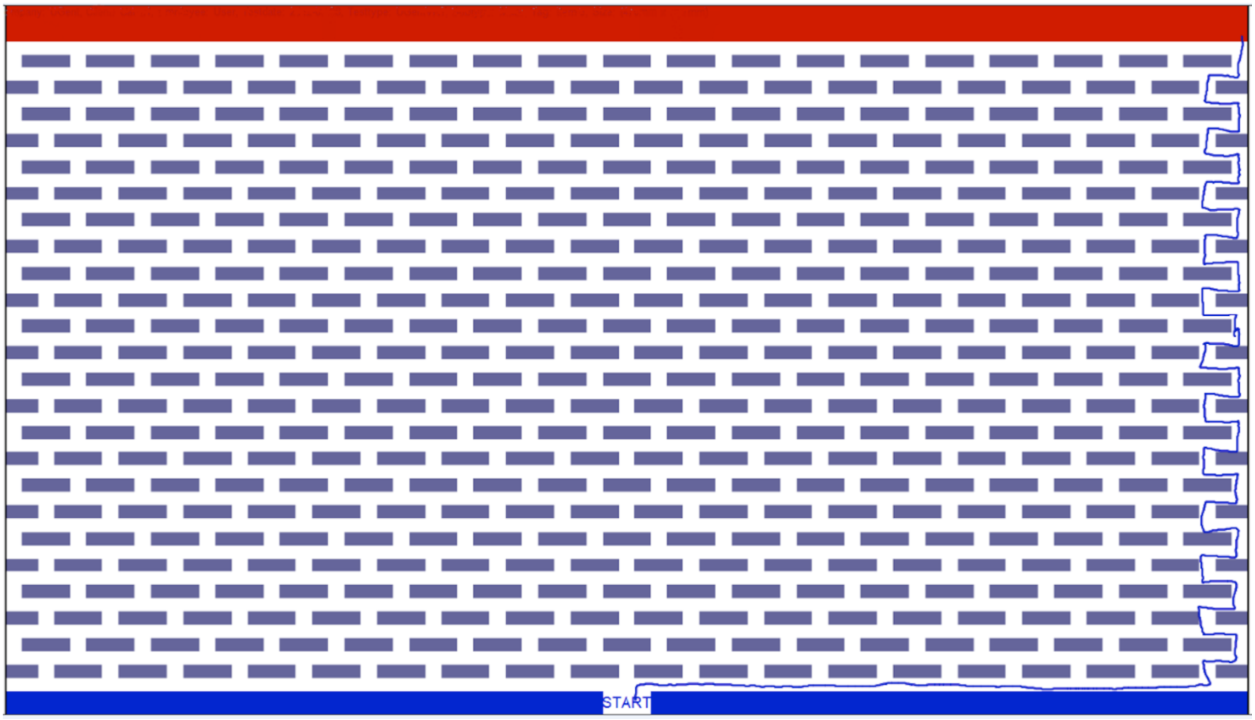

*Figure 1***.** Visuospatial Navigation Test (Vaes et al., 2015), including a typical performance pattern of a clear SN patient, despite the instruction to navigate upwards by the shortest route.

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[7] $CoN = \frac{100}{x_e}\left(\frac{1}{n}\sum_{i=1}^{n} x_i\right)$, where x_i is a pen coordinate at the route, along the X-axis with respect to 0, x_e the most extreme absolute value a pen coordinate can have along the X-axis, and n the total amount of pen coordinates at the route.

Research Questions and Statistical Evaluations

All statistical tests were implemented in IBM SPSS Statistics, version 22. The effects were considered to be significant when the p-values were smaller than .05. Starting with the quest for equal distributions of the various descriptive characteristics in the NP^+ and NP^- groups, two-sided Kolmogorov-Smirnov Tests were conducted on the multi-valued variables. With regard to the dichotomous variables, two-sided Fisher's Exact Tests were used.

Concerning our first research question, we investigated whether the peripersonal visuospatial behavior of the NP^+ and NP^- groups differed, by analyzing their results of the navigational terminus and the CoN index from the VNT. Because these variables are bounded and the test results of SN-patients typically are skewed, we conducted two-sided Mann-Whitney U Tests on the data. Complementary to this query, we looked into the visuospatial performance of one patient that rather unexpectedly demonstrated posterior pushing. These data will be described qualitatively instead of analyzed quantitatively, because our current dependent variables do not qualify for measuring changes related to the sagittal plane.

Second, we questioned whether the number of cross-over in long line bisection (SLBT) would be considerably distinct in the NP^+ and the NP^- groups. Additionally, it was inspected whether this would be more pronounced in the left, central or right SLBT section. Because it is not unusual that SN patients skip lines due to general or spatially graded attentional deficits, we needed to take the number of bisected lines into account. For this reason and given that the absence or occurrence of cross-over is a binary event, we modeled the observations with a generalized linear model with a binomial distribution and the logit as link function. To test hypotheses about the model, two-sided Wald Chi-Square Tests were used.

Results

Patient Flow and Descriptive Characteristics

After applying the exclusion criteria and after some patient losses due to a sudden discharge or medical deterioration, the case-control study could be implemented in 17 patients. It is supplemented with a qualitative single case study of a peculiar casus with PP. Apparently, this patient met the pushing criteria, but they were directed posteriorly instead of contralaterally. We decided not to exclude this case totally, but to record the nature of its navigational visuospatial functioning. The patient flow and counts are represented in Figure 2, as encouraged by the ‘Strengthening the Reporting of Observational Studies in Epidemiology’ (STROBE) Statement (von Elm et al., 2008). The lesions of the NP^+ and NP^- patients, as inferred from CT or MRI scans, are middle cerebral artery (MCA) infarctions (n = 5 in NP^+ and n = 6 in NP^-, including two in each group with hemorrhagic transformation) or MCA hemorrhages (n = 2 in NP^+), posterior cerebral artery infarction (n = 1 in each group) and thalamic hemorrhages (n = 1 in each group).

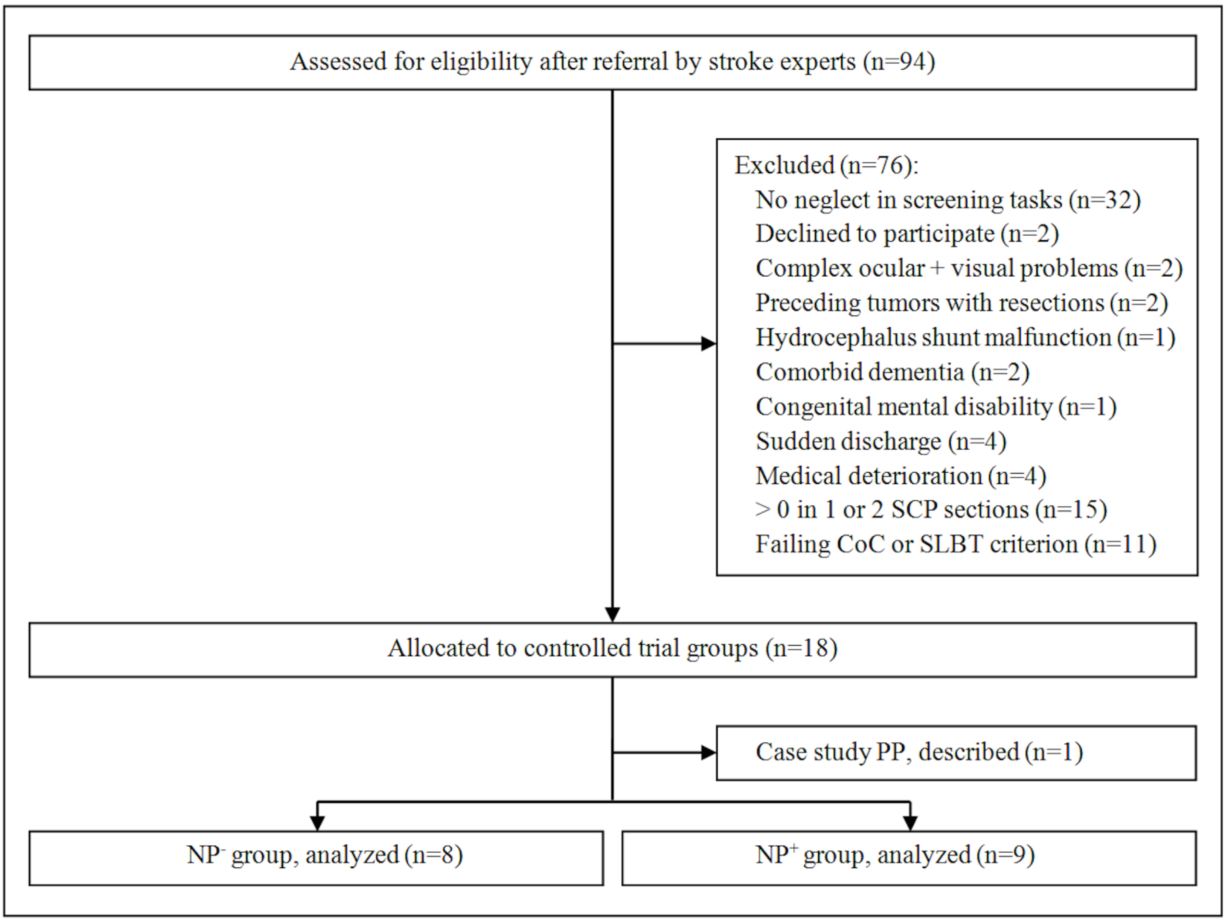

Figure 2. Diagram of the patient flow in the case-control study, as suggested by STROBE. The consecutive phases are the enrollment, group allocation and analyses. Information is provided on the counts and excluded patients.

Table 1 displays the results of the comparative intergroup analyses regarding the demographic and stroke related descriptives. The NP^+ and NP^- groups did not differ significantly regarding their age, amount of education, sex and handedness. Likewise, the days post-stroke, the presence of hemianopia, the degree of head and gaze deviation, the AS-, UAT- and FAC-scores were not significantly distinct in both groups. The amount of SN as measured by the

CoC index at the Bells Test and the mean percentage of SLBT deviation, did not differ significantly between the groups either.

Table 1

Descriptive Characteristics

Characteristics	NP^+ group[a] n = 9	NP^- group[a] n = 8	p-value[b]
Male/female	6/3	4/4	.637
Handedness R/L	9/0	6/2	.206
Hemianopia +/-	3/6	2/6	1.00
Age	68.00	66.50	.734
Educational years	12.00	11.50	1.00
Days post-stroke	32.00	22.50	.864
Head and gaze deviation	2.00	1.00	.167
AS fingers	1.00	.50	.993
AS upper limb (wrist + elbow)	2.00	1.00	.985
AS lower limb (knee + ankle)	2.00	.00	.189
UAT	.00	1.00	.213
FAC	.00	1.00	.591
CoC Bells Test	.87	.67	.780
SLBT mean deviation %	14.85	39.00	.146

NP^+: neglect with contraversive pushing; NP^-: neglect without contraversive pushing; AS: Ashworth Scale; UAT: Utrecht Arm/Hand Test; FAC: Functional Ambulation Categories; CoC: Center of Cancellation; SLBT: Schenkenberg Line Bisection Test.

[a]The values of multi-valued variables represent the medians.

[b]p-values of the dichotomous variables according to two-sided Fischer's Exact Tests, of the other variables according to two-sided Kolmogorov-Smirnov Tests.

Navigational Visuospatial Behavior

The medians of the navigational terminus and CoN index are presented in Figure 3, together with their lower and upper quartiles. The comparative intergroup analyses with respect to these variables revealed significant differences. The p-value concerning the navigational terminus was .011 and the one concerning the CoN index .027. Figure 4 illuminates this discrepancy in visuospatial behavior between both groups, by depicting their mean navigational routes.

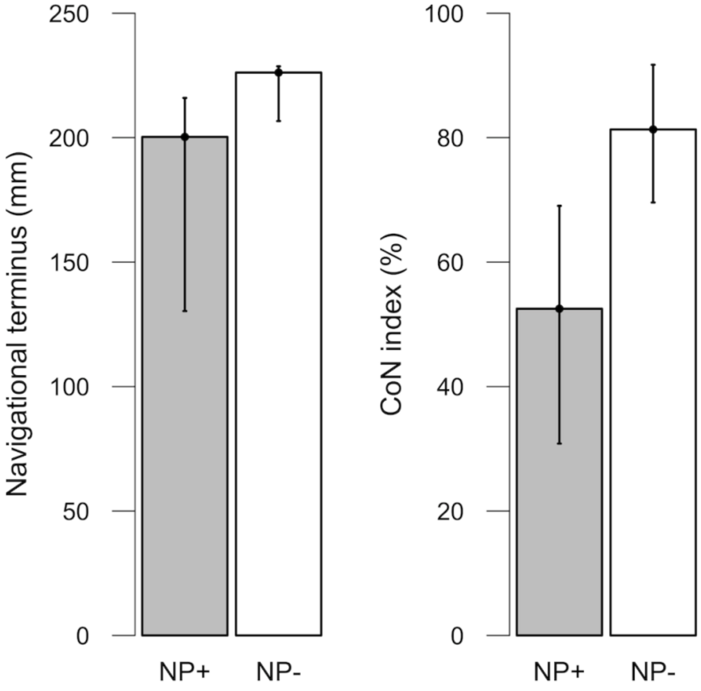

Figure 3. Results of the NP$^+$ and NP$^-$ groups at both variables of the digital VNT. Navigational terminus (mm) NP$^+$: median 200.30, lower-upper quartile [130.32–215.95]; Navigational terminus (mm) NP$^-$: median 226.15, lower-upper quartile [206.66–228.65]; CoN index (%) NP$^+$: median 52.50, lower-upper quartile [30.83–69.04]; CoN index (%) NP$^-$: median 81.32 %, lower-upper quartile [69.58–91.71].

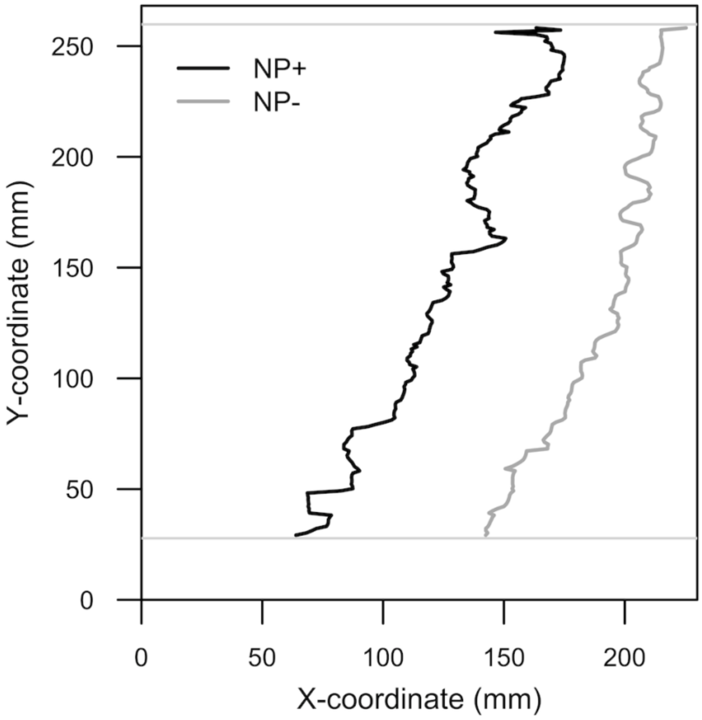

Figure 4. The mean navigational curves of the NP^+ (left) and NP^- (right) groups, visualizing the difference in visuospatial functioning. For representational facilitation, this graph can be superimposed on the right half of the VNT (Vaes et al., 2015). The lower and upper horizontal lines represent the onset (second white line at the bottom of the VNT) and the terminus (the red bar in the VNT) of the measurements. The curves could be reproduced thanks to the storage of the registered pen coordinates in the Metrisquare DiagnoseIS software[8] running the VNT.

The case demonstrating PP, was a 69-year-old right-handed woman, educationally trained until the age of 14. She suffered from a left hemiplegia and rightward head and gaze deviation after a spontaneous frontoparietal intracerebral hematoma. The post-stroke delay numbered 63 days. Her AS scores were 1 (fingers), 2 (upper limb) and 1 (lower limb). On both the UAT and FAC she scored zero. The CoC of her Bells Test was .91 and the mean SLBT deviation 36.4 %.

She could not sit or stand independently, due to a severe posterior tilt and backward pushing with the trunk and legs, especially when the physiotherapist tried to correct her posture forward. Interpreting the SCP posteriorly instead of contraversively, a maximum score was reached. At the moment of VNT administration, it first seemed that the patient had

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[8] www.diagnoseis.com, www.metrisquare.com

forgotten the instruction of navigating upward to the red bar via the shortest route, because she made some backward navigational movements. Therefore, the test leader (for whom the SCP-score was unknown), needed to encourage compliance by repeating the instruction. Then it appeared that moving forward took her some effort, as if the backward direction was a more attractive alternative. Figure 5 demonstrates her task performance.

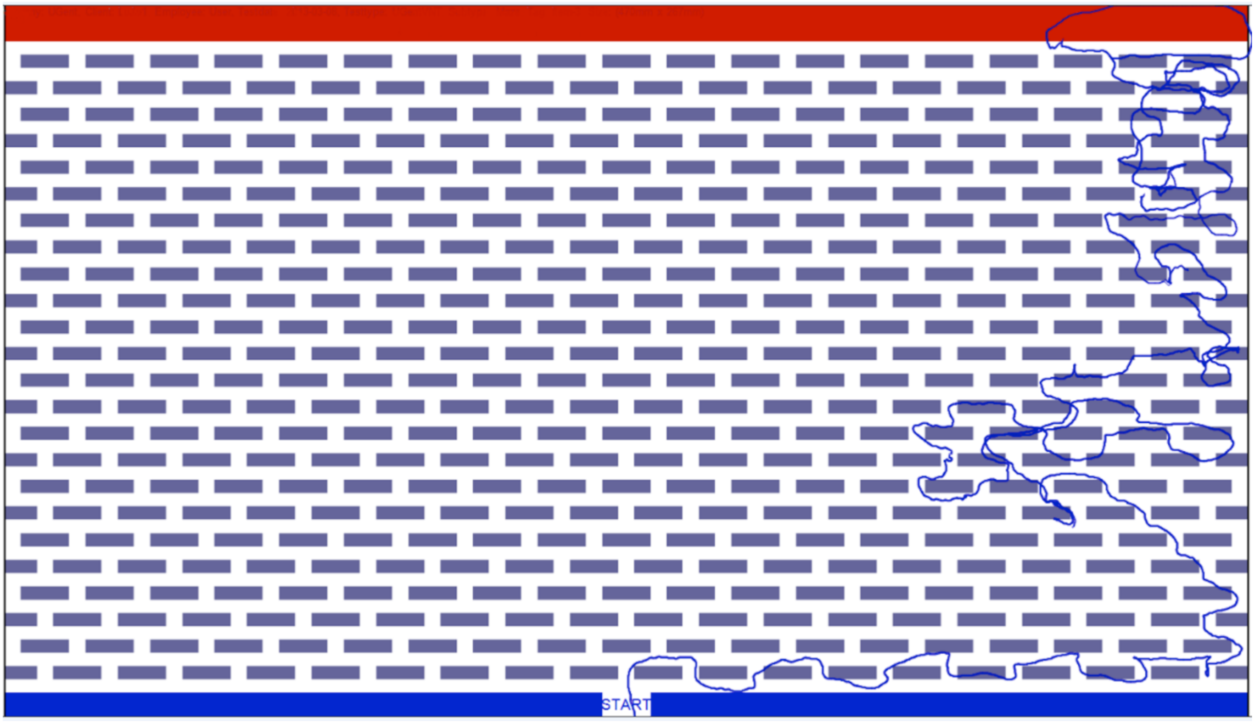

Figure 5. The VNT performed by the casus with posterior pushing.

Cross-over in Long Line Bisection

The output of the comparative intergroup analyses concerning the number of cross-over in long line bisection is displayed in Table 2. The differences between the NP^+ and NP^- groups are significant concerning the total, the middle and right SLBT section. The patient counts are also displayed, because of some excluded cases in the left and middle subsection, due to absences of trials when all lines of a subsection were neglected. The Wald Chi-Square statistic could not be computed for the left test section, because in none of both groups there was an event of cross-over at the left positioned lines.

Table 2

Comparisons of the number of cross-over in long line bisection between NP$^+$ and NP$^-$

SLBT section		EM Mean	95% Wald CI		Wald χ^2	p-value
			Lower	Upper		
Total	NP$^+$ (n = 9)	.25	.18	.34	17.128	< .001
	NP$^-$ (n = 8)	.05	.02	.12		
Left	NP$^+$ (n = 7)	.00	.00	.00	NA	NA
	NP$^-$ (n = 6)	.00	.00	.00		
Mid	NP$^+$ (n = 7)	.11	.04	.26	4.500	.034
	NP$^-$ (n = 7)	.00	.00	.00		
Right	NP$^+$ (n = 9)	.43	.31	.57	13.808	< .001
	NP$^-$ (n = 8)	.13	.06	.25		

NP$^+$: neglect with contraversive pushing; NP$^-$: neglect without contraversive pushing; SLBT: Schenkenberg Line Bisection Test; EM Mean: estimated marginal mean according to the fitted generalized linear model; CI: confidence interval; NA: non-available (no cross-over in both groups).

Discussion

The present case-control study reveals a clear difference in peripersonal visuospatial functioning between NP$^+$ and NP$^-$ patients. In SN patients with CP, the navigational terminus and Center of Navigation of the computerized VNT, were significantly shifted towards the contralesional side, compared to the more ipsilesional localization of both variables in SN patients without CP. Additionally, the NP$^+$ demonstrated distinctly more cross-over in long line bisection than the NP$^-$ group. Apparently, CP is associated with a contralesionally directed shift in SN behavior, in other words, with ‘contraversive neglect’. The contraversive similarity at the postural and visuospatial level hints at a coherence or interaction between the neural processing system for postural control, and the one for non-predominantly postural spatial behavior. Interestingly, this similarity seems not only to be oriented sideward, but also backward. Although this finding is preliminary because it is based on a single case description, our casus with PP also showed signs of a more posteriorly directed visuospatial performance at the VNT. The systems for space related body orientation adjustments in the coronal (CP), axial (SN) and sagittal (PP) plane, thus seem to analogously regulate trunk posture and peripersonal visuospatial behavior. It is proposed that human posture in these three planes is controlled by distinct neural networks (Karnath, 2007). The described analogue regulations may suggest that these networks are interconnected through a common neural interface. Furthermore, it is intriguing to draw the following parallel. The decrease in contralesional SN after displacing the trunk to the left by Karnath et al. (1993), could be considered as an experimentally manipulated "compensation" for SN. In parallel, CP can be viewed as a spontaneous (pathological) compensation mechanism attenuating manifest SN, effectuated by the nervous system to accommodate for the dysregulated central transformation of sensory coordinates.

Monaghan and Shillcock (1998) noticed that right displacements in long line bisection turn into left displacements for short lines at the group level, but that there is substantial variability at the individual level. They cite studies were some SN subjects demonstrate cross-over in lines as long as 10 cm, and 20 cm in one subject. Possibly, characteristics of CP were present in these patients. It is meaningful for subsequent investigations focusing on SN, to take postural variables into account, because their coherence with other spatial functions can distort or mitigate the nature of SN at the group level. Also in mathematical modeling of spatial neglect, posture should be included. Our SLBT results demonstrated a spatial gradient related to the quantity of cross-over in NP^+, with a maximum at the right side, less in the middle and no cross-over at the left side. McIntosh, Schindler, Birchall, and Milner (2005) presented a mathematical approach based on the weightings of line endpoints in determining the bisection response. Their endpoint weighting analysis can account for the effects of line length and spatial position on bisection error, including cross-over. The asymmetry in the endpoint weightings in patients with SN, called the 'endpoint weighting bias' (EWB), is measured by the difference between the right and left endpoint weightings. They hypothesized that the EWB could be considered as a measure of lateral attentional bias, in which the right endpoint outcompetes the left one for limited attentional resources. Following their quantitative model, the bisection error can be predicted by subtracting the peripersonal location of the line midpoint, from the sum of the weighted left and right endpoints plus a regression constant *k*. The authors acknowledge that a theoretical interpretation of *k* still needs to be proposed. We suggest that the constant *k* might be significantly impacted by interindividual differences in the orientation of the trunk midline or the egocentric reference frame. It would be an appealing endeavor to inspect whether these variables can predict the response position for a given stimulus to a higher degree. Consequently, in this way the model should also be able to distinguish between NP^+ and NP^- patients.

The observations in NP^+ patients, of a spatial gradient related to the quantity of cross-over and a contralesionally directed shift in the VNT, puts forward the inquiry about 'ipsilesional neglect'. It should be investigated whether contraversive neglect emanates from a corrective neural reorganization in the egocentric reference frame, leading to less contralesional neglect thanks to a constructive compensation mechanism. The alternative would be a pathological compensation mechanism for their posturospatial bias, averting patients away from their ipsilesional side. As such, the field of their attentional and motor behavior would be narrowed due to their contralesional, plus a quantum of ipsilesional neglect.

An important issue to deal with in future studies, is the underlying mechanism of the currently reported observations. Central neurologic causal mechanisms that are theorized for CP are a misperception of verticality at the body oriented gravitational (Karnath et al., 2000b), or transmodal level (Pérennou et al., 2008). The central neurologic origin of contraversive neglect in association with CP has to be ensured. If factors such as ipsilesional hypertonia or rigidity are more pronounced in patients with CP, it is not inconceivable that they experience more movement constraints than patients without CP. Even the more contralesionally tilted trunk orientation could lead to less ipsilesionally elongated arm movements in NP^+ compared to NP^- patients. However, these potential peripheral motor causes are less likely, because ipsilesionally extended arm movements are surely present in the NP^+ patients to enlarge their physical support base. Additionally, it will be extremely interesting to unravel with refined paradigms, whether contraversive neglect is primarily encountered at the motor or at the perceptual level, or at the attentional and representational level as well. An excellent example would be to investigate whether similar performance differences between NP^+ and NP^- emerge in a spatial task at least as sensitive as the VNT, but on the representational level and requiring verbal responses, in analogy with the Piazza Del Duomo experiment (Bisiach & Luzzatti, 1978) or the verbal Landmark Task (Bisiach, Ricci, Lualdi, & Colombo, 1998). Similar research questions can be formulated regarding the personal or extrapersonal dimensions (instead of the peripersonal one as discussed here) and regarding other sensory modalities than the visual one. Finally, robust brain imaging studies in NP^+ and NP^- patients will be of great relevance to unravel to quest for the underlying neural mechanism, preferably by voxel-based lesion-symptom mapping (Bates et al., 2003).

Unraveling these issues does not only advance the theoretical understanding of the coherence between different neural processing systems of space representation. It is of practical relevance as well, by complementing neurorehabilitation and refining neuropsychological diagnostics. Specific interventions for CP rehabilitation are proposed already, using visual feedback to correct body orientation (Broetz, Johannsen, & Karnath, 2004; Broetz & Karnath, 2005), taking into account the spatial body misperception and fear of falling (Shepherd & Carr, 2005), learning compensation strategies through vocal and visual feedback (Paci & Nannetti, 2004) and forced control of upright position in machine-supported gait training (Krewer et al., 2013). Gaining more insight into the contraversive shift in spatial behavior of NP^+ patients can contribute to targeted interventions, by integrating the findings into a holistic rehabilitation approach.

The present observations of peripersonal visuospatial contraversive neglect in patients with CP, can encourage larger controlled trials to investigate this topic in greater depth. Additionally, they foster nuanced diagnostics of SN in CP and advocate targeted posturo- and visuospatial rehabilitation.

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References

Ashworth, B. (1964). Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner, 192*, 540-542.

Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J. M., . . . Rousseaux, M. (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *Journal of Neurology Neurosurgery and Psychiatry, 73*(2), 160-166. doi: DOI 10.1136/jnnp.73.2.160

Baccini, M., Paci, M., Nannetti, L., Biricolti, C., & Rinaldi, L. A. (2008). Scale for Contraversive Pushing: Cutoff scores for diagnosing "Pusher Behavior" and construct validity. *Physical Therapy, 88*(8), 947-955. doi: 10.2522/Ptj.20070179

Bateman, A., & Riddoch, M. J. (1996). Neuropsychological perspectives on ″pusher syndrome″. *European Journal of Phyical Medicine and Rehabilitation, 6*(3), 93-96.

Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nature Neuroscience, 6*, 448–450. doi: 10.1038/nn1050

Binder, J., Marshall, R., Lazar, R., Benjamin, J., & Mohr, J. P. (1992). Distinct syndromes of hemineglect. *Archives of Neurology, 49*(11), 1187-1194.

Bisiach, E., Capitani, E., & Porta, E. (1985). Two basic properties of space representation in the brain: evidence from unilateral neglect. *Journal of Neurology Neurosurgery and Psychiatry, 48*(2), 141-144. doi: 10.1136/jnnp.48.2.141

Bisiach, E., & Luzzatti, C. (1978). Unilateral neglect of representational space. *Cortex, 14*(1), 129-133. doi: 10.1016/S0010-9452(78)80016-1

Bisiach, E., Ricci, R., Lualdi, M., & Colombo, M. R. (1998). Perceptual en response bias in unilateral neglect: Two modified versions of the Milner Landmark task. *Brain and Cognition, 37*(3), 369-386. doi: 10.1006/brcg.1998.1003

Broetz, D., Johannsen, L., & Karnath, H. O. (2004). Time course of 'pusher syndrome' under visual feedback treatment. *Physiotherapy Research International, 9*(3), 138-343.

Broetz, D., & Karnath, H. O. (2005). New aspects for the physiotherapy of pushing behaviour. *Neurorehabilitation, 20*(2), 133-138.

Brunnstrom, S. (1966). Motor testing procedures in hemiplegia: based on sequential recovery stages. *Physical Therapy, 46*(4), 357-375.

Cardoen, S., & Santens, P. (2010). Posterior pusher syndrome: A report of two cases. *Clinical Neurology and Neurosurgery, 112*(4), 347-349. doi: 10.1016/j.clineuro.2009.12.007

Chatterjee, A. (1995). Cross-over, Completion and Confabulation in Unilateral Spatial Neglect. *Brain, 118*, 455-465. doi: 10.1093/brain/118.2.455

Davies, P. M. (1985). *Steps to follow. A guide to the treatment of adult hemiplegia.* New York: Springer.

Davies, P. M. (2000). *Steps to follow. A guide to the treatment of adult hemiplegia.* New York: Springer.

Doricchi, F., Guariglia, P., Figliozzi, F., Silvetti, M., Bruno, G., & Gasparini, M. (2005). Causes of cross-over in unilateral neglect: between-group comparisons, within-patient dissociations and eye movements. *Brain, 128*, 1386-1406. doi: 10.1093/Brain/Awh461

Ferber, S., & Karnath, H. O. (2001). How to assess spatial neglect - Line bisection or cancellation tasks? *Journal of Clinical and Experimental Neuropsychology, 23*(5), 599-607. doi: 10.1076/jcen.23.5.599.1243

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology, 11*(2), 49-54.

Halligan, P., Wilson, B., & Cockburn, J. (1990). A short screening test for visual neglect in stroke patients. *International Disability Studies, 12*(3), 95-99.

Halligan, P. W., & Marshall, J. C. (1988). How long is a piece of string? A study of line bisection in a case of visual neglect. *Cortex, 24*(2), 321-328.

Heilman, K. M., & Valenstein, E. (1979). Mechanisms underlying hemispatial neglect. *Annals of Neurology, 5*(2), 166-170. doi: 10.1002/ana.410050210

Holden, M. K., Gill, K. M., Magliozzi, M. R., Nathan, J., & Piehlbaker, L. (1984). Clinical gait assessment in the neurologically impaired - Reliability and meaningfulness. *Physical Therapy, 64*(1), 35-40.

Honoré, J., Saj, A., Bernati, T., & Rousseaux, M. (2009). The pusher syndrome reverses the orienting bias caused by spatial neglect. *Neuropsychologia, 47*(3), 634-638. doi: 10.1016/j.neuropsychologia.2008.11.008

Ishiai, S., Koyama, Y., Nakano, N., Seki, K., Nishida, Y., & Hayashi, K. (2004). Image of a line is not shrunk but neglected - Absence of crossover in unilateral spatial neglect. *Neuropsychologia, 42*(2), 251-256. doi: 10.1016/S0028-3932(03)00153-2

Johannsen, L., Broetz, D., Naegele, T., & Karnath, H. O. (2006). "Pusher syndrome" following cortical lesions that spare the thalamus. *Journal of Neurology, 253*(4), 455-463. doi: 10.1007/s00415-005-0025-7

Karnath, H. O. (1994). Disturbed coordinate transformation in the neural representation of space as the crucial mechanism leading to neglect. *Neuropsychological Rehabilitation, 4*(2), 147-150. doi: 10.1080/09602019408402273

Karnath, H. O. (2007). Pusher Syndrome - a frequent but little-known disturbance of body orientation perception. *Journal of Neurology, 254*(4), 415-424. doi: 10.1007/s00415-006-0341-6

Karnath, H. O., & Brotz, D. (2007). Instructions for the Clinical Scale for Contraversive Pushing (SCP). *Neurorehabilitation and Neural Repair, 21*(4), 370-371. doi: 10.1177/1545968307300702

Karnath, H. O., Brotz, D., & Gotz, A. (2001). Clinical symptoms, origin, and therapy of the ,,pusher syndrome". *Nervenarzt, 72*(2), 86-92. doi: 10.1007/s001150050719

Karnath, H. O., Christ, K., & Hartje, W. (1993). Decrease of contralateral neglect by neck muscle vibration and spatial orientation of trunk midline. *Brain, 116,* 383-396. doi: 10.1093/brain/116.2.383

Karnath, H. O., Ferber, S., & Dichgans, J. (2000a). The neural representation of postural control in humans. *Proceedings of the National Academy of Sciences of the United States of America, 97*(25), 13931-13936. doi: 10.1073/pnas.240279997

Karnath, H. O., Ferber, S., & Dichgans, J. (2000b). The origin of contraversive pushing: evidence for a second graviceptive system in humans. *Neurology, 55*(9), 1298-1304.

Karnath, H. O., Johannsen, L., Broetz, D., & Kuker, W. (2005). Posterior thalamic hemorrhage induces "pusher syndrome". *Neurology, 64*(6), 1014-1019. doi: 10.1212/01.WNL.0000154527.72841.4A

Karnath, H. O., Schenkel, P., & Fischer, B. (1991). Trunk orientation as the determining factor of the contralateral deficit in the neglect syndrome and as the physical anchor of the internal representation of body orientation in space. *Brain, 114,* 1997-2014. doi: 10.1093/brain/114.4.1997

Karnath, H. O., Suchan, J., & Johannsen, L. (2008). Pusher syndrome after ACA territory infarction. *European Journal of Neurology, 15*(8), e84-85. doi: 10.1111/j.1468-1331.2008.02187.x

Kerkhoff, G., & Schenk, T. (2011). Line bisection in homonymous visual field defects - Recent findings and future directions. *Cortex, 47*(1), 53-58. doi: 10.1016/j.cortex.2010.06.014

Kerr, N. M., Chew, S. S. L., Eady, E. K., Gamble, G. D., & Danesh-Meyer, H. V. (2010). Diagnostic accuracy of confrontation visual field tests. *Neurology, 74*(15), 1184-1190. doi: 10.1212/WNL.0b013e3181d90017

Krewer, C., Riess, K., Bergmann, J., Muller, F., Jahn, K., & Koenig, E. (2013). Immediate effectiveness of single-session therapeutic interventions in pusher behaviour. *Gait & Posture, 37*(2), 246-250. doi: 10.1016/j.gaitpost.2012.07.014

Kruitwagen-van Reenen, E. T., Post, M. W. M., Mulder-Bouwens, K., & Visser-Meily, J. M. A. (2009). A simple bedside test for upper extremity impairment after stroke: Validation of the Utrecht Arm/Hand Test. *Disability and Rehabilitation, 31*(16), 1338-1343. doi: 10.1080/09638280902846855

Kuhn, C., Bublak, P., Jobst, U., Rosenthal, A., Reinhart, S., & Kerkhoff, G. (2012a). Contralesional spatial bias in chronic hemianopia: the role of (ec)centric fixation, spatial cueing and visual search. *Neuroscience, 210,* 118-127. doi: 10.1016/J.Neuroscience.2012.03.020

Kuhn, C., Rosenthal, A., Bublak, P., Grotemeyer, K.H., Reinhart, S., & Kerkhoff, G. (2012b). Does spatial cueing affect line bisection in chronic hemianopia? *Neuropsychologia, 50*(7), 1656-1662. doi: 10.1016/J.Neuropsychologia.2012.03.021

Lafosse, C., Kerckhofs, E., Troch, M., Santens, P., & Vandenbussche, E. (2004). Graviceptive misperception of the postural vertical after right hemisphere damage. *Neuroreport, 15*(5), 887-891.

Lafosse, C., Kerckhofs, E., Troch, M., Vereeck, L., Van Hoydonck, G., Moeremans, M., . . . Vandenbussche, E. (2005). Contraversive pushing and inattention of the contralesional hemispace. *Journal of Clinical and Experimental Neuropsychology, 27*(4), 460-484. doi: 10.1080/13803390490520463

Lenworth, N. J., & Frank, G. B. (1991). The accuracy of confrontation visual field test in comparison with automated perimetry. *Journal of the National Medical Association, 83*(10), 895-898.

McIntosh, R. D., Schindler, I., Birchall, D., & Milner, A. D. (2005). Weights and measures: A new look at bisection behaviour in neglect. *Cognitive Brain Research, 25*(3), 833-850. doi: 10.1016/j.cogbrainres.2005.09.008

Mikolajewska, E. (2012). Posterior pusher syndrome - case report. *Central European Journal of Medicine, 7*(3), 354-357. doi: 10.2478/s11536-011-0145-7

Monaghan, P., & Shillcock, R. (1998). The cross-over effect in unilateral neglect. Modelling detailed data in the line-bisection task. *Brain, 121*(5), 907-921.

Mourey, F., Manckoundia, P., Martin-Arveux, I., Tavernier-Vidal, B., & Pfitzenmeyer, P. (2004). Psychomotor disadaptation syndrome - A new clinical entity in geriatric patients. *Geriatrics, 59*(5), 20-24.

Nichelli, P., Rinaldi, M., & Cubelli, R. (1989). Selective spatial attention and length representation in normal subjects and in patients with unilateral spatial neglect. *Brain and Cognition, 9*(1), 57-70. doi: 10.1016/0278-2626(89)90044-4

Paci, M., & Nannetti, L. (2004). Physiotherapy for pusher behaviour in a patient with post-stroke hemiplegia. *Journal of Rehabilitation Medicine, 36*(4), 183-185. doi: 10.1080/16501970410029762

Paci, M., & Nannetti, L. (2005). The pusher syndrome in a patient with cerebellar infarction. *Physiotherapy Research International, 10*(3), 176-177.

Pérennou, D. A., Mazibrada, G., Chauvineau, V., Greenwood, R., Rothwell, J., Gresty, M. A., & Bronstein, A. M. (2008). Lateropulsion, pushing and verticality perception in hemisphere stroke: a causal relationship? *Brain, 131*(9), 2401-2413. doi: 10.1093/brain/awn170

Pfitzenmeyer, P., Mourey, F., Tavernier, B., & Camus, A. (1999). Psychomotor desadaptation syndrome. *Archives of Gerontology and Geriatrics, 28*(3), 217-225. doi: 10.1016/S0167-4943(99)00005-9

Richard, C., Honoré, J., Bernati, T., & Rousseaux, M. (2004). Straight-ahead pointing correlates with long-line bisection in neglect patients. *Cortex, 40*(1), 75-83. doi: 10.1016/S0010-9452(08)70921-3

Rode, G., Mauguière, F., Fischer, C., & Boisson, D. (1995). Lésions hémisphériques droites et négligence unilatérale; La part de la déafférentation. *Annales de Réadaptation et de Médecine Physique, 38*, 324.

Rorden, C., & Karnath, H. O. (2010). A simple measure of neglect severity. *Neuropsychologia, 48*(9), 2758-2763. doi: 10.1016/j.neuropsychologia.2010.04.018

Rousseaux, M., Beis, J. M., Pradat-Diehl, P., Martin, Y., Bartolomeo, P., Bernati, T., . . . Azouvi, P. (2001). Présentation d'une batterie de dépistage de la négligence spatiale. Normes et effets de l'âge, du niveau d'éducation, du sexe, de la main et de la latéralité. *Revue Neurologique, 157*, 1385-1400.

Saj, A., Honoré, J., Coello, Y., & Rousseaux, M. (2005). The visual vertical in the pusher syndrome - Influence of hemispace and body position. *Journal of Neurology, 252*(8), 885-891. doi: 10.1007/s00415-005-0716-0

Santos-Pontelli, T. E. G., Pontes-Neto, O. M., Colafemina, J. F., de Araujo, D. B., Santos, A., & Leite, J. P. (2004). Contraversive pushing in non-stroke patients. *Journal of Neurology, 251*(11), 1324-1328. doi: 10.1007/s00415-004-0532-y

Santos-Pontelli, T. E. G., Pontes-Neto, O. M., & Leite, J. P. (2011). 'Posterior pusher syndrome' or 'psychomotor disadaptation syndrome'? *Clinical Neurology and Neurosurgery, 113*(6), 521-521. doi: 10.1016/j.clineuro.2011.01.012

Schenkenberg, T., Bradford, D. C., & Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30*(5), 509-517.

Shepherd, R. B., & Carr, J. (2005). New aspects for the physiotherapy of pushing behaviour, D. Broetz and H.-O. Karnath, Neurorehabilitation 20 (2005),133-138. *Neurorehabilitation, 20*(4), 343-345.

Ticini, L. F., Klose, U., Nagele, T., & Karnath, H. O. (2009). Perfusion imaging in Pusher syndrome to investigate the neural substrates involved in controlling upright body position. *Plos One, 4*(5), e5737. doi: 10.1371/journal.pone.0005737

Twitchell, T. E. (1951). The restoration of motor function following hemiplegia in man. *Brain, 74*(4), 443-480.

Utz, K. S., Keller, I., Artinger, F., Stumpf, O., Funk, J., & Kerkhoff, G. (2011). Multimodal and multispatial deficits of verticality perception in hemispatial neglect. *Neuroscience, 188*, 68-79. doi: 10.1016/J.Neuroscience.2011.04.068

Vaes, N., Lafosse, C., Nys, G., Schevernels, H., Dereymaeker, L., Oostra, K., Hemelsoet, D., & Vingerhoets, G. (2015). Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes. *Behavior Research Methods, 47,* 27-44. doi: 10.1037/neu0000205

Ventre, J., Flandrin, J. M., & Jeannerod, M. (1984). In search for the egocentric reference. A neurophysiological hypothesis. *Neuropsychologia, 22*(6), 797-806.

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gotzsche, P. C., Vandenbroucke, J. P., & Initiative, S. (2008). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Journal of Clinical Epidemiology, 61*(4), 344-349. doi: 10.1016/j.jclinepi.2007.11.008

Walker, R., Findlay, J. M., Young, A. W., & Welch, J. (1991). Disentangling neglect and hemianopia. *Neuropsychologia, 29*(10), 1019-1027. doi: 10.1016/0028-3932(91)90065-G

Chapter 5: Discussion

5.1 Conclusions

In Chapter 2, a digital method was presented tailored to SN patients and designed for studying peripersonal visuospatial processes. By means of a case study, the digital neglect measurements were illustrated. The VNTB consists of nine visuospatial tests: two cancellation tests, two bisection tests, a drawing test, a search time test, an extinction test, a memory test, and a peripersonal navigation test. To add a familiar part to the battery, two well-known tests are included, namely the Schenkenberg Line Bisection Test (Schenkenberg, Bradford, & Ajax, 1980) and the Bells Test (Gauthier, Dehaut, & Joanette, 1989, cited in Lezak, Howieson, & Loring, 2004, and Strauss, Sherman, & Spreen, 2006). The Visuospatial Search and Memory Tests, have a parallel version, to minimize their test-retest sensitivity. As discussed in the introduction, neglect patients' performances on neglect tasks can be very diverse, and even dissociated from each other. This finding argues in favor of a battery that gauges various neglect modalities via different tests. However, the battery allows for flexible employment by selecting tests according to one's needs. The discriminative value of the tests was demonstrated by means of comparative analyses. The test variables that were expected to differ between SN and healthy participants, showed lateralized performance differences between the two groups. An advantage of the reported method is online performance monitoring, thanks to the dual-screen technology. At the investigator's own computer screen, the interim results of a participant working at the pen display can be observed and designated. Related to the VNTB data collection, the experimental benefits of exact and less time-consuming measurements because of automated scoring and calculation are self-explanatory. Additionally, important measures are directly available by combining the Metrisquare DiagnoseIS software with a pen display, such as the number of perseverations, the Center of Navigation, Center of Drawing, and Center of Cancellation indices, as described in the method article. These measures are not obtainable from paper-and-pencil tests. Reliable and sensitive gauging of extinction and lateralized search times is of clinical relevance as well, for instance with respect to advice on driving capabilities.

The VNTB was used for the outcome assessments of the RCT described in Chapter 3. Despite the heterogeneous post-stroke delays in our SN patients, a mild PA regime ameliorated visuospatial processes in peripersonal navigation, extinction, centered bisection, drawing and memory (with caution), assessed after a short time interval. The effects on drawing and bisection have been documented previously, but PA impact on peripersonal navigation, anterograde memory and visual extinction is reported here for the first time. The treatment schedule was insufficient to maintain the PA benefit for centered bisection and extinction in the long term. Despite the mild regime however, a trend towards better performance in navigation, drawing and memory remained visible after 3 months. Cancellation and lateralized visual search times were not influenced by PA. A first potential explanation is that the effect assessments followed immediately after PA in multiple studies, as opposed to our post-tests at mid- and long-term assessment intervals. A second potential reason is the short-term repetitive PA of 7 sessions combined with the mild treatment regime. A recent review of the PA literature concludes that 10 to 20 sessions, at a frequency of 2 per week to 2 per day, appears to produce positive results (Jacquin-Courtois et al., 2013). To enhance the probability of extending and consolidating PA effects, we encourage clinicians and researchers to offer PA daily and over an extended time period. However, when patients' stay is short, they can still benefit from short-term repetitive PA. In addition, when the implementation of treatment sessions is practically constrained, a mild regime with a maximum of 2 days between sessions can still be beneficial.

The results concerning memory and visual extinction are particularly interesting. Unlike the PA training, their assessments did not require arm or ocular movements. The expansion of PA effects to processes that differ from the modalities exposed during PA is important because it demonstrates that PA may impact higher levels of cognitive functioning (Jacquin-Courtois et al., 2013). Additionally, these results provide support for the view that PA affects not only intentional-motor cerebral functions, but also attentional and non-motor memory functions.

The exploratory analyses of the acute, subacute and chronic subgroups in the EG and CG did not yield different results. However, care should be taken when interpreting these results because of the small subgroup sizes. Currently, the results suggest not to withhold PA from SN patients based on a certain time window post-stroke.

The Schenkenberg Line Bisection Test (Schenkenberg, Bradford, & Ajax, 1980) and the Visuospatial Navigation Test (VNT) from the digital VNTB (Vaes et al., 2015), were also used for the theoretical article of Chapter 4. The corresponding case-control study revealed a clear difference in peripersonal visuospatial functioning between SN patients with and without CP. SN patients with CP demonstrated distinctly more cross-over in line bisection, and a significant contralesionally directed shift in navigational behavior, compared to SN patients without CP. We termed this shift in SN behavior ‘contraversive neglect’, by analogy with the same shift in body posture in CP. See Figure 1 for a visualization of this phenomenon.

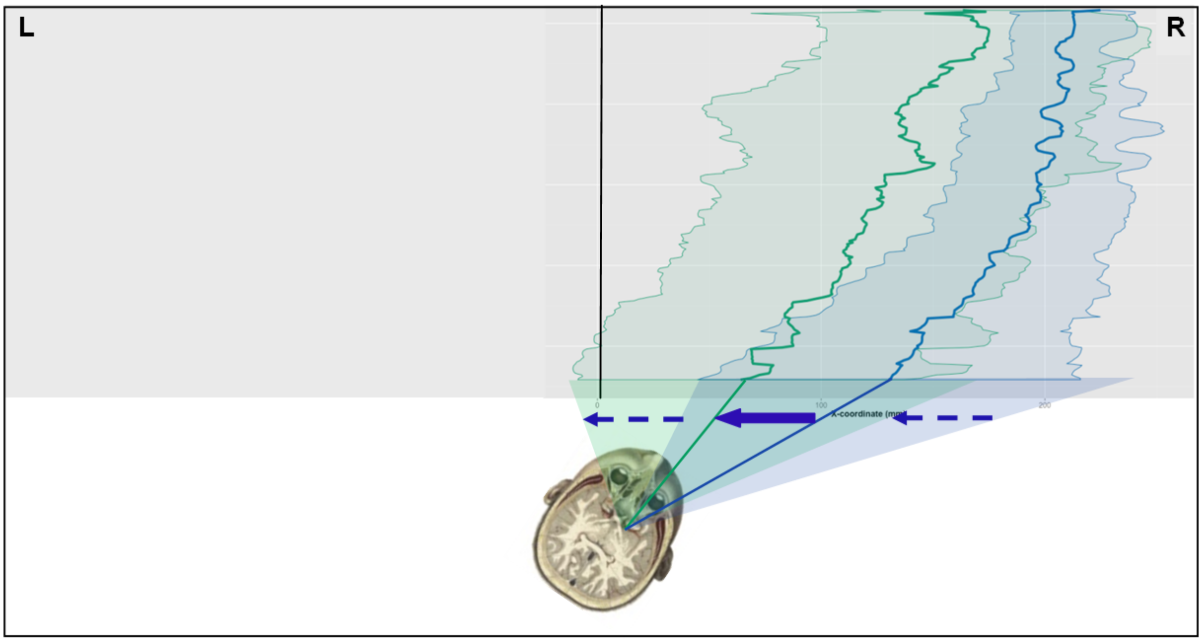

Figure 1. Visualization of the difference in neuropsychological functioning between SN patients with CP (green region) and without CP (blue region). The behavioral region of SN patients with CP is shifted from right to left (*contraversively*). The reproduction of the regions is based on the means and standard deviations of the VNT pen coordinates registered in Metrisquare DiagnoseIS.

The contraversive similarity at the postural and visuospatial level hints at a coherence or interaction between the neural processing system for postural control, and the one for non-predominantly postural spatial behavior. Interestingly, this similarity seems not only to be oriented sideward, but also backward. Although this finding is preliminary because it is based on a single case description, our case with PP also showed signs of a more posteriorly directed visuospatial performance at the VNT. The systems for space-related body orientation adjustments in the coronal (CP), axial (SN) and sagittal (PP) plane seem to analogously regulate trunk posture and peripersonal visuospatial behavior. It is proposed that human posture in these three planes is controlled by distinct neural networks (Karnath, 2007). The described analogue regulations may suggest that these networks are interconnected through a common neural interface. Posture and peripersonal visuospatial behavior may share a regulating neural representation related to these three planes. Rousseaux, Honoré, Vuilleumier and Saj (2013) propose that the anatomy of postural disorders (imbalance) and spatial representation biases in right hemisphere patients overlaps to some extent (partly regarding subjective straight ahead, especially regarding subjective vertical) in the temporoparietal, superior temporal and posterior insular regions of the cortex (Figure 2).

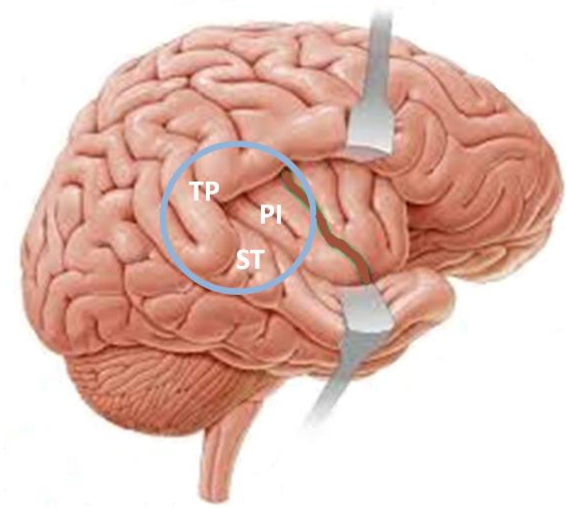

Figure 2. The anatomy of postural disorders and spatial representation biases overlap to some extent in the temporoparietal (TP), superior temporal (ST) and posterior insular (PI) regions of the cortex.

5.2 Study Limitations and targets for future research

Besides the described benefits of the digital measurement method (Chapter 2), the peripersonal dimension of the pen display is an evident limitation. The VNTB measures multiple SN processes, but all restricted to the peripersonal level. Future investigations can extend the measures to the extrapersonal level, for instance by using the MDIS software with a distant smart screen instead of a pen tablet, or by 3D technology. For measuring processes at the personal level, the test battery can be extended accordingly, for instance with scales of tactile extinction, spontaneous gaze deviation and other lateralized kinetic disturbances. Expanding the research on the psychometric properties of the VNTB (such as validity, sensitivity and reliability) is useful as well. In this respect, we are currently collecting data for the comparison of results between stroke patients with SN on the one hand and without SN on the other, and between repeated subtest administrations in the same group of SN patients.

An obvious limitation of the treatment article (Chapter 3) is the lack of functional or daily life measures. The VNTB measurements are situated at the impairment level. Future research should include disability scales that gauge activities of daily living (ADL). Valid and sensitive measures should be used. Hence patients might for instance still need help for housekeeping (a typical item of an instrumental ADL scale) because of their hemiplegia, while they are able to read again and avoid obstacles better, items that are typically not included in ADL scales (Kerkhoff and Schenk, 2012). The Catherine Bergego Scale (CBS) is recommended in this respect, a sensitive, reliable and valid scale for behavioral SN assessment (Azouvi et al., 2003; Bergego et al., 1995). The CBS consists of 10 items related to for instance difficulties in adjusting the left sleeve and in paying attention to or colliding with people on the left side. Furthermore, we think that a useful endeavor would be to develop another neglect-specific scale that can be administered at hospital admission and after a long-term interval, with appropriate items that measure quality of life and leisure activities such as ability to read, to use a phone, tablet or PC, play a card or parlor game, supervised preparation of breakfast or lunch. Appropriate and well-validated tools for measuring quality of life in the general stroke population exist already, for example the Stroke-Specific Quality of Life Scale (SS-QOL Scale) of Williams, Weinberger, Harris, Clark and Biller (1999). The aphasia-adapted version of this scale (Hilari & Byng, 2001) is translated in Dutch by Nys and van Zandvoort (2002, unpublished). In addition, the upcoming field of virtual reality is very promising for the development of appropriate ecologically valid measures of daily life in SN patients. Finally, the relationship between SN measures at the impairment level and functional disabilities is not always obvious, although correlations between both have been reported (Azouvi et al., 2003; Chen, Hreha, Fortis, Goedert, & Barrett, 2012; Cherney, Halper, Kwasnica, Harvey, & Zhang, 2001). Based on correlational analyses between VNTB variables and the FIM, the instrumental ADL and SS-QOL scales, we can confirm this relationship (results unpublished).

Another research impetus with clinical importance emanated from Chapter 3. Unraveling the quest for the most optimal post-stroke phase for PA remains important. This is especially true for RCT’s with large groups. Ideally, more answers will be formulated about SN patients’ best post-stroke delay for optimal enhancement of cerebral plasticity by PA, and about the best PA regime depending on their post-stroke phase.

The distinct pattern of cognitive functioning in SN patients with versus without CP, as discussed in the case control study of the theoretical article (Chapter 4), is not described elsewhere yet. Other authors are invited to investigate this phenomenon, preferably with large patient numbers, to verify or replicate the data. Furthermore, it should be investigated whether contraversive neglect emanates from a corrective neural reorganization in the egocentric reference frame, leading to less contralesional neglect thanks to a constructive compensation mechanism. The alternative would be a pathological compensation mechanism for the posturospatial bias, averting patients away from their ipsilesional side. As such, the field of their attentional and motor behavior would be narrowed due to their contralesional, plus an amount of ipsilesional neglect. Specific interventions for CP rehabilitation have been proposed. Gaining more insight into the contraversive shift in spatial behavior of SN patients with CP fosters nuanced diagnostics and contributes to targeted interventions, by integrating the findings into a holistic rehabilitation approach.

5.3 Outro: embodied cognition in peripersonal space

The chapters of this thesis fit into the broader context of embodied cognition in space, a topic that is still much debated on in the scientific literature. Reed, Garza and Roberts (2007) state that any theory of spatial attention is incomplete if it does not emphasize the importance of sensorimotor experience and the interaction of the body with the environment. They discuss studies which focus on the trunk and the hands, demonstrating that the body and the orientation of its parts can attentionally prioritize certain regions of space for better perceptual processing, targeting current or upcoming actions from a functional point of view. The trunk, the structural hub to which the head, arms and legs are attached, guides the direction of locomotion through the environment. Therefore it is important for action. Besides, the trunk influences the parts of space in which the hands can interact. Reed et al. (2007) summarize studies suggesting that spatial attention incorporates multimodal inputs and the functional properties of the hands to change the distribution of attention across peripersonal visual space. Our VNTB measures neglect processes in peripersonal visual space (see Chapter 2). The test battery revealed an amelioration in certain spatial cognitive processes, after sensorimotor reintegration of visual and kinesthetic information of the arm/hand by PA (see Chapter 3). Hence, PA is an indirect way to affect our sense of where we are in relation to the world around us, by improving processes involved in brain plasticity related to multisensory-motor integration and space representation (Farnè et al., 2002; Kerkhoff & Schenk, 2012). Furthermore, a difference in peripersonal spatial functioning was found in two patient groups with different patterns of body/trunk posture (see Chapter 4). Noel et al. (2015) and Serino et al. (2015) suggest that peri-chest and -trunk space are vitally important for unified representation of the PPS around the whole body within the environment. They also conceive the role of PPS, represented by multisensory neurons from a network of parietal and premotor areas, as a multisensory-motor interface between the body and the environment. In this multimodal neural network, tactile information of the body is integrated with visual and auditory information of external stimuli in space, to support appropriate motor behaviors related to approach or defense. PPS representation modulates the motor system and conversely, actions determine what is coded as far and near space. This representation appears to be extremely plastic and can be dynamically shaped as a function of the interaction between the individual and the environment (Làdavas & Serino, 2008; Noel et al., 2015; Serino, in press). Patients with cerebral hemisphere damage can have a complex distortion of their body representations in space, as we have discussed in right hemispheric SN patients with and without CP. This distortion is not only reflected in their postural control and movements in PPS, but also in activities of daily living (Rousseaux, Honoré, & Saj, 2014). It is of vital importance to further the understanding of the interplay between their spatial representational distortions and their cognitive and postural environmental behavior. As such, rehabilitation techniques can be optimized based on the latest knowledge, to be able to benefit maximally of the plastic potential of the brain and the ability to reshape patients' multisensory-motor PPS representation. From a theoretical and clinical point of view, we adhere to the broader premise of a dynamic and intense cohesion instead of a dichotomy between sensory and motor spatial representations, between perception and action in space.

References

Azouvi, P., Olivier, S., de Montety, G., Samuel, C., Louis-Dreyfus, A., & Tesio, L. (2003). Behavioral assessment of unilateral neglect: Study of the psychometric properties of the Catherine Bergego Scale. *Archives of Physical Medicine and Rehabilitation, 84*(1), 51–57.

Azouvi, P., Samuel, C., Louis-Dreyfus, A., Bernati, T., Bartolomeo, P., Beis, J.M., ..., Rousseaux, M. (2002). Sensitivity of clinical and behavioural tests of spatial neglect after right hemisphere stroke. *J Neurol Neurosurg Psychiatry, 73,* 160–166.

Bergego, C., Azouvi, P., Samuel, C., Marchal, F., Louis-Dreyfus, A., Jokic, C., et al. (1995). Validation d'une echelle d'evaluation fonctionnelle de l'heminegligence dance la vie quotidienne: l'echelle C.B. *Annales de Readaptation et de Medecine Physique, 38,* 183–189.

Chen, P., Hreha, K., Fortis, P., Goedert, K.M., & Barrett, A.M. (2012). Functional assessment of spatial neglect: a review of the Catherine Bergego Scale and an introduction of the Kessler Foundation Neglect Assessment Process. *Top Stroke Rehabilitation, 19*(5), 423–435.

Cherney, L.R., Halper, A.S., Kwasnica, C.M., Harvey, R.L., & Zhang, M. (2001). Recovery of functional status after right hemisphere stroke: Relationship with unilateral neglect. *Archives of Physical Medicine and Rehabilitation, 82*(3), 322-328.

Farnè, A., Rossetti, Y., Toniolo, S., & Làdavas, E. (2002). Ameliorating neglect with prism adaptation: Visuo-manual and visuo-verbal measures. *Neuropsychologia*, *40*, 718–729.

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The Bells Test: A quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology*, *11,* 49-54.

Hilari, K, & Byng, S. (2001). Measuring quality of life in people with aphasia: the Stroke Specific Quality of Life Scale. *International Journal of Language & Communication Disorders, 36*(1), 86-91. doi: 10.3109/13682820109177864

Jacquin-Courtois, S., O'Shea, J., Luaute, J., Pisella, L., Revol, P., Mizuno, K., …, Rossetti, Y. (2013). Rehabilitation of spatial neglect by prism adaptation. A peculiar expansion of sensorimotor after-effects to spatial cognition. *Neuroscience and Biobehavioral Reviews, 37*(4), 594-609. doi: 10.1016/j.neubiorev.2013.02.007

Karnath, H. O. (2007). Pusher Syndrome - a frequent but little-known disturbance of body orientation perception. *Journal of Neurology, 254*(4), 415-424. doi: 10.1007/s00415-006-0341-6

Kerkhoff, G., & Schenk, T. (2012). Rehabilitation of neglect: an update. *Neuropsychologia*, 50(6), 1072-1079.

Làdavas, E., & Serino, A. (2008). Action-dependent plasticity in peripersonal space representations. *Cognitive Neuropsychology, 25*(7-8), 1099-1113. doi: 10.1080/02643290802359113

Reed, C. L., Garza, J.P., & Roberts Jr., R.J. (2007). The influence of the body and action on spatial attention. In: L. Paletta & E. Rome (Eds), *Attention in Cognitive Systems. Theories and Systems from an Interdisciplinary Viewpoint* (Vol. 4840, pp. 42-58). Berlin, Germany: Springer. doi: 10.1007/978-3-540-77343-6_3

Noel, J.P., Grivaz, P., Marmaroli, P., Lissek, H., Blanke, O., & Serino A. Full body action remapping of peripersonal space: the case of walking (2015). *Neuropsychologia, 70*, 375-384. doi: 10.1016/j.neuropsychologia.2014.08.030

Rousseaux, M., Honoré, J., & Saj, A. (2014). Body representations and brain damage. *Clinical Neurophysiology, 44*(1), 59-67. doi: 10.1016/j.neucli.2013.10.130

Rousseaux, M., Honoré, J., Vuilleumier, P., & Saj, A. (2013). Neuroanatomy of space, body, and posture perception in patients with right hemisphere stroke. *Neurology, 81*(15), 129-297. doi: 10.1212/WNL.0b013e3182a823a7

Schenkenberg, T., Bradford, D.C., & Ajax, E.T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30,* 509-517.

Serino, A. (in press). Variability in multisensory responses predicts the self-space. *Trends in Cognitive Sciences*. doi: http://dx.doi.org/10.1016/j.tics.2016.01.005

Serino, A., Noel, J.P., Galli, G., Canzoneri, E., Marmaroli, P., Lissek, H., Blanke, O. (2015). Body part-centered and full body-centered peripersonal space representations. *Scientific Reports, 5*, 18603. doi: 10.1038/srep18603

Vaes, N., Lafosse, C., Nys, G., Schevernels, H., Dereymaeker, L., Oostra, K., …, Vingerhoets, G. (2015). Capturing peripersonal spatial neglect: An electronic method to quantify visuospatial processes. *Behavior Research Methods, 47*(1), 27-44. doi: 10.3758/s13428-014-0448-0

Williams, L.S., Weinberger, M., Harris, L.E., Clark, D.O., & Biller, J. (1999). Development of a stroke-specific quality of life scale. *Stroke, 30*(7), 1362-1369.

Summary

Spatial neglect (SN) is the syndrome in patients with unilateral cerebral lesions, in which they are unaware of the contralateral side of space. Typically, SN patients' attention, responses and body posture are directed towards the ipsilesional side. SN adversely affects patients' progress and length of stay in rehabilitation and has an unfavorable impact on their daily functioning. Therefore, research about SN symptomatology and the optimization of its diagnostics and treatments remains important. Sensorimotor realignment by prisms or prism adaptation (PA) is a well-known treatment procedure for SN. However, the ideal treatment regime and post-stroke phase for clinical application requires further research.

This doctoral thesis contains a methodological, an interventional and a theoretical study in right-hemispheric stroke patients with SN. The methodological study describes the development of a digital Visuospatial Neglect Test Battery (VNTB) for administration on an electronic pen display. The VNTB measures various SN processes via different tests. The discriminative value of the tests was demonstrated by lateralized performance differences between SN patients and healthy control participants. The digital measurement method has a number of advantages for experimental and clinical usage, such as exact and less time-consuming measurements because of automated scoring and calculation, and the direct availability of relevant and more exact measures that are not compatible with paper-and-pencil tests. Finally, variables of the VNTB are used for answering the research questions formulated in the interventional and theoretical studies.

The interventional study (an RCT) examined whether a mild treatment regime of 7 PA sessions can improve SN processes in hospitalized patients. Despite the heterogeneous post-stroke delays in our SN patients, a mild PA regime ameliorated visuospatial processes in peripersonal navigation, extinction, centered bisection, drawing and memory (with caution), assessed after a short time interval. The effects on drawing and bisection have been documented previously, but the PA impact on peripersonal navigation, anterograde memory and visual extinction is reported here for the first time. The results concerning memory and visual extinction provide support for the view that PA affects higher levels of cognitive functioning, and not only intentional-motor cerebral functions but also attentional and non-

motor memory functions. The treatment scheme was insufficient to maintain the PA benefit for centered bisection and extinction in the long term. Despite the mild regime however, a trend towards better performance in navigation, drawing and memory remained visible after 3 months. To enhance the probability of extending and consolidating PA effects, we encourage clinicians to offer PA daily and over an extended time period. However, when patients' stay is short, they can still benefit from short-term repetitive PA. The interventional study also includes an explorative investigation about the potential difference in PA influence between acute, subacute and chronic subgroups of patients. The exploration did not yet indicate more PA effects in one subgroup or another. In anticipation of larger RCT's, the current results suggest not to withhold PA from SN patients based on a time window post-stroke.

In the theoretical study we investigated whether visuospatial behavior manifests itself differently in SN patients with versus without contraversive pushing (CP, a neurologic disorder characterized by a contralesionally directed postural imbalance). A clear difference in peripersonal visuospatial functioning between SN patients with and without CP was found. SN patients with CP demonstrated distinctly more cross-over in line bisection, and a significant contralesionally directed shift in navigational behavior, compared to SN patients without CP. We termed this shift in SN behavior 'contraversive neglect', by analogy with the same shift in body posture in SN patients with CP compared to SN patients without CP. The contraversive similarity at the postural and visuospatial level hints at a coherence between the neural processing system for postural control and the one for non-predominantly postural spatial behavior.

In sum, from an experimental point of view, our investigations contributed to (1) a deeper understanding of SN patients' peripersonal visuospatial functioning, (2) more clarity about the levels of impact of PA, and to (3) direct and exact digital SN measurements. From a clinical point of view, our research provided (1) a battery to test multiple SN processes - comfortable to administer and quick in performance evaluation, (2) recommendations regarding a PA treatment regime in hospitalized patients, and (3) handles for the fine-tuning of SN diagnostics and rehabilitation by taking the coherence of patients' postural and neuropsychological functioning into account. These findings will in turn stimulate continued investigations, leading to the ideal clinical practice with the ultimate goal of improving SN-patients' quality of life as much as possible.

Samenvatting

Spatiaal neglect (SN) is het syndroom waarbij patiënten met unilaterale cerebrale letsels zich niet bewust zijn van de contralaterale zijde van de ruimte. SN-patiënten richten hun aandacht, responsen en lichaamshouding doorgaans naar de ipsilesionale zijde. SN heeft een negatieve invloed op de progressie en opnameduur van revalidanten, en na de revalidatie op hun dagelijks functioneren. Verder onderzoek naar de SN-symptomatologie, en naar de optimalisatie van de diagnostiek en behandeling ervan zijn daarom belangrijk. Sensorimotorische reorganisatie via prisma's, prisma-adaptatie (PA) genoemd, is een gekende behandelingsprocedure voor SN. Er is echter nog meer onderzoek nodig naar het ideale behandelingsschema en de ideale timing voor de klinische toepassing van PA na een cerebrovasculair accident (CVA).

Deze doctoraatsthesis is opgebouwd rond drie studies bij rechts-hemisferische CVA-patiënten met SN: een methodologische, een interventionele en een theoretische studie. De methodologische studie beschrijft de ontwikkeling van een digitale Visuospatiale Neglect Testbatterij (VNTB), om af te nemen op een elektronische pentablet. De VNTB bestaat uit 9 testen die verschillende SN processen meten. De discriminatieve waarde van de testen werd aangetoond door gelateraliseerde performantieverschillen tussen SN-patiënten en gezonde controlepersonen. De digitale meetmethode heeft een heel aantal voordelen voor experimenteel en klinisch gebruik, zoals tijdsefficiënte metingen via automatische scoring en berekening, en de directe beschikbaarheid van relevante en exactere metingen die niet altijd compatibel zijn met pen-en-papiertaken. Tot slot, de variabelen van de VNTB worden gebruikt om de onderzoeksvragen van de interventionele en de theoretische studie te beantwoorden.

De interventionele studie onderzocht via een RCT of een mild behandelingsschema van 7 sessies SN-processen kan verbeteren bij gehospitaliseerde patiënten. Ondanks de heterogene timing na hun beroerte, was er op korte termijn na PA verbetering op vlak van peripersoonlijke navigatie, extinctie, gecentreerde bisectie, tekenen en (met enige voorzichtigheid) geheugen. De PA-effecten op tekenen en bisectie waren reeds eerder beschreven, maar deze op peripersoonlijke navigatie, anterograad geheugen en visuele extinctie nog niet. De resultaten betreffende visuele extinctie en geheugen leveren bijkomende evidentie voor de visie dat PA hogere niveaus van cognitief functioneren kan beïnvloeden; en niet alleen intentioneel-motorische cerebrale functies, maar ook aandacht en niet-motorisch geheugen. Het behandelingsschema was ontoereikend om de gunstige PA-invloed op gecentreerde bisectie and extinctie te behouden op lange termijn. Ondanks het milde schema bleef er na drie maand echter wel een trend tot betere performantie aanwezig binnen navigatie, tekenen en geheugen. Om de kans op uitbreiding en consolidatie van PA-effecten te vergroten, moedigen we clinici aan om PA dagelijks aan te bieden en over een lange periode. Als de hospitalisatieduur kort is, kunnen patiënten echter wel baat hebben bij korte-termijn repetitieve PA. De interventionele studie bevat tevens een exploratief onderzoek naar het verschil in PA-invloed naargelang de acute, subacute of chronische fase na CVA. Deze exploratie leverde voorlopig geen inter-subgroep verschillen in PA-effecten op. In afwachting van grootschaligere RCT's, suggereren de huidige resultaten dat een bepaald tijdsvenster na CVA geen criterium is om PA aan SN-patiënten te ontzeggen.

In de theoretische studie onderzochten we of SN-patiënten met versus zonder contraversief pushen (CP, een neurologische stoornis gekarakteriseerd door een contralesionaal gericht posturaal onevenwicht) zich cognitief anders gedragen. Er werd een duidelijk verschil gevonden in peripersoonlijk visuospatiaal functioneren tussen SN-patiënten met versus zonder CP. In vergelijking met SN-patiënten zonder CP, vertoonden SN-patiënten met CP beduidend meer cross-over in lijnbisectie en een significante contralesionaal gerichte verschuiving in navigatie. We noemden deze verschuiving in SN-gedrag 'contraversief neglect', naar analogie met dezelfde verschuiving in lichaamspostuur bij SN-patiënten met CP ten opzichte van SN-patiënten zonder CP. De contraversieve gelijkenis op posturaal en visuospatiaal niveau doet een samenhang of interactie vermoeden tussen het neurale informatieverwerkingssysteem voor posturale controle en dat voor cognitief spatiaal gedrag.

Samenvattend, vanuit experimenteel standpunt leveren de huidige studies een dieper begrip op (1) van het cognitieve visuospatiale functioneren in samenhang met het posturale patroon bij SN-patiënten, en (2) van de niveaus die bij SN beïnvloed worden door PA, en (3) praktisch gezien leveren ze exacte digitale SN-metingen op, met direct gebruiksklare data. Vanuit klinisch standpunt leveren de studies (1) een batterij op om meerdere SN-processen te testen - eenvoudig af te nemen en met snelle prestatie-evaluaties, (2) aanbevelingen betreffende een PA-behandelingsschema in gehospitaliseerde SN-patiënten, en (3) handvatten voor de verfijning van SN-diagnostiek en -revalidatie door de samenhang van posturaal en neuropsychologisch functioneren in rekening te brengen. Deze bevindingen zullen op hun beurt voortgezet onderzoek stimuleren, met het oog op een ideale klinische praktijk, met als ultiem doel de levenskwaliteit van SN-patiënten zo goed mogelijk te bevorderen.