Sede Amministrativa: Università degli Studi di Padova

Sede Consorziata: IRCCS Ospedale San Camillo, Venezia-Lido

Dipartimento di Psicologia dello Sviluppo e della Socializzazione

SCUOLA DI DOTTORATO DI RICERCA IN SCIENZE PSICOLOGICHE
INDIRIZZO SCIENZE COGNITIVE
CICLO XXII

REHABILITATION OF UNILATERAL LEFT NEGLECT: EFFECTIVENESS OF DIFFERENT TREATMENTS

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1. INTRODUCTION

Neuropsychology is "the scientific study of brain-behaviour relationships" (Meier, 1974), and, in general, rehabilitation is the provision of planned experience to foster brain changes leading to improve daily life functioning (Robertson, 1999). Like other kinds of rehabilitation, the purpose of neuropsychological rehabilitation is to enable people with disabilities to achieve their optimum level of well being, to reduce the impact of their problems in everyday life and to help them return to their most appropriate environments (Wilson, 2003). Neuropsychological rehabilitation has shown tremendous growth in the last few decades, largely based on clinical acumen and experience. More recently, there has been much ado about the need for evidenced-based rehabilitation based on the best available scientific evidence to support the effectiveness of interventions. The emphasis on evidence-based rehabilitation is often interpreted as standing in opposition to clinical judgment, when in fact these are complementary aspects of care, with sound clinical judgment required to apply the appropriate principles and techniques of treatment to the individual with a neurological disability. In addition, evidence-based treatment must incorporate the client's values, preferences, and goals in the decision-making process in order to make the treatment accommodations that may ultimately determine the effectiveness of treatment (Wilson et al., 2009).

With the present work, we aimed to understand in a broader and deeper way the effectiveness (or the ineffective/negative consequences) of three rehabilitation techniques for a multifaceted neuropsychological syndrome: the left unilateral neglect. Based on recent knowledge about rehabilitation methodologies, we have directly compared, for the first time, three of the most effective treatments for left unilateral neglect. We have used the Visual Scanning Training (VST) (Diller et al., 1977; Diller & Weinberg, 1977; Pizzamiglio et al., 1992; Antonucci et al., 1995), the Limb Activation Treatment (LAT) (Robertson, Hogg, & McMillan, 1998; Robertson et al., 2002), and the Prism Adaptation (PA) (Frassinetti et al., 2002; Serino et al., 2009). Our results may explain some theoretical questions and problems on the nature of left unilateral neglect, and may contribute to better understand what is the best way

to lead a rehabilitation protocol for patients affected by this complex syndrome. Moreover, our goal was to promote theoretical- and evidence-based suggestions regarding the best strategies to treat patients with unilateral neglect, considering both individuals and groups.

1.1 Neuropsychology and rehabilitation

During the last century, interest in human brain-behaviour relationships has increased rapidly, conveying considerable knowledge to theory and practice. There is a large number of examples of the validity of neuropsychological research findings as well as of successful applications of neuropsychological intervention methods with people in every stage of life (see Sohlberg & Mateer, 2001; Wilson, Gracey, Evans, & Bateman, 2009).

During the World War II, Alexander Romanovich Luria developed an approach to the study of higher cerebral functions, their recovery and rehabilitation, based on work with victims of missile wounds. This approach formed the foundation for the modern neuropsychology and neuropsychological rehabilitation. Luria (1963, 1973) acknowledged the presence of functional systems mediating cognitive functions, components of which might be located in different brain regions. As a consequence, the manifestations of cerebral dysfunction would differ according to which part of the functional system has been disrupted by brain injury. Luria emphasized the importance of a detailed neuropsychological examination of the brain-injured people as a means of establishing the precise nature of the cognitive disabilities. This approach formed the basis of an individualized rehabilitation program which was based on extensive practice as a means of retraining the impaired function in order to rebuild previous abilities. With a more comprehensive perspective, he also acknowledged the influence of a number of factors on successful recovery, including the nature of the lesion (brain injury, ischemic factors, etc.), particularly the extension of the lesion and the presence of complications in the recovery process; the state of the brain before the injury, including the age of the brain, and the person's premorbid personality and coping style.

Despite these cogent insights, which remain relevant to today's practice of neuropsychological rehabilitation, neurorehabilitation was slow to develop after World War II and remained more focused on the alleviation of physical disability. The main problem for neuropsychologists is that each patient has a unique

combination of cognitive problems with different degrees of disabilities. Additionally, no specific treatment protocol or theoretical framework addresses how to treat problems at a complex individual level. In fact, there are controversies regarding recovery of cognitive functioning and cognitive models of normal function and abnormal function of brain. As a result, particular neuroscientific models of brain function and recovery may differentially apply across individuals and patients' groups, which could influence which strategies are effective in particular cases and for specific disabilities.

The fact that neurons in the brain cannot regenerate, leads easily to the conclusion that, once a particular function is lost because of brain damage, that function cannot be recovered (Robertson, 1994). Nevertheless, it is now clear that there is latent function in some non-functioning and apparently permanently damaged neural circuits and that the brain can generate new neurons and create new connections (Nakatomi et al., 2002). In the absence of specific training, even cortical areas not directly affected by the damage may lose their function, possibly due to the lack of stimulation to these areas previously connected with the lesioned areas. It therefore seems likely that behaviour and learning can play an important role underlying neural recovery. The implications of this are that we require cognitive theories in order to know what are the correct inputs which maximize the completion of neural network circuits and minimize the competitive inhibition between neural networks. This requires appropriate models of the underlying cognitive systems. Otherwise, rehabilitative interventions may activate a system which is actually inhibitory of the damaged network to repair, and the treatment may fail to stimulate appropriate networks which would provide patterned input to the damaged network (Robertson, 1999).

Despite this lack of a recognized common approach for cognitive rehabilitation, there are essential methodologies. Furthermore, within the past decade significant effort has been made to draft appropriate standards of care and paradigm changes for cognitive rehabilitation based on recent reviews of empirical studies (Cappa et al., 2003; Cicerone et al., 2000, 2005). These studies have provided guidance regarding which rehabilitation techniques have substantial support from dividing studies according to the level of scientific rigor. Such studies included single case and group designs, although few randomized control designs are found in the rehabilitation literature. Therefore, adequate cognitive neuropsychological models are essential for

providing common replicable treatments to help the restoration of lesioned circuits and prevent their decay and loss.

In the last decades, there has been an enormous body of basic neurosciences research focusing on mechanisms of neuronal injury associated with traumatic brain injury, stroke, and a range of degenerative diseases and processes occurring following brain damage. Cognitive neurosciences research has developed our understanding of brain mechanisms that underpin a range of cognitive functions, an understanding that has developed significantly with the advent of functional neuroimaging techniques. Unfortunatly, however, this knowledge in human rehabilitation and the development of the cognitive neurosciences have been conducted in parallel with clinical practice, with minimal communication between them. In fact, relatively little rehabilitation research has been based on neurosciences research or even solid theoretical underpinnings; many rehabilitation therapists are not cognizant of research in these other areas, which has profound implications for their work. Although there is a number of texts that focus on either theories of recovery of function or approaches to rehabilitation, relatively few books have successfully integrated the scientific evidence relating to impairment and recovery of specific cognitive and behavioural disorders with the clinical application of rehabilitative interventions.

1.2 Left unilateral neglect: story

According to Heilman, Watson, and Valenstein (1979), patients with left unilateral neglect, following a right hemisphere lesion, fail to report, orient to, or verbally describe stimuli in the contralesional space (Heilman et al., 1979). The structure of space representation is elusive and difficult to characterise in a precise way (Bisiach, 1996). Evidence of this difficulty can be seen from the diversity of terms that have been used to describe unilateral neglect: "neglect of the left half of visual space" (Brain, 1941), "unilateral visual inattention" (Allen, 1948), "unilateral spatial agnosia" (Duke-Elder, 1949), "imperception for one half of external space" (Critchley, 1953), "left-sided fixed hemianopia" (Luria, 1972), "hemi-inattention" (Weinstein & Friedland, 1977), "hemi-neglect" (Kinsbourne, 1977), "unilateral neglect" (Hecaen & Albert, 1978), "hemi-spatial agnosia" (Willanger, Danielsen, & Ankerhus, 1981), and "contralesional neglect" (Ogden, 1985).

The term "neglect" was first used consistently by Pineas (1931), who described a 60-year-old woman whose *vernachlässigung* (neglect) of the left side was

both severe and long-lasting, despite the absence of a field defect or sensori-motor loss. Although Holmes (1918), Poppelreuter (1917), and Pineas (1931) documented some of the behavioural features of neglect and suggested an attentional explanation, it was not considered as a specific syndrome until World War II and the work of Russell Brain. Brain's article in 1941 was the first report that isolated and characterised some of the main features of visual neglect.

Brain's article (1941) remains an important milestone in the conceptualisation of neglect as a distinct neurological condition. Brain set out to provide a coherent sub-classification of the syndrome commonly referred to as "visual disorientation". As a clinical description, Brain recognised that the term visual disorientation had become a "loose and comprehensive description covering a number of disorders of function differing in their nature". Brain's subsequent analysis is one of the first attempts to describe and explain unilateral neglect in terms of disturbance of perceptual space. The main conclusions of the article, which served as the basis for many subsequent investigations, indicated a strong association with posterior lesions of the right hemisphere, the inadequacy of a purely sensory explanation, and the distinction from topographical memory loss, visual agnosia, and left-right discrimination problems.

Studies of visual neglect can be divided into two periods: early case studies and detailed single-case descriptions and group studies. Single-case and group studies illustrate some of the difficulties encountered by clinicians attempting to formulate a coherent description of the syndrome. The first studies fall within the framework of clinical neurology and emphasised neuroanatomy and pathology, whereas the latter attempt to describe the range and types of neglect, using a wide variety of operational definitions, clinical tests and groups of patients (Robertson & Marshall, 1993).

Factors responsible for the relative paucity of neglect research until the early 1970s include the failure to differentiate and characterise the essential spatial features of the syndrome, the widespread acceptance of inadequate infra-cognitive interpretations, and the absence of theoretical frameworks to guide the design of new experiments (Robertson, 1999). However, during the 1970s there was a fast-growing awareness of the needs to evaluate and treat cognitive deficits of people with traumatic brain injury. Indeed, improved medical management led to a growth in the number of survivors of brain injury, who were predominantely young adults. It became apparent that rehabilitation models developed for people with primarily physical disabilities did not meet the needs of people with cognitive disabilities

following brain lesion. In fact, while physical disabilities were present for some people, the more preminent and common disabilities were deficits of attention, memory, reasoning, and other cognitive abilities; communication difficulties; changes in behaviour and personality. As a consequence, the care of people with cognitive disabilities encountered a lot of difficulties for hospitals, rehabilitative centres, and their families.

The period comprised between the '70s and the '90s has seen a great increase in the number of studies of neglect phenomena (Bisiach & Vallar, 1988; De Renzi, 1982; Heilman, Watson, & Valenstein, 1985a; Jeannerod, 1987; Mesulam, 1985; Prigatano & Schacter, 1991; Riddoch, 1991; Weinstein & Friedland, 1977). This growth of interest is partly due to the potential significance of neglect for theories of normal spatial processing (Delis et al., 1985; Jeannerod, 1987), selective attention (Posner & Rafal, 1987), mental representations (Bisiach & Vallar, 1988; Farah, 1989), awareness (Levine, 1990; McGlynn & Schacter, 1989), and pre-motor planning (Rizzolatti & Camarda, 1987; Tegner & Levander, 1991). Neglect can be a major disability in the acute phases of recovery from stroke and can impede later attempts to rehabilitate the patients (Denes, Semenza, Stoppa, & Lis, 1982; Diller & Weinberg, 1977; Kinsella & Ford, 1980).

1.3 Left unilateral neglect: description

It is now accepted that left unilateral neglect results from the interplay of damage to several different cognitive processes (Vallar, 1998). However, these deficits in performance cannot be attributed to primary sensory or motor deficits, which may occur in the absence of neglect (Bisiach & Vallar, 1988). Even though "neglect" is not a unitary deficit, the label remains useful as an umbrella-term for spatially selective disorders (Driver, 1994). Hereafter the term "unilateral neglect" will be used (Hecaen & Albert, 1978).

Because unilateral neglect is typically observed under conditions where movements of the eyes and head are permitted, early accounts of neglect have tended to assume that the term "left" refers to the left of the patient's midline or mid-sagittal plane. However, it is probably more accurate to consider a gradient in spatial locations from left to right (Kinsbourne, 1993; Marshall & Halligan, 1989a). The more a stimulus is located to the left, the more frequently it is neglected. There is no constant boundary between the neglected and non-neglected spaces for many patients.

However, it has been suggested that the presence of unilateral neglect may involve several different frames of reference, including retinal, head, trunk, gravitational, object-centered, and object-based coordinate systems (Halligan & Marsahll, 1993b). Nevertheless, the body midline is probably one of the most important frames of reference involved.

Unilateral neglect may be viewer-centered (egocentric), object-centered, or environment-centered (allocentric). Viewer-centered unilateral neglect may be defined in relation to the position of the trunk, the head, or the eyes (for a review, see Landis, 2000), whereas object-centered and environment-centered unilateral neglect is based with respect to the midline of the object (or environment), indipendently from the position of the viewer (Behrmann & Moscovitch, 1994; Hillis et al., 1998).

Many subtypes or forms of neglect have been described. These are usually distinguished by their presumed underlying mechanism or type of behaviour. The various forms of neglect (i.e. attentional, motor-intentional, representational, personal, etc,) are not mutually exclusive and a patient may have one or more forms of neglect at the same time. Patients may exhibit different behavioural manifestations of neglect at different times, and some never demonstrate certain manifestations. For example, neglect may occur selectively in near space (Halligan & Marshall, 1991a; Mennemeier et al., 1992) or be more severe in far space (Cowey et al., 1994). Such dissociations are rare (Guariglia & Antonucci, 1992) and are often task-dependent (Keller et al., 1999), since in most patients unilateral neglect occurs both in near and in far space (Pizzamiglio et al., 1989). Apart from the dissociations in external space, neglect may selectively occur in the representational space (Guariglia et al., 1993; Beschin et al., 1997).

In addition to the most common horizontal neglect, neglect of lower (Rapesak et al., 1988) and upper (Shelton et al., 1990) vertical space, and neglect of radial space (Shelton et al., 1990) have been reported. Mark and Heilman (1998) demonstrated that many patients with spatial neglect have a combination of horizontal, vertical, and radial neglect. Most commonly this three-dimensional neglect is left-sided, lower vertical, and proximal radial (Heilman et al., 2003).

The characteristic spatial bias of neglect patients has been observed in some form for all of the sensory modalities (vision, audition, touch, proprioception, even smell; see Bellas, Novelly, Eskenazi, & Wasserstein, 1988; Heilman, Watson, & Valenstein, 1993; Mesulam, 1981; Vallar, Guariglia, Nico, & Bisiach, 1995).

Analogous spatial biases may also be apparent in motor-output systems (e.g., with eye or hand movements being biased towards the ipsilesional side; see Bisiach, Geminiani, Berti, & Rusconi, 1990; Coslett, Bowers, Fitzpatrick, Haws, & Heilman, 1990; Heilman, Bowers, Coslett, Whelan, & Watson, 1985).

Additionally, neglect may selectively impair different spatial domains: (1) personal body space (personal neglect or body neglect), that is the space of the body; (2) peripersonal space (peripersonal neglect, which affects the space within reaching and grasping); (3) extrapersonal space (extrapersonal neglect, which affects stimuli beyond reaching and grasping space); (4) representational or imaginal space (representational or imaginal neglect), that is the space of visual images like that of a room, a well-known personal or public place, or the map of a country.

1.4 Left unilateral neglect: clinical signs

Several studies have shown consistently that left unilateral neglect is both more frequent and severe after right hemisphere damage than right unilateral neglect following left hemisphere damage (Bisiach, Cornacchia, Sterzi, & Vallar, 1984; Caltagirone, Miceli, & Gainotti, 1977). In the acute or transitory phase, immediately following a cerebral lesion, the most typical signs of severe unilateral neglect can be easily recognized. Patients with unilateral neglect have an obvious ipsilesional deviation of the eyes, the head, and the trunk. Some patients will shave or groom only the right side of their body, they may fail to eat food placed on the left side of the plate, they fill out only the right side of a form, omit to wear the left sleeve or slipper, forget to place the left foot on the weelchair rest, knock against the left part of a door with the weelchair or with their left body part. Patients with unilateral neglect may also report personal belongings as missing even when the objects are clearly in front of them and often lose their way travelling in the hospital, not recognising their own room if it is placed on their left side. In general, their spontaneous behaviour is characterised by what appears to be a gross inattention to the left side of space (Halligan & Robertson, 1992).

This syndrome has been shown to constitute a substantial impairment for functional recovery. Furthermore, unilateral neglect can limit the effectiveness of rehabilitation, often to a greater extent than more obvious motor, sensory, and speech deficits (Halligan & Cockburn, 1993). Some patients with unilateral neglect may be unaware of or deny their deficits. This phenomenon has been called "anosognosia"

(Babinski, 1914). Consequently, they attempt to explain their condition by minimizing or denying their problems. Anosognosia is commonly associated with neglect in the early stages of the condition, although the two conditions are not the same. In fact, patients may demonstrate neglect without anosognosia, and vice versa. Anosognosia is a key reason why neglect is so strongly predictive of poor functional outcome following right hemisphere lesions. In severe cases, patients may also fail to recognise their contralateral extremities as their own ("somatoparaphrenia", Gerstmann, 1942). They may experience difficulties in remembering left-sided details of internally represented familiar scenes (Meador et al., 1987) and in general they only attend to events and objects located on the ipsilesional side of space. Consequentely, patients can easily become excessively isolated as a result of their deficit.

Clinical observations show that neglect may be task-specific (Horner et al., 1989). For example, patients with visuo-spatial neglect on drawing may not necessarily demonstrate neglect on reading or writing tasks (Costello & Warrington, 1987), and vice versa. Although some spontaneous recovery occurs in the majority of patients after stroke, left unilateral neglect remains severe in many patients and may persist in the chronic phase (Katz et al., 1999; Hier et al., 1983; Samuelsson et al., 1997). In a recent study, Farnè et al. (2004) have shown that only 43% of neglect patients improved spontaneously during a two-week long assessment in the acute phase (up to six weeks post-stroke) and only 9% of patients showed complete recovery. Commonly associated with left hemiplegia, the presence of left unilateral neglect renders motor-associated deficits more severe (Denes et al., 1982). Most clinicians recognize that left unilateral neglect is one of the major factors associated with a poor functional outcome (Denes et al., 1982; Edmans et al., 1991; Fullerton et al., 1988; Jehkonen et al., 2000; Kalra et al., 1997; Stone et al., 1992; Boisson & Vighetto, 1989). Consequently, it is not surprising that over the past decades, many different rehabilitation techniques or treatments have been put forward to alleviate, reduce or remediate the deficits of patients with this complex syndrome.

1.5 Left unilateral neglect and extinction

Extinction is usually defined as the inability to respond to one of two simultaneously presented stimuli (visual, tactile, auditory), despite the fact that each stimulus is correctly detected and localized in isolation (Rapsak, Watson, & Heilman,

1987). Among the multiple deficits of perception and exploratory behaviour that constitute the neglect syndrome, extinction is often taken as a cardinal sign indicating an attentional deficit (Critchley, 1953; Bisiach, 1991; Rafal, 1994). Patients with extinction can perceive a single stimulus if it is presented alone, but they are unaware of the same stimulus when another is presented simultaneously on the ipsilesional side (Vuilleumier & Rafal, 2000).

A number of evidence has now systematically shown that extinction in particular can emerge even when concurrent stimuli are presented in different sensory modalities, that is, different sensory inputs delivered to the ipsi- and contra-lateral side of the patient's body (Bender & Feldman, 1952; Di Pellegrino et al., 1997). For example, tactile extinction can be modulated by visual events simultaneously presented in the space region near the tactile stimulation, increasing or reducing tactile perception, depending upon the spatial arrangement of the stimuli (see Brozzoli et al., 2006). In particular, the visual stimulation in the ipsilesional side exacerbates contralesional tactile extinction, whereby the presentation of visual and tactile stimuli on the same contralesional side can reduce the deficit (Làdavas et al., 1998).

Extinction is more frequent after right hemisphere damage (Barbieri & De Renzi, 1989; Vallar et al., 1994) and often persists after recovery from a more severe neglect disorder (Karnath, 1988). However, some early (Bender & Teuber, 1946; Denny-Brown et al., 1952; Bay, 1953) and more recent (Birch et al., 1967; Farah et al., 1991; Vallar et al., 1994: Marzi et al., 1996) studies have suggested that extinction might result from sensory imbalance due to weakened or delayed afferent inputs in the affected hemisphere rather than from attentional factors. Furthermore, the view that extinction and spatial neglect share a common underlying mechanism has been questioned on the basis of a few patients with spatial neglect, but no clinically noticeable extinction (Barbieri & De Renzi, 1989; Bisiach, 1991; Liu et al., 1992) and the somewhat different neuroanatomical correlates of the two disorders (Vallar et al., 1994). In fact, behavioural and neuroanatomical evidence clearly demonstrate a double dissociation between unilateral neglect and extinction (Findlay & Walker, 1996; Goodrich & Ward, 1997; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994).

Since the earliest studies, it has been unclear whether neglect and extinction are related to sensory, attentional, or other factors (see Friedland and Weinstein, 1977). Some theories argued for an imbalance between the sensory capabilities of the two

hemifields (Bender, 1952; Denny-Brown et al., 1952; Birch et al., 1967); others gave more weight to an impairment of attentional processes (Critchley, 1949; Heilman and Watson, 1977; Kinsbourne, 1987, 1993) or to an incomplete mental representation of the contralesional space (Bisiach & Luzzatti, 1978). The non-visual manifestations of neglect and extinction clearly showed that in many circumstances neglect and extinction can be specific for a single sensory modality, or for multiple sensory modalities in a given patient (De Renzi et al., 1984; Vallar et al., 1994).

Out of a shared explanation theory, extinction is one aspect of the neglect syndrome that clearly involves a loss of perceptual awareness and that should be assessed and described in details in clinical practice.

1.6 Anatomical correlates of unilateral spatial neglect

Unilateral spatial neglect can be observed in some form after various unilateral brain lesions, but is most common and long-lasting when the damage involves the inferior parietal lobe, particularly in the right hemisphere (Vallar, 2003). Studies seeking to determine the critical cortical areas, by looking for overlap in the lesions of different cases, have pointed to the angular and supramarginal gyri, corresponding to Brodmann areas 39 and 40, respectively (Heilman et al., 1993; Leibovitch et al., 1998; Perenin, 1997; Vallar, 1993; Vallar & Perani, 1986). Concomitant damage to white-matter fibre-bundles beneath the parieto-temporo-occipital junction is also common (Leibovitch et al., 1998; Samuelsson, Jensen, Ekholm, Naver, & Blomstrand, 1997), and may result in a larger functional lesion than that implied by considering only the grey-matter damage (e.g., see Gaffan & Hornak, 1997). Moreover, neglect may be caused by cerebral lesions involving temporal (Karnath, Ferber, & Himmelbach, 2001), parietal (Mort et al., 2003; Vallar & Perani, 1986), frontal (Heilman & Valenstein, 1972; Husain, Mattingley, Rorden, Kennard, & Driver, 2000), or subcortical areas (Karnath, Himmelbach, & Rorden, 2002), particularly of the right hemisphere. Another line of findings suggested the involvement of more rostral portions of the superior temporal gyrus (Karnath et al., 2001, 2004). In addition, damage to several other brain structures has been reported to be associated with neglect, including the thalamus, the basal ganglia, and the dorsolateral prefrontal cortex (Karnath et al., 2002; Vallar, 2001).

However, at variance with interpretations of neglect stressing the role of damage to local brain modules, it has long been proposed that spatial processing that

may be disrupted in neglect does not result from the activity of single-brain areas, but rather emerge from the interaction of large-scale networks (Mesulam, 1981; Heilman et al., 1993). In fact, small lesions confined to parietal cortex rarely cause marked neglect. Persistent and severe neglect following parietal lobe damage, almost always indicates a large lesion with considerable subcortical extension (Mesulam, 2002).

The symptoms and signs of neglect are numerous and it is difficult to speak about a single neural network underlying spatial processing. Neural networks referred to neglect are organized at the level of a distributed large-scale networks revolving around different cortical components, each of which supports a different neural representation of space. Each of these components serves a dual purpose: it provides a local network for regional neural computations and it constitutes a nodal point for the linkage of distributed information (Mesulam, 2002). The cortical components of the network are interconnected with each other and with key subcortical areas in the striatum, the thalamus, the superior colliculus, and the reticular activating system. Any task involving spatial processing, regardless of input or output modality, activates these components. The component of spatial processing networks can collectively specify whether and how an event in extrapersonal space will attract covert attentional shifts, orientation, foveation, manual grasp, and overt search behaviours. Damage to any network component or to its interconnections can potentially elicit neglect behaviours. Lesions within the network are likely to cause multimodal neglect, whereas lesions that disconnect it with specific sensory or motor areas could yield modality-specific neglect syndromes. The complexity of the network and the variability of lesion sites are likely to account for the clinical heterogeneity of unilateral left neglect.

1.7 Anatomo-functional correlates of unilateral spatial neglect

Recent proposals have suggested that parietal or superior temporal gyrus dysfunction may lead to different types, respectively personal/extrapersonal neglect (Comitteri et al., 2007) and viewer-centered/stimulus-centered neglect (Hillis et al., 2005). However, the lesion overlap method lacks spatial resolution and may reflect differences in vascular territories rather than true functional architecture; this method does not satisfactorily deal with multiple lesions (Godefroy et al., 1998; Bartolomeo, 2006).

Other neuroimaging techniques have recently been applied to the study of the

neural bases of neglect, such as functional magnetic resonance imaging (fMRI). The recent discovery that magnetic resonance imaging can be used to map changes in brain hemodynamics that correspond to mental operations extends traditional anatomical imaging to include maps of human brain function. The ability to observe both the structures and also which structures are active in specific functions is due to fMRI provides high resolution, noninvasive reports of neural activity detected by a blood oxygen level dependent (BOLD) signal (Ogawa et al., 1992; Belliveau et al., 1990, 1991). This new ability to directly observe brain function opens an array of new opportunities to advance our understanding of brain organization, as well as a potential new standard for assessing neuroanatomical status of patients with brain lesions. Functional MRI is based on the increase of blood flow to the local vascular area that accompanies neural activity in the brain. Consequently, neural activity corresponds to local reduction in deoxyhemoglobin because the increase of blood flow occurs without an increase of similar magnitude in oxygen extraction. Thus, deoxyhemoglobin is considered as an endogenous contrast enhancing agent, and serves as the source of the signal for fMRI. Using an appropriate imaging sequence, human cortical functions can be observed without the use of exogenous contrast enhancing agents on a proper scanner. The interpretation of fMRI (Ogawa et al., 1992; Logothetis & Wandell, 2004; Logothetis et al., 2001) typically makes the crucial assumption of a uniform linear predictive relationship between neuronal and haemodynamic signals. However, recently Sirotin and Das (2009) showed that this model is valid for visually evoked signals, but it fails profoundly to predict another class of signals, of almost comparable magnitude and behaviourally linked structure. These results raise the further possibility that there may be other assumption that haemodynamic signals uniformly imply equivalent underlying neuronal activity. Although the interpretation of haemodynamic signals is under debate, it cannot be excluded the potential of fMRI to promote new insights into physiological bases of disfunctions and the clinical applications in neurorehabilitation.

The functional neuroimaging results support models of neglect which postulate a dysfunction of large-scale right-hemisphere networks (Mesulam, 1999). Particularly, parietal components of the network may determine the perceptual salience of extrapersonal objects and frontal components may be implicated in the production of an appropriate response to behaviourally relevant stimuli (Bartolomeo, 2007). The demonstration of anatomically intact, but functionally inactivated areas,

may also open perspectives for rehabilitation treatments, aimed to restore normal neural activity in the lesioned areas.

1.8 Neural recovery of unilateral spatial neglect

Understanding the anatomical substrate of the neuropsychological deficits is not only of theoretical, but also of great clinical importance. The pioneer study of Pizzamiglio et al. (1998) opened new perspectives in studying the cerebral changes after neuropsychological treatments. In this study, they designed a positron emission tomography (PET) activation paradigm to evaluate the brain's functional correlates of recovery from unilateral left neglect in patients with right-sided lesions. They measured the regional cerebral blood flow (rCBF) changes during the execution of a visuospatial task before and after rehabilitation training (Visual Scanning Training; Pizzamiglio et al.,1992) administered for a period of 2 months between the 2 PET measurements. The 3 patients with unilateral left neglect studied by Pizzamiglio et al. (1998) showed a considerable improvement between the first (from 2,5 to 11 months after stroke) and the second examination (realized during the first week after the treatment procedure, which had a duration of 8 weeks), both in the raw scores of the 5 measures of neglect (line cancellation, Albert, 1973; letter cancellation, Diller & Weinberg, 1997; Wundt-Jastrow area illusion test, Massironi et al., 1988; sentence reading, Pizzamiglio et al., 1992; test for personal neglect, Zoccolotti & Judica, 1991) as well as in the global evaluation (e.g., awareness, space exploration, and searching strategies). The behavioural improvement was associated with specific patterns of cerebral activation that included predominantly ipsilesional, right hemispheric areas. The activations observed in recovered patients were in similar locations to those found in normal controls performing the same task. The authors concluded that these findings in patients with unilateral neglect point to a pattern of functional reorganization underlying recovery, which involves areas relevant to visuospatial orientation predominantly located in the right hemisphere.

Hypoperfused regions surrounding the acute infarct are likely to contribute to the behavioural manifestations (Hillis et al., 2000). It is now possible to investigate the cerebral activation of the entire region of both densely ischemic tissue and hypoperfused tissue at the very onset of stroke (24 hours), through the relative newly developed techniques of diffusion-weighted imaging (DWI) and MR perfusion imaging (MRPI). Precisely, DWI shows areas of brain where there is decreased

diffusion of water due to cytotoxic edema and it is highly sensitive in discerning densely ischemic tissue within the first few hours of stroke. Instead, MRPI reveals regions of tissue that are hypoperfused and may be dysfunctional. A recent study by Hillis et al. (2000) demonstrated that in many cases the region of infarct which has induced cognitive deficit (like aphasia or unilateral neglect) was limited to the subcortical tissues, and there was concurrent cortical hypoperfusion in each case. Unlike other studies, the authors showed that early pharmacological intervention successfully reperfused the lesioned cortex and was associated with simultaneous recovery of the language or cognitive deficit (within 12 hours of intervention, when both MRPI and cognitive testing were repeated), providing stronger evidence that the hypoperfused cortical regions were responsible for impairment. In at least one patient, there was also reperfusion of subcortical tissue that might have also contributed to the observed improvement. This study also showed that DWI and MRPI together provide an estimate of the extent and site of potentially recoverable tissue that corresponds to reversible clinical deficits in acute stroke (Hillis et al., 2000).

It has been shown that recovery of function may depend on the restoration and rebalancing of activity in structurally normal, but functionally impaired, task-relevant neural networks. The studies previously reported show that recovery of unilateral neglect is associated with the restoration of normal activity in ipsilateral subcortical or in right hemisphere regions after cortical-subcortical damage in patients with unilateral neglect (Hillis et al., 2005; Pizzamiglio et al., 1998). In a recent study, Corbetta et al. (2005) show that spatial attention deficits in patients with unilateral neglect after right frontal damage correlate with abnormal functional activation of structurally intact regions and that recovery of the deficits correlates with the normalization of activity within these regions. The authors performed a prospective longitudinal study of individuals with spatial neglect following unilateral strokes. All participants underwent standard rehabilitation for at least 3 months after stroke. Patients were tested at the acute (about 4 weeks) and chronic stages of recovery (~ 39 weeks) using a battery of neuropsychological and computerized tasks which assessed the presence of spatial or body neglect, anosognosia, vigilance, spatial attention, and reading deficits and the whole-brain fMRI of the BOLD signal was acquired at 4 weeks and 39 weeks after stroke. On average the neglect group was representative of the most common lesion sites in neglect (see Karnath et al., 2004). Clinically, from the acute to the chronic stage of recovery, patients improved on traditional measures

of spatial neglect (star cancellation and reading task from Behavioural Inattention Test, Wilson et al. 1987; Mesulam cancellation test, Mesulam, 1985). In fact, Corbetta et al. (2005) reported that there was a significant decrement in the rightward processing bias, as shown by a greater improvement in reaction time to targets in the contralesional (left) rather than the ipsilesional (right) visual field and there was a significant improvement in attentional reorienting, expressed as an improvement in the hit rate and reaction time for detecting invalidity cued rather than validly cued targets. In the neglect group, at 4 weeks after stroke, a significant alteration was evident in the activation pattern. In the damaged right hemisphere, large portions of occipital visual cortex, posterior parietal cortex, and dorsolateral prefrontal cortex showed weak or no task-related activity, even though these regions were anatomically intact. In the left hemisphere, there was decreased activity in occipital visual cortex and prefrontal cortex, but there was a strong activation in parietal cortex and sensory motor cortex. Definitely, a strong reactivation occurred in many right hemisphere regions, but also in many left hemisphere regions. Specifically, changes in the BOLD response during recovery showed a strong correlation with performance and, although in many areas recovery was associated with larger BOLD responses, in other areas neurorehabilitation induced an attenuation of a relatively hyperactive response. These results show that a neurological deficit like unilateral neglect after focal brain injury does not reflect only local dysfunction at the site of injury, but also is determined by the distributed impairment of connected neural systems that are structurally intact. This dysfunction may be reflected neurally by deactivation, hyperactivity or interhemispheric imbalance during task processing.

These results have great implications for the field of neuropsychology. For example, the localization of specific neuropsychological syndromes on the basis of anatomical information should be re-examined by combining both anatomical and functional information.

The notion of competition between hemispheres and the negative influence of activity in the intact hemisphere is emerging as an important principle at the systems level to understand recovery of function, not only in spatial neglect, but also in studies of motor and language recovery (Murase et al., 2004; Heiss et al., 1999). Modulation of these competitive interactions either by increasing the excitability of the ipsilesional cortex or by decreasing the excitability of the intact cortex should have a positive effect in neurologically impaired patients (Naeser et al., 2005).

All these examples of brain plasticity, and particularly those dealing with complex learning, can account for a persistent functional readjustment following an appropriate training and for its association with a structural reorganization of the cerebral cortex. With this caution, it might be speculated that the rehabilitation program used for these patients might facilitate a functional reorganization based on the recruitment of brain areas that are involved in the neural organization of activities, such as oculomotor exploration or spatial short-term memory, related to visual exploration.

To summarize, the notion of the neural correlates of spatial representation involves cortico-subcortical neural circuits, and may offer insight into the neural mechanisms of functioning and also of recovery. Recovery in unilateral neglect may be attributed either to the takeover by undamaged cerebral regions (or neural circuits) not primarily committed to spatial representation, or to the regression of diaschisis in areas far removed from, but connected with, the damaged region. According to this view, the neural correlates of cognitive functions are complex circuits: a deficit such as neglect reflects both the structural damage and the dysfunction of remote areas, while recovery is based on restoration of neural activity in connected regions, not directly damaged by the lesion, in which the healthy hemisphere can play a critical role.

Although unilateral neglect remains a highly controversial topic, both concerning its mechanisms and its neural bases, its study still remains of clinical importance and has implications for our understanding of attention, consciousness, and perception (Bartolomeo, 2007).

1.9 Explanatory theories about unilateral spatial neglect

In the absence of an adequate primary sensory or motor explanation, a variety of neuropsychological accounts have been put forward to explain neglect. Most of these characterise the condition as a set of attentional disorders, although other explanations emphasise perceptual, representational, intentional, and pre-motor factors (Robertson & Halligan, 1999). Many different explanatory theories have been proposed for the numerous dissociations within the constellation of neglect symptoms that have been described in the literature (Mesulam, 1981; Milner & Goodale, 1997; Posner & Petersen, 1990; Rizzolatti & Gallese, 1988). It is important to note that a single explanation cannot encompass all signs and types of this complex syndrome.

1.9.1 Attentional theories

1.9.1.1 The orienting vector model

According to the orienting vector model proposed by Kinsbourne (Kinsbourne, 1987, 1993, 1994), both hemispheres contain a kind of orienting vector that directs attention to the contralateral space. Leftward movements are under right-hemisphere influence and rightward movements are under left-hemisphere influence. These orienting tendencies are not only active in the exploration of external space, but also in the exploration of internal spatial representations (Kinsbourne, 1993). Lesion to the putative vector of the right hemisphere therefore leads to hypoexploration of the left hemispace and a hyperattention for stimuli located in the ipsilesional, right hemispace due to the intact attentional vector in the healthy left hemisphere which operates in right hemispace. Kinsbourne's theory claims that the imbalance that occurs between the opponent processing systems not only biases attention to the ipsilesional hemispace, but also biases attention to the ipsilesional region within both hemispaces. The expectation is that a monotonic gradient of attention along the left-right axis will be created, so that the area most activated (ipsilesional to the lesion) will be best represented, and the area least activated (contralesional to the lesion) will not be experienced. Another important claim is that the particular subtype of unilateral neglect demonstrated is determined by which of the many uniquely localized lateral opponent processors are damaged, and to what degree they are damaged (Kinsbourne, 1994). More generally, for a right-hemisphere-damaged patient, the neglected stimuli may be those to the left in a viewer-centered, in an environment-centered, or in an object-centered frame of reference. Therefore, it is probably more accurate to consider a gradient in spatial locations from left to right (Kinsbourne, 1993). The more a stimulus is located to the left, the more frequently it is neglected. The theory of gradient of attention predicts that superior performance will be found in the extreme lateral position within the ipsilesional hemispace, that a gradual decline in performance will be evident as early as the more central (compared with the more lateral) region within the ipsilesional hemispace, and that this performance will deteriorate further as it moves toward the central and lateral regions of the contralesional hemispace.

Kinsbourne further proposed that the right and left hemisphere opponent processors that direct attention laterally are not equal in power. Most importantly, he

proposed that the left hemisphere activation is the more powerful in neurologically healthy individuals, especially in conditions of orienting conflict such as location uncertainty or competing stimulation (Kinsbourne, 1987; Reuter-Lorenz, Kinsbourne, & Moscovitch, 1990). In these conditions, the right hemisphere's leftward directional orienting vector is believed to be weak and barely able to maintain control of the left hemisphere's rightward directional orienting vector. Therefore, unilateral neglect is believed more likely to occur following right than left hemisphere damage because the more powerful rightward directional orienting vector of the left hemisphere takes over and dramatically shifts attention rightward.

1.9.1.2 Attentional hemispheric unbalance

Another attentional theory focuses on the asymmetries of attentional vectors. This theory postulates that the right hemisphere is dominant for spatial attention because it has neural mechanisms for attending to both hemispaces, whereas the left hemisphere attends only to the right hemispace (Heilman & Valenstein, 1979; Mesulam, 1981; Weintraub & Mesulam, 1987). Heilman and Van Den Abell (1980) proposed that the right hemisphere might be dominant for attention in both hemispaces while the left is specialized only for the right hemispace. Mesulam later repeated this idea in anatomical terms. His theory states that the right hemisphere contains a neural network for directed visuo- or tactile-spatial attention which is specialized for both the left and right hemispace, whereas, the comparable system in the left hemisphere subserves only the right hemispace. The neural network includes the lateral premotor cortex (frontal eye fields), the posterior parietal cortex, the cingulate cortex and subcortically the basal ganglia and the thalamus (Mesulam, 1998). While the more anterior areas in each hemisphere are relevant for shifting the focus and guiding exploration, posterior areas in the parietal cortex deal with visual salience of stimuli in external space. Lesions to the right hemisphere would produce left neglect while left hemisphere lesions lead only rarely to contralesional neglect since the stronger right-hemispheric attentional system may compensate for the deficit as a result of its bilateral attentional focus. Furthermore, the different regions of the neural network would explain why neglect occurs after lesions to structures as divergent as the thalamus, the basal ganglia, the dorsolateral frontal lobe and the posterior parietal cortex. This theory predicts that unilateral neglect is less severe following a left hemisphere lesion because the right hemisphere can continue to direct

attention to both the left and right hemispaces. There is more severe unilateral neglect following a right hemisphere lesion because attention is limited to the contralesional hemispace.

1.9.1.3 The disengagement theory

Posner and Petersen (1990) proposed that the attentional system is divided into three subsystems that perform different, but interrelated functions: (1) the anterior attentional system, which is believed responsible for target detection (the selection of focal awareness of a relevant target); (2) the posterior attentional system, which has directional components that control orienting of attention; and (3) the non-directional attentional system, which has components that function to alert or sustain attention. Disruption of the directional components that orient attention toward a contralesional target is believed to cause left or right neglect because those components are located in the posterior attentional system of both hemispheres. In contrast, the non-directional components for generalized attention are located principally in the right hemisphere, so that the right hemisphere is dominant for maintaining a state of alertness or sustained attention. Thus, a right hemisphere lesion may cause more severe and persisting neglect because both the directional and non-directional components of attention are affected.

Posner and Petersen (1990) consider that a distinction between neural mechanisms for alerting and for target detection is vital, because the alert state is a disengaged state. In the alert state, action is suspended while the subject waits for low probability or unpredictable signals. This is in contrast to the engaged state of target detection, which involves action on the part of the subject.

Posner et al. (1987) proposed that the posterior-parietal attentional system is designed to disengage attention from its current focus in preparation for movement to a new target. Following damage to this area, the ability to disengage attention for a contralesional shift is disadvantaged in comparison to disengaging for an ipsilesional shift. In fact, Posner et al. (1987) were the first to propose that covert orienting of attention to a target involved the following three separate cognitive operations each of which could be disrupted as a result of damage to specific anatomic structures within the posterior cerebral system: (1) the operation of disengaging attention from the current attentional focus to direct attention to a contralesional target, which is affected by damage to the posterior parietal lobe; (2) the operation of moving attention to a

new focus, which is affected by damage to the superior colliculus (and surrounding midbrain areas); and (3) the operation of fully engaging selective attention at a new target location in such a way as to avoid any distracting events, which is affected by damage to the lateral pulvinar nucleus of the thalamus (Posner, 1995; Posner, Inhoff, Friedrich, & Cohen, 1987; Posner & Petersen, 1990).

Posner and Driver (1992) have argued that the disengagement of attention from a current ipsilesional focus to a contralesional stimulus is the core deficit in neglect patients. In support of their "spotlight-of-attention" theory, it was found that patients with superior parietal lesions show such disengagement deficits and that valid cueing of their attention towards a target appearing later in the contralesional hemispace reduced this deficit significantly (Posner et al., 1984). Similarly, Baynes et al. (1986) found that both left and right hemisphere lesions cause a slowing of reaction several times, but only right parietal lesions cause a selective deficit in the orienting of attention towards the contralesional left hemispace.

1.9.1.4 The global/local processing theory

The global/local processing theory provides an alternative explanation for the fact that right hemisphere damage is more likely to lead severe and persisting unilateral neglect than left hemisphere damage (Halligan & Marshall, 1994b). According to this theory, a right cerebral lesion may result in damage to the global guidance system of the right hemisphere that is believed to be responsible for directing focal attention to the spatial locations that require further analysis. A right hemisphere lesion thus leaves the individual with unilateral neglect with a left-hemisphere processing system that amplifies local-level information. Marshall and Halligan (1994a) suggest that even in severe unilateral neglect, the issue is not that the individual cannot redirect focal attention leftward, but that this act is not done voluntarily or without prompting. They argue that the overall global representation, which may be available at the preattentive stage of processing, is lost (or unable to be sustained) once local level attention is engaged.

This theory complements Kinsbourne's theory of mutual inhibitory interaction between the hemispheres, and indicates that a right hemisphere lesion leads to ipsilesional capture and the ultimate failure to redirect attention leftward because of the unopposed influence from the non-lesioned left hemisphere (Kinsbourne, 1987, 1993, 1994). Halligan and Marshall (1991b, 1994a, 1994b) proposed that attention is

not only shifted rightward by this unopposed left hemisphere influence, but that local-level ipsilesional information is amplified at the cost of global-level information.

Together, these two theories predict that the damaged right hemisphere (with a predilection for global processing and leftward attention shifts) is competing against the undamaged left hemisphere (with a predilection for focal processing and rightward attention shifts), and this competition is resolved by an attentional shift to a local-level rightward feature, followed by ipsilesional capture and the ultimate failure to redirect attention leftward. Further, these authors believe that ipsilesional capture could be the key to understand unilateral neglect, and that the difficulties that patients with unilateral neglect have with contralesional shifts of attention are a consequence of this process rather than the main component (Halligan, Marshall, & Wade, 1989).

1.9.2 Representational theory

Bisiach et al. (1978) formulated a model of topological space representation (Bisiach & Luzzatti, 1978; Bisiach et al., 1981). This model assumes that every sensory event has a representation. This mental representation can be activated either through sensory afferences or by memory engrams. More particularly, the model assumes that this topological space is not coded veridically in neglect patients. Their left side of representational space is enlarged, whereas the right side is constricted compared with normal individuals (Bisiach et al., 1996). According to these findings, widespread cortical areas in each cerebral hemisphere interact with each other in memory retrieval to produce a retinotopically organized representation of the contralateral visual world.

1.9.3 Pre-motor theory

Rizzolatti and Berti (1990, 1993) have proposed a theory of neglect which takes into account the physiological organisation of the cortical areas, damage to which produces neglect as well as other clinical and neuropsychological aspects of the syndrome. The main tenet of the theory is that neglect is basically a disorder of space awareness (SA). According to this theory, SA depends on the joint activity of several perceptuo-motor, cortical and subcortical, pragmatic maps (oculomotor, for head movements, for arm movements, for walking), each with its own neural space representation. By the term "neural space representation" these authors mean the coding of the external world in a system of non-retinal coordinates. Damage to one or

more pragmatic maps would cause a spatially structured disturbance of awareness (i.e., neglect). However, the functional diversity of the various pragmatic maps implies that localised brain damage impair a specific aspect of space awareness. Therefore, the model can accommodate the apparent paradox of the existence of different types of neglect related to different space sectors (Rizzolatti, Matelli, & Pavesi, 1983; Rizzolatti & Gallese, 1988). A fundamental aspect of the pragmatic maps is that, beside coding space, they programme movements toward the coded space. Thus, in addition to an inability to consciously process information coming from the neglected sector of space, damage to pragmatic maps determines an imbalance in movement programming. This imbalance produces a shift of processing capacity toward the side ipsilateral to the lesion; as a consequence, the rightmost stimuli, even in the normal hemifield, are better perceived and are responded to faster than the leftmost stimuli (Làdavas, Petronio, & Umiltà, 1990).

1.9.4 Transformational theories

These theories assume that the transformation of sensory input information into motor output action, which is necessary due to the different reference frames, in which sensory and motor informations are coded in the brain, is impaired in spatial neglect (Jeannerod & Biguer, 1987, 1989). Following the line of reasoning of Jeannerod and Biguer (1987, 1989), some authors (Karnath, 1994; Vallar et al., 1997) have argued that a deviation of the egocentric reference system toward the side of the brain lesion occurs in unilateral neglect. In turn, this ipsilesional deviation will prevent neglect patients from exploring the opposite side of space and from responding to stimuli that occur on that side (Karnath, 1994). Along the same line, it has subsequently been proposed that the whole frame for exploratory behaviour, whatever the modality (tactile, visual, auditory), is shifted to a new equilibrium on the right of the patient's sagittal body midline (Karnath, 1997; Karnath et al., 1998; Karnath & Perenin, 1998). In this hypothesis, left neglect is interpreted as a supramodal spatial bias caused by an ipsilateral deviation of the egocentric frame of reference. This hypothesis implies four distinct assertions: (1) it takes for granted the existence of an ipsilesional deviation of the egocentric reference in patients with left unilateral neglect; (2) this deviation is considered to be the cause of the neglect behaviour, and one would accordingly expect a positive and significant correlation between the amplitude of the ipsilesional deviation of the egocentric frame of

reference and the presence and/or severity of left-neglect signs; (3) the restoration of the true position of the egocentric reference should improve neglect signs (and vice versa); and (4) an experimental deviation in normal subjects should produce a neglect-like spatial bias. While Karnath (1997) assumes a rotation around the subject's body midline, Vallar (1997) postulates a translation of the egocentric midsagittal representation in relation to the trunk midline; therefore, the two theories differ in their assumptions regarding the type of spatial error.

1.10 What is rehabilitation

The term "rehabilitation" derives from the latin name *rehabilitationem* ("restoration"), that derives from the latin verb *rehabilitare* (*re-* "again" + *habilitare* "make fit"). In these terms, the goal of rehabilitation is to foster and guide natural recovery processes, to decrease the development of maladaptive neural patterns, and to implement physical, pharmacological, cognitive, and behavioural interventions that will increase the rate and level of functional recovery to "make fit again". Inside the all-comprehensive meaning of rehabilitation, cognitive rehabilitation is "the systematic use of instructions and structured experiences to manipulate the functioning of cognitive systems to improve the quality and quantity of cognitive processing in a particular domain. Cognitive rehabilitation is, therefore, a specialized component of more general rehabilitation, the aim of which is the maximization of the functional independence and adjustment of the brain-damaged individual (Robertson, 1999a).

Some rehabilitation interventions (e.g., Repetitive Optokinetic Stimulation (R-OKS), Kerkhoff et al., 2006; Prism Adaptation (PA), Frassinetti et al., 2002; Limb Activation Treatment (LAT), Robertson et al., 2002; Visual Scanning Training (VST), Antonucci et al., 1995) may have effects on cognition (e.g., level of participation, mood, social activities), but this is not cognitive rehabilitation per se, because the result is an effect of a more general goal (i.e., the rehabilitation of the person), and the intervention is not specifically and directly planned to recover cognitive abilities. If we not understand the recovery processes that underpin cognitive recovery, we cannot replicate rehabilitation treatments and we cannot improve the knowledge of the basic functioning of the human cognitive system. Nevertheless, according to the World Health Organization, "Health is a state of complete physical, mental, and social well-being and not merely the absence of

disease or infirmity" (WHO, 1948). Cognitive rehabilitation is, therefore, a part of a more extensive intervention in people who suffered a brain injury.

Following the tradition of Kurt Goldstein, Luria (1973) proposed a compensatory process underlying recovery known as *functional reorganization* (or *functional adaptation*). In his view, given the fact that the central nervous system neurons, outside the hippocampus, do not regenerate, recovery of cognitive functions is achieved by the reorganization of surviving neural circuits to recover brain functions in a different way. Luria's emphasis was on *compensation* (the increase in size or activity of one part of brain that makes up for the loss or dysfunction of another part) as a mechanism of recovery, rather than *restitution* (the return to or restoration of a previous functional state) of impaired neuropsychological process. Traditionally, rehabilitation has focused on assisting patients to learn to compensate for impaired function, while attempting to maximize functioning of impaired systems.

Recent advances in our understanding about the plasticity of the adult central nervous system (e.g., Nudo et al., 1996) require that a new attempt be made to formulate a theory of recovery of function that allows not only for compensation as a mechanism of recovery, but also for at least partial restitution of the impaired cognitive process. This can happen given the evidence that cell genesis is now known to be possible in adult humans (Eriksson et al., 1998). Evidence from neuroscience shows that the brain can be altered by experience, following the notion of *neuroplasticity* (i.e., the brain's capacity to change and alter its structure and function) – (Draganski et al., 2006; Rakic, 2002; Nudo & Garrett, 1996; Kerkhoff & Rossetti, 2006). This is particularly relevant for rehabilitation in order to understand the recovery process. In fact, several mechanisms underlying neuroplasticity have important implications for rehabilitation (e.g., diaschisis, functional reorganization, modification of synaptic connectivity, influence on neural circuitry, and impact of interhemispheric competition) – (Frost et al., 2006; Mahncke & Merzenich, 2006; Nowak et al., 2009). The understanding of all these mechanisms involved in recovery of functions and neuroplasticity may contribute to a stronger theoretical basis for rehabilitation efforts (Sohlberg & Mateer, 2001).

Although a strict distinction between compensation and restitution is difficult to do, this distinction is important in pragmatic clinical terms. In general, different degrees of lesion severity caused by brain damage indicate what are the perspectives of rehabilitation treatments. For example, a mild lesion may recover spontaneously

and rehabilitation is unnecessary; with a moderate lesion, restitution may be possible given appropriate type, timing, and frequency of treatments; finally, a severe lesion has relative little chance to recover and only compensation by other brain areas is possible (Robertson & Murre, 1999). These considerations about recovery give rise to some difficulties in clinical practice and raise important questions; for example, when there is a patient, who suffers from neglect, it is better for him/her to train the lost attention/awareness abilities, or it is better to teach him/her an alternative means to change his/her behaviour to compensate his/her deficits? This is a fundamental dilemma for clinical practice and policy, and it is important to maintain the distinction between compensation and restitution, even if this distinction is difficult to define within clear borders.

Finally, compensatory, functionally orientated rehabilitation methods are an important part of the cognitive rehabilitation approach. However, they are not in themselves sufficient to allow the development of a science of rehabilitation that is grounded in the latest understanding about brain function (Robertson, 1999a).

1.10.1 Evidence based medicine (EBM)

The evidence-based medicine (EBM) is the conscientious, judicious use of current best evidence in making decisions about patient care (Sackett et al., 1996). The concept of EBM emerged in 1980, when health-care specialists first performed systematic reviews of the evidence for preventive services as a step in determining clinical practice guidelines. There are six steps in the provision of evidence-based medicine:

1) decide what information is needed;

2) formulate the information needed in the form of a question that a research study could answer;

3) search the published literature to find the evidence;

4) decide which studies are valid and applicable to patients;

5) apply the findings to patients;

6) evaluate the outcomes.

Two types of EBM have been proposed (Eddy, 2005): evidence-based guidelines (EBG), which is the practice of evidence-based medicine at the organizational or institutional level, that includes the production of guidelines, policy, and regulations; and evidence-based individual decision (EBID) making, which is the EBM as

practiced by each health-care specialist. Evidence-based medicine categorizes different types of clinical evidence and ranks them according to the absence of biases in medical research. For example, it is commonly assumed that the strongest evidence for therapeutic interventions is provided by systematic review of randomized controlled trials (RCTs) involving a homogeneous sample of patients and medical conditions. In contrast, patient testimonials, case reports, and even expert opinion have little value as proof because of the placebo effect, the biases inherent in observation and reporting of cases, difficulties in ascertaining who is an expert, and more.

Systems to stratify evidence by quality have been developed, such as the one by the U.S. Preventive Services Task Force for ranking evidence about the effectiveness of treatments or screening, in the following levels:

Level I: evidence obtained from at least one properly designed randomized controlled trial;

Level II-1: evidence obtained from well-designed controlled trials without randomization.

Level II-2: evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

Level II-3: evidence obtained from multiple time series with or without the intervention.

Level III: opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Other systems to stratify evidence by quality have been developed by the UK National Health Service, which uses a similar system with categories labeled A, B, C, and D. For example, the Oxford Centre for Evidence-based Medicine suggests levels of evidence (LOE) according to the study designs and critical appraisal of prevention, diagnosis, prognosis, therapy, and harm studies, in the following parameters:

Level A: consistent RCTs, cohort studies, and clinical decision rules validated in different populations.

Level B: consistent retrospective cohorts, exploratory cohorts, ecological studies, outcomes research, case-control studies, or extrapolations from level A studies.

Level C: case-series study or extrapolations from level B studies.

Level D: expert opinion without explicit critical appraisal, or based on physiology, and any research done in a controlled laboratory setting using non-human subjects.

Finally, the purpose of EBM is to objectively evaluate the quality of clinical research by critically assessing techniques reported by researchers in their publications.

Although EBM is becoming to be considered as the "gold standard" for clinical practice, there are a number of limitations and criticisms of its use, also regarding neurorehabilitation:

Ethics: in some cases, conducting placebo RCTs is commonly considered to be unethical (i.e., all patients have the right to be treated).

Generalizability: evidence-based guidelines do not remove the problem of extrapolation to different samples or longer timeframes. Even if several top-quality studies are available, questions always remain whether, their results can be reliably generalised to the polulation of reference. The quality of studies varies, making it difficult to compare them and to generalize their conclusions.

Publication bias: it is recognised that not all evidence is made accessible by means of publication. This can limit the effectiveness of any approach and efforts to reduce various publication and retrieval biases is required. Failure to publish trials reporting negative findings is the most dangerous bias.

Populations, **clinical experience**, and **dubious diagnoses**: evidence-based medicine applies to groups of people, but this does not preclude clinicians from using their personal experience in deciding how and for how long to treat a patient. For example, Sackett et al. (1996) claimed that the knowledge gained from clinical research does not directly answer the primary clinical question of what is best for the patient and suggested that evidence-based medicine should not discount the value of clinical experience.

To summarize, EBM definitely provides a fundamental resource for clinical practitioners, but some difficulties arise from the wide variability of the population treated and the impossibility to have a unique treatment "good for all".

1.10.2 The Cochrane Collaboration

To counterbalance for the lack of specific and rigorous rules to make good rehabilitation, in 1993, an international, non-profit, independent organisation, was

established to ensure that up-to-date, realiable, and accurate information about the effects of healthcare interventions is readily available worldwide. This organization produces and disseminates systematic reviews of healthcare interventions, and promotes the search for evidence in the form of clinical trials and other studies of the effects of interventions. This organization was named *The Cochrane Collabration* in honour of Archie Cochrane (1909-1988), a British medical researcher who contributed greatly to the development of epidemiology as a science. The organisation benefits from thousands of contributors worldwide, working collaboratively from many independent groups of people. For this reason, the term "collaboration" is used. Members of the organisation work together to provide evidence to help practitioners make decisions about health care. The Cochrane Collaboration publishes *Cochrane Reviews* and aims to update them regularly with the latest scientific evidence. Cochrane Reviews are needed to ensure that healthcare decisions throughout the world can be informed by high quality research evidence; it has had a real and significant impact on practice, policy decisions, and research around the world, and it follows the EBM guidelines to make good clinical decisions and efficient research protocols.

1.10.3 The CONSORT Statement

To comprehend the results of a randomized controlled trial (RCT) study, readers should understand study design, procedure, statistical analysis, and data interpretation. This goal can be achieved only through complete transparency in reporting rehabilitation studies. Despite several decades of educational efforts, the majority of the reports of RCTs has been of low quality (Moher et al., 2001). Recent methodological analyses indicate that inadequate reports and design are associated with biased estimates of treatment effects and that such systematic error seriously damage the RCTs; in fact, systematic error in RCTs reflects poor science, and poor science damages proper ethical standards (Altman et al., 2001). For these reasons, in 1993, 30 experts including medical journal editors, epidemiologists, and methodologists met in Ottawa (Canada) with the aim of developing a new scale to assess the quality of RCT reports. One of the results of the meeting was the Standardized Reporting of Trials (SORT) Statement. This Statement consisted of a 32-item checklist and flow-chart diagram, for reporting the various aspects of conducted RCTs. Parallelly to the SORT Group, another group of experts, the

Asilomar Working Group on Recommendations for Reporting of Clinical Trials in the Biomedical Literature, met in Asilomar (California, USA) to eloborate on similar questions. This group also published a proposal which included a checklist of recommended items for authors to consider when reporting RCTs. Subsequently, representatives from both these groups met in 1996 in Chicago (Illinois, USA) to merge the best of the SORT and Asilomar group proposals into a single, coherent evidence-based recommendation. The result was the Consolidated Standards of Reporting Trials (CONSORT) Statement (Begg et al., 1996). Further meetings of the Group in 1999 and 2000 led to the publication of the revised CONSORT Statement in 2001, and following a meeting in January 2007, a further revision is underway.

The checklist items of the revised CONSORT Statement are concerned with reporting the contents of the Title, the Abstract, the Introduction, the Methods, the Results, and the Comments (i.e, conclusions). The revised checklist includes 22 items selected, because empirical evidence indicates that not reporting the information is associated with biased estimates of treatment effect or because the information is essential to judge the reliability or relevance of the findings (Moher et al., 2001). Therefore, the revised CONSORT Statement is an evidence-based, minimum set of recommendations for reporting RCTs, which offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting and aiding their critical evaluation and interpretation. The CONSORT Statement provides a flow diagram depicting information from 4 stages of a trial (enrollment, intervention allocation, follow-up, and analysis) and explicitly includes the number of participants, according to each intervention group included in the primary data analysis. In sum, the CONSORT Statement is intended to improve the reporting of RCTs, enabling readers to understand all parts of a clinical trial and to assess the validity of its results.

Although the main CONSORT Statement is based principally on the two-group parallel design, there are several different types of randomized trials, some of which have different designs, data, and intervention methodologies. In fact, non-pharmacologic treatments (NPT), such as surgery, neurorehabilitation, and behavioural interventions remain suboptimal respect to the main CONSORT Statement. To help improving the reports of these non-standard trials, the CONSORT Group has been involved in extending and modifying the main CONSORT Statement for application in these various areas. This extension of the CONSORT Statement for

RCTs of NPT built upon the CONSORT checklist, takes into consideration specific issues when assessing NPT, such as difficulties in obtaining a double-blind intervention, the complexity of intervention, and the influence of care providers' expertise (Boutron et al., 2008b).

1.10.4 Critical thinking about Cochrane

The aims of the Cochrane Collaboration are to make readily available up-to-date, accurate information about the effects of health care, to produce and disseminate systematic reviews of health care interventions, and to promote the search for evidence in the form of clinical trials and other intervention studies. However, systematic reviews are criticized for frequently offering inconsistent evidences and absence of straightforward recommendations (Browman, 1999). Their value seems to be depreciated when the conclusions are uncertain or based on less than the highest grading of evidence (Egger, Smith, & Phillips, 1997). Moreover, both readers and authors of systematic reviews usually, but erroneously, use to conceive "absence of effect" or "absence of differences between treatments", instead of "there is insufficient evidence either to support or to refute" (Alderson & Chalmers, 2003), or simply indications such as "this treatment seems to have harm effects".

El Dib, Atallah, and Andriolo (2007) analysed the conclusions of a group of selected reviews and allocated the conclusions to one of six categories describing the implications for practice and research, as follows:

1. **beneficial interventions**, for which the authors did not recommend further research (treatment is more beneficial/effective than control for the primary outcome);

2. **interventions likely to be beneficial**, for which the authors recommended further research (treatment may have a positive effect, but a major unresolved methodology issue, such as all studies being very low quality, or findings based on only one study, precluded making a definitive statement);

3. **harmful interventions**, for which the authors did not recommend further research (treatment damages the target functions);

4. **interventions likely to be harmful**, for which the authors did suggest more research (treatment may have a negative effect, but a major unresolved issue, such as all studies were of very low quality or findings were based on only one study, precluded making a definitive statement (see Ezzo et al., 2001);

5. **insufficient evidence,** for which the authors did not suggest further research

(there was insufficient evidence to assess effectiveness, but should be difficult to do further research without ethic problems);

    6. **insufficient evidence**, for which the authors asked for further research (there is insufficient evidence to assess effectiveness).

The results of the "review of the reviews" study by El Dib et al. (2007) show that the majority of Cochrane Reviews highlight the absence or poor evidence around the questions on health care. Moreover, the Cochrane Systematic Reviews could be split between those studies in which the authors concluded that intervention was beneficial and those in which the evidence neither supported nor refuted the intervention tested. The authors also reported that around half of the reviews analysed in the study (47.83%) did not offer enough evidence for clinical practice.

In only 1.67% of the 1016 systematic reviews analysed, in which the evidence suggested that the interventions of interest were harmful, the authors of the reviews discouraged further research. Overall, in 95.96% of all the reviews analysed, the authors recommended more research. This important finding was similar to that found by Vlassov (2004), who investigated how frequently recommendations such as "more research is needed" were made and how these are related to the results from the reviews. Vlassov evaluated 100 Cochrane reviews and found that 93% of them concluded by making recommendations of this type.

1.11 What about neglect rehabilitation?

As a preliminary consideration, according to Cappa et al. (2005), the present status of studies on the effectiveness of cognitive rehabilitation is unsatisfactory. Cappa et al. (2005) claimed that the standards required for the evaluation of pharmacological and surgical interventions can also be applied to cognitive rehabilitation, but with some basic differences. In particular, it is necessary to show that cognitive rehabilitation is effective not only in modifying the impairment, but also in having sustained effects at the disability level. Unfortunately, the majority of RCTs in this area are of poor methodological quality, have insufficient sample size and/or fail to assess the outcome at the disability level. In general, the latter analysed studies show evidence that cognitive rehabilitation resulted in significant and persisting improvements in performance on impairment level assessments (Cicerone et al., 2005). However, there is insufficient evidence to confirm or exclude an effect of cognitive rehabilitation at the level of disability (Bowen & Lincoln, 2007).

The review by Cappa et al. (2005) shows that several methods of neglect rehabilitation were investigated in level I or II studies. For example, the present evidence confers level A recommendation to visual scanning training and to visuo-spatio-motor training, and level B recommendation to the combined training of visual scanning, reading, copying and figure description; to trunk orientation; to neck muscle vibration; and to forced use of left eye. The use of prism goggles obtains the same level of recommendation for transient effect and level C for long-term effect if used over longer periods. The authors assert that there is enough evidence to award a grade A, B or C recommendation to some forms of cognitive rehabilitation in patients with neuropsychological deficits in the post-acute stage after a brain lesion, although this general conclusion is based on a limited number of RCTs, and is supported by a considerable amount of evidence coming from class II and III studies. In particular, the use of a rigorous single-case methodology should be considered as a source of acceptable evidence in this specific field, in which the application of the RCTs methodology is difficult for a number of reasons related to the lack of consensus on the target of treatment, the methodology of the intervention, and the assessment of the outcomes (Cappa et al., 2005).

The main difficulty of the cognitive rehabilitation approach lies in the highly heterogeneous nature of cognitive deficits. Research in neuropsychology has focused on the assessment of specific, theoretically driven treatments on well-defined areas of impairment, usually by means of single-case methodology. At the present, both approaches represent potentially good ways for research in this field. Future studies should also aim at a better clinical and theoretical definition of inclusion criteria used for selecting patients.

Patients with unilateral neglect were studied principally because their damaged brain should reveal some important information about the functional architecture of the normal functioning brain. In this way, the theoretical importance of unilateral neglect led to a disproportionate amount of basic research into this phenomenon, with respect to clinical applied research. As a matter of fact, as with all advances in health care, these treatments will require funds to be implemented and specific abilities to do research in the clinical field. Rehabilitation has suffered in many parts of the world because it is labour intensive, difficult, and because its evidence base has been lacking (Robertson, 2002). In fact, according to Bowen and Lincoln (2007), most reports of the effectiveness of rehabilitation techniques have been based on single-case

experimental designs, rather than RCTs (Lincoln, 1995), even if unilateral neglect rehabilitation is probably the cognitive area in which most RCTs have been conducted and contains some of the oldest rehabilitation RCTs (e.g., Weinberg, 1977). Some studies have shown positive results of their efficacy, although generalisation of training to untrained situations is rarely examined as weel as the maintenance in the long term of benefits observed in the short term. Thus, it is currently difficult to draw definite conclusions regarding whether patients with neglect benefit from cognitive rehabilitation, or whether specific rehabilitation facilitates independence in activities of daily living (Bowen & Lincoln, 2007).

Bowen and Lincoln (2007) reviewed studies to determine the persisting effects of cognitive rehabilitation specifically aimed at spatial neglect following stroke, as measured on impairment and disability level outcome assessments and on destination on discharge from hospital. They included RCTs of cognitive rehabilitation and excluded studies of general stroke rehabilitation, and studies with mixed patient groups, unless more than 75% of their sample were stroke patients or separate data for stroke patients were available. The authors reported that cognitive rehabilitation did improve performance on some, but not all, standardised neglect tests. For example, the number of cancellation errors was reduced and the ability to find the midpoint of a line improved immediately and persisted at follow up. These effects appeared likely to generalise from the samples studied to the target population, but were based on a small number of studies. Based on these results, the authors concluded that several types of neglect-specific treatments are now available, but there is insufficient evidence to support or refute their effectiveness at reducing disability and improving everyday independence. Although the review found that rehabilitation specifically targeted at neglect appeared to improve a person's ability in completing tests such as finding visual targets and marking the mid-point of a line, however its effect on their ability to carry out a meaningful everyday task or to live independently was not clear. In summary, the benefit of cognitive rehabilitation for unilateral spatial neglect is unclear; patients with neglect should still continue to receive general stroke rehabilitation interventions, but better quality research is needed to identify optimal treatments.

Beyond the Cochrane Collaboration, several investigators (Calvanio, 1993; Gianutsos, 1991; Robertson, 1990) have reviewed interventions that have been designed specifically to improve cognitive functioning following stroke and other

forms of neurological damage. They concluded that there is now growing evidence that such interventions may produce a beneficial effect across a variety of cognitive deficits. Nevertheless, the definition of a treatment's effectiveness does not describe the causal mechanism of the effects (i.e., improving or worsening), but indicates "only" that there is or not an effect of the treatment.

1.12 Neglect rehabilitation treatments: an overview

Robertson and Murre (1999) have proposed a distinction between bottom-up and top-down processes in rehabilitation. According to these authors, bottom-up processes refer to the provision of perceptual, motor, or other externally generated or cued inputs to the lesioned brain network. On the contrary, top-down processes are based on experimental findings indicating that brain areas subserving higher cognitive functions (e.g., the frontal lobes and the thalamus) play a role in determining what sensory information is selected for further processing. In general, top-down therapies require patient agency and taking an active role in implementing new learned cognitive strategies to compensate for spatial bias (Làdavas, Menghini, & Umiltà, 1994). However, an obvious prerequisite for such training is that patients have awareness of their deficits. The frequent association of unilateral neglect and anosognosia may limit the utility of top-down therapies for many individuals. On the contrary, bottom-up methods are more passive and require less active patient participation. Such strategies aim to reconfigure or enhance processing of external stimuli, potentially through modulation of biased spatial representations (Pierce & Buxbaum, 2002). Out of the theoretical considerations, data suggest that combining both top-down and bottom-up interventions may act synergistically and all cognitive rehabilitation treatment share, at least in part, bottom-up and top-down components. Therefore, a strict distinction between these two methods is not useful.

Some studies (e.g., see Drevets et al., 1995; Meyer et al., 1991) suggest that attention and alertness, both requiring internally generated processes, enhance brain activation in response to sensory input. Robertson and Murre (1999) argued that synaptic activity, which forms the basis for plastic changes in the brain, is principally modulated in a top-down fashion by frontal attentional circuits. According to this line of thinking, recovery of function should be, at least in part, related to the integrity of frontal attentional brain systems. An obvious implication of these findings is that impaired attention may impede neuroplastic changes during recovery, and that efforts

to improve attention may have widespread positive impact on recovery of a variety of functions, not just attention per se (Sohlberg & Mateer, 2001).

Over the past 60 years, many different rehabilitation techniques or treatments have been put forward to alleviate, reduce, or remediate left unilateral neglect (Luauté et al., 2006). Early treatment approaches for unilateral neglect were mainly based on clinical experience and were less theory-driven than more recent approaches to the rehabilitation of the syndrome (Robertson, 1999). However, in the past recent years a variety of different theory-driven techniques has been used to modulate neglect, based on specific theories that aim to understand the underpinnig mechanisms of cognitive functioning.

Many treatments for unilateral neglect syndrome have been developed since the first years of the XXth century. In the following session the main rehabilitation methods will be described, focusing particularly on the three rehabilitation methods used in the present study (i.e., visual scanning training, limb activation treatment, and prismatic adaptation).

1.13 Foremost rehabilitation treatments for unilateral spatial neglect

1.13.1 Caloric vestibular stimulation (CVS)

Caloric vestibular stimulation is a routine diagnostic technique used by neurologists to assess vestibulo-proprioceptive functioning. The technique involves the irrigation of the controlesional ear canal with cold water and/or the irrigation of the ipsilesional ear canal with warm water. In health individuals, the stimulation of the ear canal produces a vestibulo-ocular reflex in which the gaze in the slow phase of the nystagmus is directed controlesionally, whereas in the fast phase is directed ipsilesionally. Head turning is also induced in the same direction as the slow phase of the nystagmus. These automatic responses are mediated by vestibulo-spinal activity.

Rubens (1985) was the first to conduct a systematic research on the effectiveness of CVS in neglect patients. This author tested 18 patients suffering from left-sided visual neglect during the acute phase (i.e, during the first two weeks from the onset of the lesion) following a right-hemisphere stroke. He obtained a number of measures, including the patient's direction of gaze, their capacity to point to and count people standing around the bed, their ability to read and visually cross lines placed at the patient's bedside, immediately before, during, and immediately after CVS treatment. Results showed a significant improvement on the part of all patients who had a brisk

vestibulo-ocular response in their ability to direct their gaze to the left side of space. However, after about 5' from the end of stimulation, gaze direction and signs of unilateral neglect returned to pre-stimulation levels.

A number of more recent studies have also investigated the effects of CVS on left unilateral neglect following right brain damage. For example, Cappa, Sterzi, Vallar, and Bisiach (1987) and Rode et al. (1992) showed that following CVS patients with unilateral neglect experienced a significant decrease of anosognosia, somatoparaphrenic delusions, and left-sided personal neglect. These effects of CVS on tasks that do not involve visuo-spatial control were confirmed by Geminiani and Bottini (1992) and Rode and Perenin (1994) who used tasks that require representational imagery (i.e., creating a mental image of a familiar scene).

Taken together, studies investigating CVS have provided evidence to suggest that this technique represents an effective way to ameliorate, although only transiently, contralesional visuo-spatial deficits that apply to extrapersonal, personal or representational space and also to somatosensory deficits.

1.13.2 Optokinetic stimulation (OKS)

Optokinetic stimulation is based on visual stimuli (randomized allocated dots or vertical stripes) on a background, all moving coherently leftward or rightward at the same velocity in the horizontal plane. This optic flow induces an automatic response of the eyes (optokinetic nystagmus), consisting of a slow phase coherent with the direction of the stimulation and a fast phase in the opposite direction. The first study to examine the effects of OKS in right brain-damaged (RBD) patients was conducted by Pizzamiglio et al. (1990). These authors sought to investigate the effects of shifting the spatial coordinates of healthy controls, RBD patients without neglect, and RBD patients with neglect, by exposing them to OKS. Pizzamiglio et al. measured the displacement of the subjective midpoint produced by a moving background while subjects conducted a line bisection task in which they were asked to simply mark the midpoint of a visually presented line. The results showed that all groups bisected toward the direction of OKS. However,, RBD patients with neglect were more susceptible than the participants of the other two groups to the influence of the OKS. In addition, in RBD patients with neglect, the displacement toward the right side tended to be greater than the displacement toward the left side. Similarly, OKS towards the contralesional hemispace transiently reduce the size of an object as well

as the space distortions (Kerkhoff, 2000), and temporarily reduces tactile extinction (Nico, 1999).

In a subsequent series of studies, Vallar et al. (1993a, 1995a), examined the effects of OKS on position sense in RBD patients with left neglect (RBDN+ patients), RBD patients without left neglect (RBDN− patients), and left brain-damaged patients without neglect (LBD patients). Results from these studies showed that OKS did affect the position sense of only the RBDN+ group. Moreover, position sense errors were reduced with movement in the leftward direction, while movement in the rightward direction induced a decline in performance.

Karnath (1996) also examined the effects of OKS on pathological perception of body position in space. Three patients with right hemisphere damage and unilateral neglect were asked to direct a laser pointer to the position which they felt exactly "straight ahead of their body's orientation". Results demonstrated that without stimulation all three patients mislocated the sagittal midplane of their bodies to the right of the objective midpoint. However, while undergoing OKS, the subjective horizontal displacement of the sagittal midplane was reduced only after leftward OKS. On the contrary, performance worsened following rightward OKS. Bisiach, Pizzamiglio, Nico, and Antonucci (1996) suggested that the transient effect of OKS on unilateral neglect, may simply reflect a temporary suppression or mitigation of neglect signs without restoring the underlying spatial representation of the patients (i.e., restoring the neural circuits involved to a normal functional level).

However, based on the positive, but transient effects of OKS, Kerkhoff (2001) and Kerkhoff et al. (2006) tested whether repetitive OKS (R-OKS) could provide long term positive effects in patients with left unilateral neglect. These authors reported an improvement in neuropsychological tests after five sessions of leftward OKS (45' each) delivered over a period of two weeks and this improvement remained stable after two weeks from the end of the treatment. In the study by Kerkhoff et al. (2006) the improvement after leftward OKS, observed in different tasks (cancellation, reading, and visuo-spatial tasks) as well as to different input/output modes (i.e., visuoperceptual vs. visuomotor line bisection), was found to be more efficient than conventional visual scanning training, realized using a static visual display.

Considered together, studies investigating OKS have provided evidence to suggest that this technique represents an effective way to ameliorate, or reduce, contralesional visuo-spatial and tactile deficits, also in the long term (i.e., two weeks

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after the end of the treatment; Kerkhoff et al., 2006).

1.13.3 Trunk orientation (TO)

Trunk orientation (TO) has been proposed as another method by which one's egocentric reference frame can be displaced in healthy individuals or transiently realigned in neglect patients while performing various visuo-spatial tasks (Bradshaw, Nettleton, Pierson, Wilson, & Nathan, 1987; Chokron & Imbert, 1995). The use of TO is based on the notion first proposed by Ventre, Flandrin, and Jeannerod (1984) that external objects in space are represented in terms of an internal egocentric reference frame that is aligned along the longitudinal axis of the body. Such a definition based on egocentric reference frame divides the corporeal and extracorporeal spaces into left and right hemispaces (Jeannerod, 1988; Jeannerod & Biguer, 1987). To evaluate the effects of TO with respect to displacements in the egocentric reference frame commonly observed in neglect patients, Karnath et al. (1991) manipulated TO relative to the head position of patients with neglect studying saccadic reaction times (SRT). The aim of their study was to examine whether the midline of the trunk and/or head serves as a plane for dividing space into a "right" and "left" sector, creating the basis for the controlateral vs. ipsilateral division of space. Four neglect patients, four left brain-damaged patients, and 13 healthy participants were studied. The subject's trunk and head were either rotated together, or the trunk was rotated 15° to the left or right relative to the position of the head. In the other condition, the subject's head was rotated 15° left or right relative to the trunk. The results of this study showed that when head, trunk, and visual fields were aligned and corresponded to the middle of the projection screen, SRTs were longer in the left visual field compared to the right visual field. However, the left visual field deficit could be compensated for by solely turning the trunk of the patients to the left (with the head stationary), whereas turning the head to the left side (with the trunk stationary) did not compensate for the left visual field deficit. No significant effects were found for the control groups.

A similar result was obtained by Schindler and Kerkhoff (1997) with five patients with left visual neglect in line bisection and reading tasks in five conditions: head and trunk straight ahead, head or trunk oriented 20º to the left and head or trunk oriented 20º to the right, while participants fixated straight ahead. In all neglect patients, turning the head or trunk to the left reduced line bisection and reading errors

significantly, as compared with the other three conditions and with the control groups. However, compared to the study by Karnath et al. (1991), the visuo-spatial deficit in neglect patients was reduced to a similar degree by head or trunk rotation to the left during gazing straight ahead.

In a recent study, Saj et al. (2008) investigated the influence of changing body orientation in the sagittal plane on the subjective straight ahead (SSA) in 21 patients with right hemispheric lesion, of whom 12 had neglect, in comparison with six healthy participants. In order to quantify both horizontal components of SSA error (i.e., yaw rotation and lateral shift), the study used a method requiring the alignment of a luminous rod with SSA. The authors reported that neglect patients showed a significant rightward shift in the sitting position, which was greatly reduced in the supine position. No shift occurred in patients without neglect or in controls. The data showed that the body centred frame of reference, mostly translated in neglect, is strongly improved in the supine position thus changing body orientation seems to be a convenient tool to correct the representation of body midline.

Taken together, these results support the view that space representation may be modulated by both head and trunk position and that unilateral neglect may be a deficit involving also egocentric longitudinal coordinates.

1.13.4 Neck muscle vibration (NMV)

In neurologically healthy individuals (NHI), precise information about muscle length is signaled via the discharge rate of muscle spindle afferents. Moreover, when a muscle or its tendon are vibrated, the afferent discharge of the muscle spindle increases. This increased firing rate is interpreted subjectively by the proprioceptive system as a lengthening of the muscle, even if muscle length remains constant. Under such conditions, NHI displace to the left of their subjective midline when asked to stop the displacement of a point straight ahead (Karnath et al., 1993). Based on the illusory effects of NMV observed, some authors have proposed that this illusional effect may reflect an ipsilesional displacement of one's egocentric visuo-spatial frame of reference (Karnath et al., 1993; Chokron & Imbert, 1995; Schindler & Kerkhoff, 1997; Vuilleumier et al., 1999). More specifically, it was hypothesized that left NMV should improve left visuo-spatial neglect in right brain damaged (RBD) patients displacing the egocentric coordinates frames to the left respect to the body midline. Such a leftward displacement during vibration would run counter to the rightward

pathological displacement of these egocentric coordinates following a right hemisphere lesion (Karnath et al., 1993; Vallar et al., 1995b).

Karnath et al. (1993) tested this hypothesis in three RBD patients with neglect, five left brain damaged (LBD) patients and 15 non brain-damaged dermatological patients. The procedure used in this study was the same as that described in Karnath et al. (1991) (see the above session on "trunk orientation" for details); in addition to trunk orientation, they tested the effect of left and right NMV, and compared each experimental condition to three control conditions: baseline (no vibration, no rotation), left hand vibration, and turning the head 15° to the left. Posterior neck muscles were vibrated during a visuo-spatial detection task. With regard to RBD patients with neglect, results demonstrated an improvement in the neglect patients' performance, both while turning the trunk and vibrating left neck muscle, that seemed independent of the presence of a conscious illusion of movement and displacement of the visual stimuli. Although the compensatory effect of the vibration could be seen in all three patients, only one reported a visual illusion. Curiously, there was no worsening of the deficit in left neglect patients either when the trunk was rotated to the right or when right neck muscles were vibrated. According to the authors, these findings indicate that trunk rotation and neck muscle vibration may act on left neglect signs by manipulating the position of the egocentric reference frames via proprioceptive inputs.

A recent study by Johannsen, Ackermann, and Karnath (2003) showed positive effects of neck muscle vibration alone. The authors reported that after a 20'/diem for 10 days, six patients with unilateral neglect improved in cancellation tasks and the improvement was stable after 1.4 year (on average) the end of the treatment.

Considered together, these studies investigating NMV have provided evidence to suggest that this technique represents an effective way to reduce (in one case also in the long term; Johannsen et al., 2003) contralesional visuo-spatial deficits, assessed by cancellation tests, visual detection, and straight ahead judgements.

1.13.5 Transcutaneous electrical neural stimulation (TENS)

On the same theoretical principle of neck muscle vibration technic, Vallar et al. (1995b) tested the effect of transcutaneous electrical neural stimulation (TENS) in patients with unilateral left neglect. This stimulation technique provides a somatosensory input to the vestibulo-proprioceptive system. The main clinical

application of TENS has been for pain relief. Vallar et al. (1995b) hypothesized that if TENS increased proprioceptive inputs through large diameter afferent axons, this type of stimulation should have positive effects on deficits of left unilateral neglect. In this study, 14 neglect patients performed a letter cancellation task while applying TENS to neck muscles. The results show that 13 patients improved when the left neck muscle was stimulated, even when head movements were prevented by a chin-rest. Conversely, stimulation of the right neck had no positive effect, or worsened exploratory performance. In a subsequent study, Vallar et al. (1997) tested the effect of TENS on contralesional tactile perception deficits, in ten right brain damaged (RBD) patients and four left brain damaged (LBD) patients. Transient somatosensory improvement was reported after stimulating contralesional neck in all RBD patients, both with and without left somatosensory neglect, and in one LBD patient with right somatosensory neglect. In three LBD patients without neglect, the treatment had no significant effects and in one RBD patient stimulation of the ipsilesional neck temporarily worsened the somatosensory deficit.

In the line with the studies using neck muscle vibration, TENS may modulate somatosensory input to the vestibulo-proprioceptive system improving the representation of egocentric spatial coordinates.

1.13.6 Sustained attention training (SAT)

Robertson et al. (1995) developed a technique, the sustained attention training (SAT), which involves the interaction of two functionally distinct attentional systems with reciprocal connections: arousal and selective spatial attention (Heilman et al., 1987). According to Posner and Petersen (Posner & Petersen, 1990), three inter-related mechanisms, operating semi-autonomously, underlie attention in humans. These mechanism are: orienting, selection, and alerting/sustained attention. The alerting/sustained attention is a system for sustaining a preparation to respond to stimuli in the absence of salient or novel external stimuli which engage attention automatically. According to Posner and Petersen (1990), the right hemisphere seems to be specialised for sustained-attention-type tasks. Nor-epinephrine (NE) may be the neurotransmitter responsible for sustained attention. Therefore, the posterior attention system can be influenced both by its own mechanisms as well as by the modulatory effects of a right-hemisphere dominant, NE-based, alerting/sustained attention system (Robertson et al., 1995). Thus, improving sustained attention would improve

unilateral neglect. In fact, right parietal-damaged patients show relatively intact phasic attention, but their ability to self-alert is impaired.

Robertson et al. (1995) trained patients to verbally self-regulate their attention through "self-instructional training". This training consisted of "talking through" the task using a series of metacognitive instructions, and gradually teaching patients to begin to use these same instructions on their own, to modulate self attention and behaviour. Finally, these instructions became covert, self-initiated, metacognitive schemata which were used by the patients to regulate their own attention during problem solving and in everyday life. Robertson et al. (1995) tested eight right brain-damaged patients all of whom had suffered from unilateral neglect for at least three months. The training was done in the context of a number of tasks requiring vigilance, including sorting coins, sorting cards, or sorting shapes of different colours, sizes, and forms. Six measures were given repeatedly over baseline and training periods. These included two measures of sustained attention, two of neglect, and two of control functions which were not expected to improve as a result of training. The results showed that all patients improved on both sustained attention and neglect tasks on which they had never been trained, and the duration of these effects ranged from 24 hr to 14 days. Within each patient, at least two out of four target measures showed a significant treatment effect, while there was not a significant effect on a control measure.

More recently, Sturm, Thimm, Küst, Karbe, and Fink (2006) investigated the effects of alertness training in patients with unilateral neglect. A three-week computerised alertness training was applied to patients with chronic (> 3 months) stable visuospatial neglect. Training effects were investigated both in a single case and in a group of seven patients by means of neuropsychological tests and functional magnetic resonance imaging (fMRI). The results showed that after the training patients significantly improved on a neglect test battery above any casual fluctuation during a three-week baseline phase. The fMRI data showed improvements in the neglect tasks related to an increase of both right and left hemisphere frontal, anterior cingulated, and superior parietal activation, areas known to be associated with both alertness and spatial attention. Four weeks after the end of the training, the tests' performance of neglect patients returned to baseline. Despite decreases of activation in some of the initially reactivated areas, increases in neural activity bilaterally remained. The authors concluded that the limited stability of the behavioral and

reactivation results over time demonstrates that a three-week alertness training alone does not result in long lasting behavioural improvements and stable reactivation patterns in every patient.

In conclusion, sustained attention training has provided both short and long-lasting effects in patients with neglect as assessed by various neuropsychological tests. Nevertheless, the contrasting data concerning long-lasting amelioration of neglect patients suggest that further studies are required to test the long-term efficacy of SAT.

1.13.7 Space remapping training

Space remapping training is a method which originates from clinical experimental trials. The idea behind this intervention derived from the observation that an elongated stick could produce a virtual extension of body space that resulted in a remapping of far space in near space (Farné & Ladavas, 2000). The principle is to generalize the effect toward the neglected left space. The use of a stick produced an extension of body space resulting in a remapping of "far" space in "near" space.

For example, using virtual reality Castiello et al. (2004) tested this method instructing six patients with left neglect to reach and grasp a real object in the right space, while simultaneously observing the grasping of a virtual object by a virtual hand located in the left space. The virtual hand was commanded in real time by the patients' real hand. The results show that after a period of adaptation, neglect patients coded the visual stimuli within the contralesional space in an identical fashion as those presented within the ipsilesional space. These results, revealing significant improvement in grasping accuracy for the left side of space following specific training, suggest that it is possible to re-create links between contra- and ipsilesional space affected by the neglect syndrome.

1.13.8 Feedback training

Given that left unilateral neglect is commonly associated with anosognosia (i.e., the lack of appropriate awareness of one's own disability), some researchers have suggested the need to alleviate anosognosia before implementing any training procedure (McGlynn & Schacter, 1989). Consequently, specific feedback training procedures were developed involving both bottom-up mechanisms to produce a feedback aimed to restore self awareness and a top-down mechanism to compensate

for neglect behaviour. For instance, Tham et al. (2001) administered a guided interview to four patients with left neglect, during which patient's neglect behaviour was pointed out to him/her in order to increase self-awareness. Improvement of extra-personal neglect was observed in at least three patients. Soderback et al. (1992) video-recorded four patients in order to provide them with feedback of their neglect-related behaviour, before employing a learning strategy. All patients exhibited an improvement in their neglect behaviour as assessed by a cancellation task and three familiar tasks.

Robertson, Nico, and Hood (1995a) asked neglect patients to "grasp and lift" a metal rod at its centre over repeated trials. Significant positive effects were found for 20' after the intervention on two out of four perceptual tests. Harvey et al. (2003) examined the effect of a 3-day experimenter-administered practice of rod lifting and, then, examined the effects of a self-administered practice for a further 2-week period and a further 1 month post-training. The results showed significant improvements of the intervention over the control group for a third of the tests given after the 3-day practice. Additionally, at one-month follow-up, patients with neglect showed significantly better results in 46% of the tests.

Taken together, the short and long-term improvements found after feedback training can be encourage the study of these techniques to ameliorate neglect-related deficits.

1.13.9 Mental imagery training

The mental imagery training was inspired by the representational theory of left spatial neglect (Bisiach et al., 1979). The purpose is to reduce left-sided representational neglect by enhancing or training contralesional mental imagery. In one study, Smania et al. (1997) used visual and movement imagery exercises with two patients with acquired brain injury who suffered from severe and long-lasting unilateral neglect consequent to large cortical and subcortical right hemisphere lesions. The training program consisted of visual and movement imagery exercises. Forty experimental sessions, each lasting 50', were performed. Six neuropsychological tests evaluating unilateral neglect and seven "functional" tests assessing neglect behaviour under daily life conditions were administered. All the measures were recorded at three different times: before, soon after, and six months after the end of the experimental training. The results showed that visuomotor

imagery training ameliorated the deficit in performance related to neglect signs in both patients. Moreover, the improvement was stable over a six-month period, suggesting that the treatment had a long-term effect.

A recent study by McCarthy, Beaumont, Thompson, and Pringle (2002) was designed to investigate whether imagined limb activation would reduce the extent of unilateral left neglect signs in patients with severe disabilities. The authors studied two patients with unilateral neglect who were instructed to image movements of their left or right hand. The results of Patient 1 suggested that imagined activation of the contralateral (left) limb had a significant effect in reducing the impact of neglect on performance. Comparing pre- and post-intervention baselines for the imaging tasks, performance on the post-intervention baseline was better than on the pre-intervention baseline. The results of Patient 2 showed that on none of the tests used were any significant differences between performance in the intervention conditions and in the baseline conditions. It is important to underline that Patient 2 showed a very different pattern of cognitive impairments respect to Patient 1. Overall, the pattern of the results is somewhat mixed but, taken across both participants, it provides some support for the hypothesis that imagined limb activation can positive affect the manifestation of neglect signs. There is also evidence that the effects are specific to the particular limb used, with left-imagined movement reducing the effects of neglect and right-imagined movement exacerbating them.

Other treatments based on the same theoretical approach are required to give more robust indications of real effectiveness of mental imagery training.

1.13.10 Fresnel prisms

Rossi et al. (1990) used Fresnel prisms to investigate whether shifting the left visual field toward the central retinal meridian could reduce left spatial neglect. They randomly assigned 39 patients with stroke and homonymous hemianopia or unilateral visual neglect into the treatment group (wearing 15-diopter plastic press-on Fresnel prisms) or into the control group (without prisms). Baseline evaluations of visual perception and activities of daily living (ADL) were similar for both groups. After four weeks, patients treated with prism performed significantly better than controls on neuropsychological tests.

Although the treatment with 15-diopter Fresnel prisms improved visual perception test scores in patients with homonymous hemianopia or unilateral visual neglect, there is a lack of further evidence.

1.13.11 Eye patching

The eye patching treatment is based on the classic "Sprague effect". In the original study by Sprague (1966), visual impairments in cats were ameliorated by destroying the superior colliculus on the side opposite to the initial visual input. This had the effect of releasing the lesioned hemisphere from the collicular inhibition and thus allowing circuits on the same side as the lesion to function again. Following this principle, several aspects of left unilateral neglect have been improved using patching of the patient's right eye or the patching of the ipsilesional hemiretina of each eye. For instance, Zeloni, Farné, and Baccini (2002) tested patients with right unilateral hemispheric damage identified with neglect; five patients were assigned to the treatment group (T+), whereas six patients were assigned to the control group (T−). The treatment consisted in wearing plastic goggles, similar to common swimming glasses, that were specially modified to ensure long term comfort. The right-sided portion of each lens was "blinded". The vertical border line of this blinded zone was aligned with the vertical meridian of the patient's pupil while looking straight ahead. While patients were wearing these hemiblinding goggles, they had no visual information about the head centred right hemispace. Patients' visuospatial abilities were tested and compared between groups immediately after the week of treatment. Both groups were further assessed one week after treatment for evaluation of long-term beneficial effects. The results showed that following the treatment, a substantial amelioration of visuospatial neglect symptoms was selectively observed in the T+ group. In contrast, untreated patients showed only weak signs of recovery. Notably, the amelioration of the T+ group was not transient, but was maintained after a further period of one week after treatment.

The present and other studies showed that visual neglect can be significantly reduced by "blinding" the patients' ipsilesional hemiretinas. In particular, after an one-week-long visual occlusion of the right hemifield, the improvement was not transient, but was maintained one week after the treatment (Zeloni et al., 2002). However, further evidence is needed to confirm the positive effects found after this treatment .

1.13.12 Repetitive transcranial magnetic stimulation (rTMS)

Following Kinsbourne's model of antagonistic vectors (1987), a competitive relation is assumed to exist between each cerebral hemisphere regarding spatial attention. According to Kinsbourne's model, the rightward bias elicited by the left hemisphere is naturally stronger than that elicited by the right hemisphere. After right brain damage, the inter-hemispheric asymmetry regarding spatial orientation is accentuated, resulting in a dramatic increase of the rightward attentional bias which, is turn, causes left visuo-spatial neglect. Following this hypothesis, some authors investigated whether the inhibition of the relative hyperactivity of the left hemisphere could reduce left unilateral neglect. In a recent study, rTMS delivered at the right posterior parietal cortex induced transitory contralateral visuospatial hemineglect in healthy participants (Fierro et al., 2000). An interesting issue that can be addressed with this method is whether neglect disorders can reflect an imbalance between the bilateral neural processes subserving spatial attention. In a subsequent study, Oliveri et al. (2001) rTMS was applied over the parietal cortex of the unaffected hemisphere at P5 or P6 locations (according to 10/20 EEG system). The stimulated area was checked by means of MRI scans of the unaffected hemisphere. The results of the study showed that transient deactivation of parietal regions of the unaffected hemisphere. induced by focal rTMS, can temporarily reduce contralesional visuospatial deficits both in right and in left brain damaged patients with unilateral neglect. These effects seemed to be limited to the trials following each rTMS train, because the patients' performance during sham rTMS trials was the same as that in baseline trials.

In a similar study, Brighina et al. (2003) treated three right brain damaged patients with left neglect, with rTMS applied over the left posterior parietal cortex for two weeks. Patients performed a computerized task requiring length judgement of prebisected lines. Neglect patients were administered the task 15 days before the rTMS treatment, at the beginning of the rTMS treatment, at the end of the rTMS treatment, and 15 days after the end of the rTMS treatment. The results showed that rTMS induced a significant improvement of visuo-spatial performance that remained quite unchanged 15 days after the end of the rTMS treatment.

Taken together, these results show that transient deactivation of parietal regions of the unaffected hemisphere, induced by focal rTMS, can reduce visuo-spatial neglect deficits.

1.13.13 Transcranial direct current stimulation (tDCS)

Non-invasive brain stimulation using magnetic or electrical instrument has been investigated as a means of modulating cortical excitability. Transcranial direct current stimulation (tDCS) is a painless, non-invasive brain stimulation technique that can be used to induce polarity-specific excitability changes in the brain. The effect of tDCS brain polarization varies depending on the polarity of the electrode. It is known that anodal polarization increases cortical excitability, while cathodal polarization decreases it. Recent studies have demonstrated that anodal polarization increases the excitability of the motor, visual, and prefrontal cortices, improving motor skills (Boggio et al., 2006), working memory (Fregni et al., 2005), and verbal fluency (Iyer et al., 2005).

In a recent study, Ko et al. (2008) investigated the effect of anodal tDCS brain polarization of right parietal cortex on visuospatial scanning in patients with unilateral neglect. Patients performed two tests for assessing neglect (figure cancellation and line bisection) before and immediately after anodal tDCS or sham stimulation. The results showed that the use of anodal tDCS, but not sham stimulation, led to significant improvement in both neglect tests as assessed by the percent of leftward deviation and the number of omissions.

In a more recent study, Sparing et al. (2009) investigated the behavioural effects of tDCS in both neurologically healthy people and patients with left unilateral neglect. The authors applied anodal, cathodal, or sham stimulation for 10' to the left or right posterior parietal cortex of participants. In the experiment with patients (n = 10), both the inhibitory effect of cathodal tDCS applied over the unlesioned posterior parietal cortex and the facilitatory effect of anodal tDCS applied over the lesioned posterior parietal cortex reduced signs of unilateral neglect.

These new findings suggest that tDCS applied over the posterior parietal cortex, both lesioned and unlesioned, may be used to modulate visuospatial processing in patients with unilateral neglect and this positive effect may influence the recovery of interhemispheric reciprocal networks.

1.13.14 Functional electric stimulation (FES)

Eskes, Butler, McDonald, Harrison, and Phillips (2003) replicated the previous findings on the therapeutic effects on unilateral neglect of active and passive left limb movement (Robertson & North, 1992; Robertson et al., 1992; Robertson & North,

1994; Frassinetti, Rossi, & Làdavas, 2001) with a new application, the functional electrical stimulation (FES) which is used to facilitate, enhance, or act as a substitute for muscle contraction after a central nervous system lesion (Benton, Baker, Bowman, & Waters, 1981; Singer, 1987). In this study, the visual scanning ability of a group of patients with neglect was investigated during active movement, passive movement, and no movement conditions. During passive movement, the authors administered the FES.

Nine patients with right-hemisphere stroke who showed left unilateral neglect were treated with FES. During the no movement condition, patients were instructed to sit with their hands in their lap and to find and read aloud all of the numbers and letters printed on a sheet in front of them within 2'. In the active movement condition, participants were instructed to place their left hand on a mouse placed in the left hemispace and to press the switch on the mouse twice to stop an ongoing auditory signal while continuing to complete the target-detection task. Finally, in the passive movement condition limb movement was obtained using FES which stimulated the finger extensors of the left forearm; participants were instructed to complete the target-detection task and ignore the stimulation.

The results showed that FES-stimulated, passive and active movement significantly improved left-sided visual scanning performance, but not the right-sided performance, in patients with unilateral neglect. For the passive movement condition, a positive effect on left-side target detection was seen in 6 of 8 patients, with an overall improvement in group performance of 17.8% relative to the no movement condition. For the active movement condition, a positive effect was obseved in 2 of 3 patients, with an overall improvement of 17% in left-sided target detection.

A subsequent study by Harding & Riddoch (2009) reported the first data on the long-term effects of FES on patients with unilateral neglect. The authors employed a number of different measures to evaluate the effects of passive hand movement and, in addition, to evaluate the effects of FES applied to the ipsilesional forearm muscles in order to establish whether positive effects in the reduction of neglect could be attributed to passive movements to the contralesional arm or to more generalised arousal effects resulting from the electrical stimulation.

The initial baseline lasted four weeks. The first treatment phase consisted of the application of FES to the ipsilesional forearm muscles, and lasted three weeks. FES was then applied to the contralesional forearm muscles in the second treatment phase

which lasted four weeks. Follow-up assessments were performed four and 24 weeks after treatment. Four patients with unilateral neglect were treated twice a day for 20', for 5 days per week.

The results, although not clearly reported, showed that three of the four patients responded positively to the FES treatment, showing good amelioration of neglect signs and also making a good physical and functional recovery. In these patients, FES may have boosted the activation of the impaired proprioceptive map in the right parietal lobe. Related also to the previous study (Eskes et al., 2003), FES-stimulated passive left-limb movement and active left-limb movement are of potential therapeutic benefit in improving visual scanning and leftward attention in patients with neglect. Nevertheless, other studies with large population of unilateral neglect patients are needed to test the efficacy of this technique.

1.13.15 Pharmacological treatment with dopaminergic agonists

Different pharmacological treatments have been used to ameliorate neglect signs. Dopamine-agonists have been shown to ameliorate patients' perfomance on tests of unilateral neglect, such as line bisection, letter cancellation, and reading (Fleet et al., 1987, Hurford et al., 1998; Geminiani et al., 1998; Mukand et al., 2001). Conversely, Grujic et al. (1998) reported a worsening of contra-lesional visual exploration in five neglect patients treated with Bromocriptine, a dopamine antagonist. Supporting evidence for the use of dopamine-agonists comes from the observation that damage to anatomical structures reported to result in left unilateral neglect may be related to a common dopaminergic bond (Fleet et al., 1987). Hurford et al. (1998) and Grujic et al. (1998) justified the use of this neurotransmitter given its implication in perceptual attentional systems. For Geminiani et al. (1998), dopamine-agonists have a potentially therapeutic utility because this medication could improve the pre-motor component of unilateral neglect.

1.13.16 Pharmacological treatment with noradrenergic agonists

A noradrenergic agonist (i.e., Guanfacine) has been recently used in three patients with left unilateral neglect (Malhotra et al., 2006), on the basis of the hypothesis that this neurotransmitter might modulate non-spatial attentional processes which have been shown to interact with spatial components of neglect (Husain & Rorden, 2003). The two patients who showed improvement on paper and pencil tasks

as well as on visual exploration had a lesion which spared the dorso-lateral, pre-frontal cortex. This was not the case for the other patient who did not improve follwing the treatment with Guanfacine.

1.14 Studies employing combined technics

There is no doubt that the development of knowledge concerning how to treat left unilateral neglect has suggested the implementation of new strategies and rehabilitation approaches. Even if it has been principally demonstrated "short-lasting" effects after the end of treatment, recently it has been suggested again the idea that combining different rehabilitation methods may increase the effectiveness of treatment. In fact, at least in some cases, there are some evidences of the therapeutic effects of combined methods suggesting that rehabilitation treatment may be more effective than one alone. Butter and Kirsch (1992, Experiment 2) tested a group of patients (n = 18) with left unilateral neglect in a line-bisection task, using monocular patching and/or lateralized visual stimulation. Each procedure (i.e., monocular patching or lateralised visual stimulation) resulted in a substantial increase of patients' performance in line bisection, but the combination of the two procedures (i.e., monocular patching and lateralised visual stimulation) resulted in significantly larger benefits than either of these techniques used separatelly.

In more recent studies, the effectiveness of combined treatments has been also reported. For example, Schindler, Kerkhoff, Karnath, Keller, and Goldenberg (2002) evaluated the effects of visual scanning training (VST) alone and in combination with neck muscle vibration (NMV), in a crossover study of two matched groups of 10 patients with left unilateral neglect. Each group received a sequence of 15 consecutive sessions of VST and a combined treatment (VST + NMV). The effects of treatment were assessed with respect to different neglect signs, such as impaired perception of the egocentric midline, exploration deficits in visual and tactile modalities, and visual size distortion. The transfer of treatment effects to activities of daily living was examined by a reading test and a questionnaire of neglect-related, everyday problems. All dependent variables were measured six times: three baseline measurements, two post-treatment measurements, and one follow-up after two months from the end of the treatment. The results showed better effects of the combined treatment (i.e., VST + NMV) than those of the VST alone. A specific and lasting reduction in the signs of unilateral neglect was achieved in the visual mode and was transferred to the tactile

mode with a concomitant improvement in activities of daily living. Notably, the improvement was still evident two months after the completion of the treatment. In contrast, VET alone resulted in only minor therapeutic benefits in visual exploration without any significant transfer of the obtained effects to other tasks.

In a very recent study, Polanowska, Seniów, Paprot, Leśniak, and Czonkowska (2009) investigated the therapeutic effectiveness of VST and left-hand TENS compared to that of VST alone. The patients (n = 40) were randomly assigned either to the experimental (E) or the control (C) groups. Patients of group E were treated with VST combined with left-hand TENS, whereas patients of group C were treated with VST and a sham stimulation of left-hand TENS. Patients were assessed twice, prior to the rehabilitation programme and after its completion, using cancellation tests and a letter-reading task. The effect of TENS on unilateral neglect was assessed following a single administration and after a month-long rehabilitation programme. Although the immediate effect of stimulation was poor, after a month-long rehabilitation period the authors found significantly greater improvement in group E patients than in group C patients.

Schröder, Wist, and Hömberg (2008) evaluated the effectiveness of three treatments of unilateral neglect by comparing their outcomes in three groups of patients. One group received VST alone, whereas the second and third groups received VST combined with either TENS) or OKS, respectively. The results showed that VST alone resulted in no improvement of both standard neglect tests and everyday-relevant measures of reading and writing. In contrast, the groups receiving VST+TENS or VST+OKS showed significant improvements in both sets of measures with the difference that for the TENS group the improvement in neglect tests scores at the end of therapy had disappeared one week following the end of the treatment. However, both treatments resulted in significant improvements in reading and writing, which were still present upon retesting one week after the end of the treatment.

The study by Pizzamiglio, Fasotti, Jehkonen, Antonucci, Magnotti, Boelen, and Asa (2004) was the first to report no effects of a combined treatment. These authors investigated whether it is possible to strengthen the rehabilitation of unilateral neglect by combiing VST with OKS. A simple randomized design was used: one group of neglect patients was treated with a combination of the two techniques (VST + OKS), and a second group received only the VST. Both treatments were six weeks long and

produced significant improvements. However, the addition of the OKS did not further improve patients' performance. In spite of these negative results, the authors reported that clinical observation suggests that individual patients benefit strongly, at least for a few sessions, of the addition of OKS.

Finally, a recent study by Keller, Lefin-Rank, Lösch, and Kerkhoff (2008) investigated whether the combination of pursuit eye movements training during OKSP and prism adaptation (PA) can lead to greater improvement of unilateral neglect signs than the application OKS alone. In addition, the effect of ipsilesional arm movements during OKS was tested. Ten patients with left unilateral neglect were studied between 2 and 4.5 months after their stroke. Each patient received four different single-session treatments (each lasting 30'): VST, OKS, OKS in conjunction with PA, and OKSP in conjunction with ipsilesional arm movements. Left unilateral neglect was assessed before and immediately after each treatment, using standard neglect tests. The results showed that VST improved neglect signs only slightly; single OKS stimulation led to a significant improvement in all neglect tests; OKS in conjunction with PA was superior to the VST alone, in the cancellation task; and the OKS in conjunction with arm movements worsened neglect signs in all tests. A comparison between these treatments indicated that the best improvements can be achieved using OKS without any additional treatment. The preliminary results of this study suggest that OKS significantly reduces symptoms of visuospatial neglect within 1 treatment session, whereas it is foundamental not performing ipsilesional movements during OKS treatment.

Although there are some unquestionably positive results, the studies reported above clearly show that not always the combination of rehabilitation treatments is the best way to progress in rehabilitation practice. Probably, the major problem is that the assessment, the neuropsychological tests, and the methods to plan a rehabilitation protocol are far from being homogeneus. Thus, it is difficult to consider the results of the available studies as a standard to guide treatments effectively improving patients with left unilateral neglect. Moreover, only few studies clearly reported the long-term effects of treatments, leaving opened questions about the argument.

1.15 Rehabilitation treatments for unilateral spatial neglect: summary

It is difficult both to reconcile any of the hypotheses underlying what we already know about unilateral neglect and to find an explanation that fits all the reported

effects of stimulations. In fact, the mechanisms underlying these stimulations are still greatly unknown. The understanding of the processes underlying the positive and/or negative effects may be helpful in defining the levels of impairment in patients with left unilateral neglect and in designing rehabilitation techniques with long-lasting positive effects. According to Kerkhoff and Rossetti (2006), animal experiments, functional imaging studies, and longitudinal outcome studies suggest that injured brain can change their function and connectivity, both on the behavioural and neural level, and both spontaneously as well as in response to specific treatments. However, many questions in this context still remain open. First of all, it would be interesting to understand what these stimulations share with other techniques that have also been reported to decrease left neglect signs. Moreover, as pointed out by Kerkhoff (2003), given the large cortical and subcortical network involved in spatial neglect, the search for multimodal effective treatments is probably the future direction in rehabilitation. In the same way, in addition to testing new therapeutical tools, researchers could also design longitudinal studies where long-lasting effects of experimental stimulations, as well as the natural course of the deficits, can be more thoroughly studied. In fact, it is not convincing the approach to combine different additive techniques, seeing that there is no such knowledge of how a single treatment works. Furthermore, the possibility of the better efficacy of certain treatments with respect to others during acute stages versus in the chronic stages should be explored. Advances in anatomical knowledge are likely to inspire and guide the development of such studies. New neuroimaging techniques, such as diffusion tensor imaging, are now shifting the focus from the prevalent consideration of cortical modules, to that of large-scale brain networks and of their white matter connections (Catani, 2006). Finally, the link between the cerebral activation and the effect of these stimulations should be exhaustively studied.

1.16 Neglect treatments we used: literature's review and description of functioning

1.16.1 Visual Scanning Training (VST)

In the early 1970s, visuo-spatial neglect was initially considered a deficit of left side visual exploration and hence the focus on visual scanning training (VST) was to bring about a re-orientation of visual scanning toward the neglected side by means of

a training program based on providing explicit instructions to help direct the patients voluntary gaze control.

The first attempt of active intervention on unilateral neglect deficits was reported by Lawson in 1962. His approach consisted in retraining patients' ability to read by directing their attention toward the left part of the stimulus material either with the use of "strong" sensory signals (e.g., a flashlight) or by "semantic" information (e.g., verbal commands to look toward the left side when the verbal content of the sentence lacked congruity). After treatment, improvements were observed in patients' reading ability. Conversely, no clear changes were observed in other visuo-spatial abilities (e.g., copying of drawing; Lawson, 1962).

In the following years, several authors have developed more systematic progressive training programs, based on the principles of ''anchoring, pacing, density, and feedback'' (Diller & Weinberg, 1977). For example, visual anchors involving visual cues, such as a coloured line, were located on the left part of the page and the patient was asked to look at the coloured line before starting the exercises (e.g., Weinberg et al., 1977). Using this paradigm, several studies reported a significant improvement of neglect signs as assessed by simple paper and pencil tasks, both in group studies and in single case reports, even though some studies reported significant changes following treatment, but only for the specific tests on which patients were trained (e.g., Gouvier, Bua, Blanton, & Urey, 1987; Wagenaar, Van Wieringen, Netelenbos, Meijer, & Kuik, 1992).

Webster et al. (1984) noted that results based on group comparisons may mask considerable individual differences in recovery. Following this observation, Pizzamiglio et al., (1992) examined the performance of unilateral neglect patients using a within-subjects design (13 patients). The authors examined the performance of unilateral left neglect patients before and after VST, and in a follow-up evaluation at least five months after the end of treatment (7 of 13 patients were tested). The training program comprised four different procedures:

       1) visuo-spatial scanning (searching for numbers in a large visual field);

       2) reading and copying;

       3) copying of line drawings on a dot matrix;

       4) figure description.

All these procedures required the patient to actively and sequentially scan various parts of the visual field in order to produce the correct response. In the execution of

the training program, some general criteria were followed, such as a slow and progressive variation of the elements of the task, and the extensive use of stimulations in different sensory modalities, slowing reduced when the patient progressively developed autonomous compensatory strategies. The entire procedure was continued for 40 sessions (five sessions a week, for eight consecutive weeks). In general, at the end of VST all patients showed a varying lack of awareness of their exploration disorder before and during the early stages of the training procedure. In all the four VST procedures, patients showed rapid improvement in the first week, followed by slower acquisition and occasional periods in which a decrease in performance was observed, often in conjunction with medical problems. After four or five weeks of VST, most, but not all patients showed considerable improvement. Statistically, the effectiveness of VST was evaluated by comparing the patients' performance before and after treatment on the various diagnostic tests. In general, the VST used in the present study showed considerable effectiveness in reducing unilateral neglect deficits; these improvements occurred in patients whose condition had substantially stabilized. However, large individual differences were present. For instance, nine patients showed consistent increases in their ability to scan the stimulus materials, whereas the other four patients showed very little changes or even a slight decrease in performance. In general, the performed follow-up testing on seven patients (after at least five months post training) showed no consistent neuropsychological differences compared with the post-test scores, indicating a long-time stability of the improvements acquired during the treatment. However, some inter-individual variability was observed; patients displaying large improvements or very small changes during training maintained their perfromance at the follow-up examination. To summarize, a general positive effect of VST was observed, both in the post-test and at the follow-up evaluations. Nevertheless, individual patients' scores showed some small increases (or decreases) between the pre- and post-test evaluations, and at the follow-up. Moreover, in comparison with marked improvement in a variety of situations which require space scanning, patients showed very small changes in a variety of tasks requiring visuo-spatial abilities. In contrast, a positive result was obtained in the extension of exploratory improvements to functional situations by means of the analysis of the patient's performance in standardized situations similar to those of real life (e.g., see Zoccolotti & Judica, 1991).

To conclude, Pizzamiglio et al. (1992) showed that VST can be an effective rehabilitation treatment, with improvement observed both in neuropsychological tests and in activities that simulate those of daily living.

In the study by Pizzamiglio et al. (1992) a within-subjects paradigm was used. In a sabsequent study, Antonucci et al. (1995) aimed to replicate the positive results obtained by Pizzamiglio et al., using the same rehabilitation treatment (i.e., visual scanning treaning) in a randomized group study. Twenty patients participated in the study. Patients were classified as having unilateral neglect when their scores were below the cut-off scores in three out of four tests of a standard neglect battery. The battery included the Letter Cancellation Test (Diller, Ben Yishay, Gerstman, Goodkin, Gordon, & Weinberg, 1974), the Barrage Test (Albert, 1972), the Sentence Reading Test (Pizzamiglio, Judica, Razzano, & Zoccolotti, 1989), and the Wundt-Jastrow Area Illusion Test (Massironi, Antonucci, Pizzamiglio, Vitale, & Zoccolotti, 1988). Patients were assigned in two groups. The first group (the *Immediate training* group; IT) received the conventional VST (Pizzamiglio et al., 1992) immediately after the first administration of the test battery. The second group (the *Delayed training* group; DT) received a general cognitive intervention after the first administration of tests. After to months of cognitive intervention, the DT also received conventional VST for the same period as the IT group. The DT group was tested three times: at T1 (first neuropsychological assessment), at T2 (after general cognitive intervention), and at the end of VST. The IT group was tested two times, one after the first neuropsychological assessment and one at the end of VST. Both groups of patients were also administered the Semi-structured scale for the functional evaluation of extrapersonal neglect (Zoccolotti & Judica, 1991) before and after VST. For both the IT and the DT group, the VST was admnistered for eight consecutive weeks, five days a week, one hour a day, The analysis of simple effects showed that the general cognitive intervention had no effect in the DT group, and that VST had a significant effect in the IT group. Moreover, a subsequent comparison between the pre- and the post-treatment performance with VST in the DT group showed a significant improvement in all sub-tests of neglect battery. Interestingly, both the IT and the DT groups improved their performance on the Semi-structured scale for the functional evaluation of extrapersonal neglect following VST. These results confirm the effectiveness of neglect rehabilitation using VST, compared to a general cognitive stimulation procedure. In fact, the performance of the DT group did not improve

following general cognitive stimulation. The authors concluded that, in general, these data are consistent with the observation that unilateral neglect does not spontaneously recover in the subacute and chronic phase (Zoccolotti et al., 1989). This is assumed by the fact that the lack of improvement in the DT group during non-specific treatment cannot be attributed to the simple presence of cognitive stimulation: in fact, the DT group showed positive changes when it was provided with VST at the end of the first two months. The positive results founded in the Semi-structured scale for the functional evaluation of extrapersonal neglect (Zoccolotti & Judica, 1991), were in contrast with those of other studies, where in some cases improvements were specific for material similar to that used during the training and where no generalization to untrained situations was reported (e.g., see Robertson, Gray, Pantland, & Wite, 1990; Wagenaar, Van Wieringen, Netelenbos, Meijer, & Kuik, 1992; Halligan, Donegan, & Marshall, 1992). Antonucci et al. suggested that this apparent inconsistency can be understood by considering the relatively short training period used in those studies (one to two weeks of duration). In fact, according to these data, studies obtaining improvement in both trained and untrained tasks typically used a considerably longer period of training, lasting from five to eight weeks of consecutive treatment. To conclude, according to Antonucci et al. (1995), systematic VST is a productive way of achieving significant and functional improvements in the treatment of unilateral neglect, both immediately after training and also in the logn term (about five weeks after the end of the treatment). Improvement can be observed both on neuropsychological tests and measures of everyday activities (e.g., the Semi-structured scale for the functional evaluation of extrapersonal neglect; Zoccolotti & Judica, 1991). Therefore, the duration and the structure of the training may be important conditions for determining rehabilitation outcome.

In summary, from the early studies of Weinberg et al. (1977) attempted to behaviourally compensate for patients' deficits in visuo-spatial scanning abilities by teaching them to reorient the sight toward the left, variations of this procedure and extensions of the design were explored by other authors (e.g., Antonucci et al., 1995; Gouvier, Bua, Blanton, & Urey, 1987; Gouvier, Cottam, Webster, Beissel, & Wofford, 1984; Pizzamiglio et al., 1992; Young, Collins, & Hren, 1983). In spite of a significant positive outcome in many of the initial studies, a review of the literature shows that treatments gains tended to be limited on test materials similar to the

training materials (Robertson, 1992). However, this might be due to the short duration, frequency, and intensity of these treatments (see Antonucci et al., 1995).

1.16.2 Limb Activation Treatment (LAT)

In 1991, Halligan, Manning, and Marshall reported the performance in line bisection of a patient with left unilateral neglect. At the time of testing, the patient had a complete left visual field deficit, but only a very slight left hemiparesis. Under conventional testing conditions, the patient performed line bisection better using his right hand than he did using his left hand. However, this pattern of performance had been modified, both quantitatively and qualitatively, by changing the starting position of the patient's hand when bisecting horizontal lines. Halligan et al. (1991) attributed this advantage of contralesional arm use in reducing neglect signs to a spatio-motor cueing process than by contralateral lesioned hemispheric activation.

Based on the assumption that activation of the left limb in the left hemispace induces changes in lateral attention or spatial representation, in a subsequent series of studies Robertson and colleagues showed that unilateral neglect could be significantly improved, at least in the short term, by inducing patients to execute even small movements with some part of the left side of their body (Robertson & North, 1992, 1993, 1994; Robertson et al., 1992, 1994).

In a first series of studies, Robertson and North (1992, 1993, 1994) showed that when patients moved their left hand in the left hemispace, the total number of omissions in visual exloratory tasks was reduced. The authors found that neglect on cancellation and reading tasks decreased significantly when patients performed the task while moving their left hand in the left hemispace. The same result was not observed neither when the left arm of the patient was moved passively by the experimenter (Robertson & North, 1993) nor in other experimental conditions: on cancellation tests, the total number of omissions did not decrease when the patient moved his left hand in the right hemispace or the right hand in the left hemispace (Robertson & North, 1992). Similarly, reading errors were not reduced by bilateral movements of the hands, executed simultaneously on both the left and the right side of space, or on either the left or the right side of space (Robertson & North, 1994). As a general result, a significant reduction of unilatarel left neglect occurred only when three conditions were simultaneously accomplished: active unilateral movement (1) of the left limb (2) in the left extrapersonal space (3). Interestingly, the same result was

observed even when the patient could not see his own moving hand (Robertson & North, 1992), suggesting the specific effect of left limb activation, instead of a visual cue effect, in reducing unilateral neglect signs. In fact, visual cues are often reported to reduce neglect (Riddoch & Humphreys, 1983; Halligan et al., 1991), but they seem not to be as effective as active movements of the left upper limb. Robertson and North (1992), indeed, did not observe any improvement on letter cancellation when the patient was instructed to gaze, at regular intervals, towards an irrelevant stimulus placed in the left hemispace. As observed by Cubelli et al. (1999), the beneficial effect of the movements of the left hand is quite different from the spatio-motor cueing described by Halligan and Marshall (1989) and Halligan et al. (1991), who found that the use of the left arm reduced neglect in cancellation and line bisection tasks. In the latter case, patients performed tasks requiring a motor response, by using their non-dominant arm, contralateral to the brain lesion. On the contrary, in the studies by Robertson and North (1992, 1994), patients performed all tasks in the standard way, by responding orally (i.e., reading tasks) or by using their right dominant hand (i.e., cancellation tasks).

It is important to note that the previous findings from the Robertson and North's studies, derived from only one patient. In all their experiments, they tested the same patient, TD, a 62-year-old right-handed man who suffered two consecutive strokes in the right cerebral hemisphere. It could be that the facilitation effect of unilateral motor activation was peculiar to TD and might not be detectable in other patients. Robertson and North (1994) tested a second patient, HS, but they could only partially replicate their previous findings. Like TD, HS also showed the greatest benefit from left movement in the left hemispace. However, compared to the baseline performance, neglect decreased in all conditions requiring associated limb movements.

In a following study, Cubelli, Paganelli, Achilli, and Pedrizzi (1999) tried to replicate the experiments of Robertson and North, in order to verify the real effectiveness of limb activation in a group of ten unilateral neglect patients. The authors conducted three experiments. Experiments 1 and 2 were similar to that of Experiment 1 by Robertson and North (1994), whereas Experiments 3 was instead similar to that of Experiment 3 by Robertson and North (1992). Experiments 1 and 2 comprised reading numbers and letters on a A4 sheet of paper, whereas the test used in Experiment 3 was the Letter Cancellation Test by Diller and Weinberg (1977). At a group level, the results showed a significant interaction (space x condition) in

Experiment 2, but not in Experiments 1 and 3. The analysis of individual data showed that the expected pattern of results was present only in the performance of one patient, in all three experiments, confirming the previous results reported by Robertson and North with patient TD. Such a result suggests that the positive effect of limb activation is not task-dependent and reflects a general improvement of spatial exploration. On the light of these results, Cubelli et al. (1999) concluded that even if the active movement of the left hand can improve spatial exploration, only a reduced number of patients benefit from this treatment.

To fill the lack of evidence of LAT effectiveness at group level, Robertson, McMillan, MacLeod, Edgeworth, and Brock (2002) conducted the first RCT study with LAT using a semi-automatic device with a new, more effective set of characteristics than the one used in the previous single-case studies. Nevertheless, to exclude the possibility of non-specific placebo bias (i.e., effects obtained by solely the novelty of the apparatus), they studied two groups of neglect patients, who both received a standard perceptual training protocol (i.e., a version of the VST): one group was treated only with VST, the second group was treated with the VST in combination with LAT. Therefore, this study evaluated the additional effects of LAT, not the effects of LAT alone.

Forty patients were randomly assigned to the experimental treatment group (LAT+VST; n = 19), or to the group considered as control (VST only; n = 21). Of these patients, 36 were followed up at three months, and 32 of these were followed up at six months. A further 26 patients were followed up at 18-24 months, 11 from the LAT+VST group and 15 from the VST group.

The presence of left unilateral neglect was documented by a score of 51 or less in the Star Cancellation sub-test of the Behavioural Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987), or a score of 7 or less on Line Bisection sub-test of the BIT, with at least two of the three lines bisected to the right of the centre. Each group received the same number of sessions, about 45' a day, once a week, for 12 weeks. Patients in both groups were received the same VST procedure. The only procedural difference between the two groups was the neglect alert device (NAD): patients in the LAT+VST group had the NAD attached to them, and were instructed about limb activation movements; patients in the VST group had an inactive NAD attached to the left side of their body to control for simple cueing effects of having a stimulus present on their left hemibody.

The VST treatment consisted of a number of exercises taken from a workbook of occupational therapy. It included training in perceptually organized reading and writing tasks, large-print crosswords, puzzles, dominoes, and in playing cards. For all duration of the treatments, patients were encouraged to scan the material starting from the left side and to continue scanning to the left while performing the task.

The VST was applied identically to patients in the LAT+VST group. In addiction, patients of this group were also treated using the NAD. The NAD consisted of a device attached to the left hemibody (wrist, leg, or shoulder). The device was programmed to emit a tone if no movement was made within a set period of time. If the patient did not perfom a movement, the device produced a sound and the patient was compelled to move the left part of his body to end the sound. In this study the period of time before the tone was emitted could be set between 2 and 120 s, depending on the patient and on the part of the body that was used.

Three tests were carried out at intake and at all follow-up periods to evaluate the effectiveness of rehabilitation:

1) Barthel Scale of functional independence (Mahoney & Barthel, 1965);

2) the Caterine Bergego rating scale of unilateral neglect (Azouvi et al., 1996);

3) the Motricity Index of limb function (Collen & Wade, 1990)

Other three tests were carried out only at the first three follow-up evaluations (up to 6 months):

1) the Behavioural Inattention Test (BIT; Wilson et al., 1987);

2) the Comb and Razor Test of personal neglect (Beschin & Robertson, 1997);

3) an adapted version of the Landmark Test (Milner, Brechmann, & Pagliarini, 1992)

The results showed that only motor function (scores at the Motricity Index of limb function; Collen & Wade, 1990) of the left arm and leg selectively improved after treatment in the LAT+VST group, with a duration of the beneficial effects over 18-24 months follow-up; no significant differences were obtained in the other tests.

The results did not show the positive effects reported in the previous single-case studies (Robertson & North, 1992, 1993, 1994), except for motor functions. Based on these results, Robertson et al. (2002) suggested that if LAT were used more intensively in a clinical setting (e.g., for 1-2 hours per day rather than for a short

period each week) over a period of 3 months, then even greater improvement in functional status following right hemisphere stroke would have been observed.

In summary, the practical implications of Robertson and North's (1992, 1993, 1994) studies concern cognitive and motor rehabilitation, as it has been emphasized by several authors (Driver, 1994; Riddoch et al., 1995). In treating neglect, requiring unilateral movements of the hemiparetic limb seems to induce enduring improvements (Robertson et al., 1992). The relevance of Robertson and North's (1992, 1993, 1994) studies is therefore remarkable. However, the partial positive results derived from the application of this method in two group studies (Cubelli et al., 1999; Robertson et al., 2002) raised new questions about the effectiveness of this treatment, which still need an answer.

1.16.3 Prism Adaptation (PA)

In the last few years, it has been shown that unilateral neglect can be ameliorated by a treatment based on prism adaptation (PA) (Farnè, Rossetti, Toniolo, & Ladavas, 2002; Frassinetti, Angeli, Meneghello, Avanzi, & Ladavas, 2002; Rossetti et al., 1998). Prismatic lenses induce an optical deviation toward the ipsilesional side (i.e., rightward for unilateral left neglect patients) as demonstrated by a rightward error in limb pointing to a visual target. If the upper limb is visible, patients perform a motor correction toward the contralesional side (i.e., leftward for unilateral left neglect patients) to compensate for the prism effect. Thus, the initial displacement of the visuo-motor behaviour is corrected through visuo-motor adaptation (i.e., an error reduction appears). When the prismatic goggles are removed and the limb pointing to the visual target is not visible, patients show a systematic leftward deviation of visuo-motor response with the limb, the so-called *after-effect*.

In a pioneering study, Rossetti et al. (1998) measured the performance of a group of patients with unilateral left neglect on standard neuropsychological tests (e.g., line bisection, line cancellation, drawing, reading) before and after a brief period of exposure to a prism-induced 10º rightward displacement of the visual field. Compared with a control group of neglect patients exposed to neutral (sham) goggles, patients treated with prisms showed significant improvement in their post-exposure performance. This improvement in performance remained stable when patients were tested two hours after the end of the adaptation procedure.

After this pioneering study by Rossetti et al. (1998), which was the first to described the effects of PA on neglect, some other studies were conducted to evaluate possible long-lasting effects of PA to ameliorate unilateral neglect signs in clinical settings.

In neglect patients this after-effect is accompanied by improvements in numerous tasks such as straight ahead pointing (Pisella et al., 2002), visual exploration toward the left contralesional space (Ferber et al., 2003), contralesional somato-sensory perception (McIntosh et al., 2002; Maravita et al., 2003; Dijkerman et al., 2004), temporal order judgment (Berberovic et al., 2004), visuo-verbal tasks (Farnè et al., 2002), wheel-chair driving (Jacquin-Courtois et al., 2008), postural control (Tilikete et al., 2001), and imagery (Rode et al., 1998b, 2001b; Rossetti et al., 2004).

Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas (2002) conducted the first study in which PA was employed as a daily treatment to evaluate its long-lasting effects in unilateral neglect patients. The primary aim of their study was to evaluate whether the short-term amelioration found after PA (e.g., Rossetti et al., 1998) could be converted into a therapeutic intervention resulting in long-term improvement.

Frassinetti et al. (2002) studied 13 patients with right hemisphere lesion and left unilateral neglect, subdivided in 2 groups: the experimental group (EG; n = 7) received PA treatment, whereas the control group (CG; n = 6) received general cognitive stimulation.

Unilateral neglect was assessed with the following neuropsychological tests:

    1) the Behavioural Inattention Test (Wilson et al., 1987)

    2) the Bells Cancellation Test (Gouthier et al., 1989)

    3) a reading test (from Làdavas et al., 1997a)

    4) a modified version of the Fluff Test (Cocchini et al., 2001)

    5) a room description test

    6) an object reaching test

The EG received PA treatment in two daily sessions (ten-20' sessions a week), over a period of 2 weeks, for a total of 20 sessions. The CG performed the neuropsychological tests the same times as the patients in the EC.

The results showed that 20 training sessions induced long-lasting improvement in unilateral neglect that was maintained for at least five weeks after the end of the treatment. The improvement found after PA was consistent across a wide variety of visuo-spatial tasks. Indeed, it was apparent in each of the test considered, which

assessed different visuo-spatial abilities. Amelioration of performance was also observed in other more ecological tests, such as room description and objects reaching. In fact, a significant improvement after PA training was found in far space (room description test) and in near space (object reaching test and paper-and-pencil tests); nevertheless, the amelioration of unilateral neglect in personal space (fluff test) was less evident. In contrast, neglect signs were not ameliorated in the the CG.

Although the PA treatment was effective in most patients of the EG, the authors reported that one patient did not show improvement. Anyway, taking together these results showed that two weeks of training with prismatic lenses can induce long-term improvement of neglect. Moreover, PA also can result in a generalized beneficial effect both in the near (i.e., peripersonal) and in the far (i.e., extrapersonal space).

In a subsequent study by Serino, Bonifazi, Pierfederici, and Làdavas (2007), the effectiveness of a neglect treatment based on PA was studied with three main aims:

        1) to replicate the previous findings about long-term effects of PA and to investigate whether the improvement can persist until six months after the end of the treatment;

        2) to investigate whether the PA treatment effects were generalized to different visuo-spatial functions (exploration of personal and extrapersonal space), sensory modalities other than vision (i.e., touch and proprioception), and in the motor domain;

        3) to directly test the hypothesis that the index of adaptation effect can discriminate patients who benefit from patients who do not benefit from PA treatment (see also Serino, Angeli, Frassinetti, & Làdavas, 2005).

Twenty-one right-brain-damaged patients with chronic left unilateral neglect participated in the study. Patients were selected on the basis of their defective performance in at least one visuo-spatial neglect score of the BIT (Conventional or Behavioural scale; Wilson et al., 1987). All patients were assessed with the following neuropsychological tests:

        1) the Behavoural Inattention Test (BIT; Wilson et al., 1987);

        2) the Bells Cancellation Test (Gauthier et al., 1989);

        3) a room description test (see Frassinetti et al., 2002);

        4) a reading test (Làdavas et al., 1997b);

        5) the Fluff Test (Cocchini et al., 2001);

        6) a clinical test for tactile extinction;

7) a scale for proprioceptive sensibility;

8) the Motricity Index (Demeurisse et al., 1980)

Additionally, to evaluate the beneficial effects of PA in the oculomotor responses, patient's eye movements were recorded at different intervals before, immediately after, and at one month after the end of the treatment. Patients were submitted to a rehabilitative programme similar to that used by Frassinetti et al. (2002). The neuropsychological evaluation was performed five times: the first screening assessment (session 1) was administered before the treatment, and the other sessions were performed one week (session 2), one month (session 3), three months (session 4), and six months (session 5) after the end of the treatment. Data from session five were, however, available only for 9 out of 17 neglect patients. The results showed an amelioration of unilateral neglect signs that lasted up to six months after the end of the PA treatment (for at least nine patients). The improvement was found for visuo-spatial abilities and for neglect dyslexia, and was also generalised to the exploration of personal space, to the oculomotor system's responses, and to tactile attention. On the contrary, no effect was found in proprioceptive sensitivity and motor functions. Interestingly, patients showing poor adaptation to prismatic optical displacement during the first week of PA also showed less amelioration of unilateral neglect signs and eye movement recovery.

Although the positive effects following PA treatment, the study by Serino et al. (2007) was carried out without a control group. Thus, studies with a control group were still required.

The first study which evaluate the effectiveness of PA comparing an experimental group with a control group was carried out by Nys, de Haan, Kunneman, de Kort, and Dijkerman (2008). In this study, Nys et al. (2008) examined the effects of repetitive PA procedure comparing the experimental prism treatment with placebo prism treatment. The effects of the repetitive PA were evaluated on a daily basis rather than providing outcome measures only. the authors studied the effects of PA in patients with neglect in a very early phase post stroke (i.e., within the 24 days post stroke). All patients received the first treatment one day after the screening. The PA procedure was a modified version of that employed by Rossetti et al. (1998). The placebo group received exactly the same procedure as the experimental group: patients were indeed instructed with the same pointing instructions, and the same task and stimuli; the only crucial difference was the type of

prism goggles (i.e., goggles with normal, not prismatic lenses). Patients were evaluated for the presence of unilateral neglect using four subtests of the Behavioural Inattention Test (BIT; Wilson et al., 1987):

1) Star Cancellation;

2) Line Bisection;

3) Figure Copying;

4) Drawing on command.

Patients who obtained a score at or below the cut-off on at least two of the four tests were included in the study. The results showed that PA resulted in non-significant differences between performance before and after training on each successive day, indicating that the faster recovery in the experimental group was not due to immediate effects, but to effects of treatment later on. Moreover, the authors did not observe any difference between the control and the experimental group after one month post treatment, suggesting that the control group might show benefits due to the repeated pointing procedure *per se*. However, patients in the experimental group improved faster on line bisection and letter cancellation than patients in the control group. Although reducing neglect in the early phase of stroke might still result in a better outcome in the long term, these data gave modest evidence of the PA effects in the early phase. Nevertheless, an important suggestion was reported: future studies on the effects of neglect treatments and prism adaptation in particular should incorporate an adequate control group in the experimental design.

A subsequent study by Serino, Barbiani, Rinaldesi, and Làdavas (2009) was the first controlled trial study conducted to investigate the effectiveness of PA treatment on neglect recovery in a group of patients, compared to a control group of neglect patients who were treated with an analogous visuomotor training performed without prisms. The aim of the study was to directly compare the effect of PA treatment with that of a treatment based on pointing with neutral goggles (NG). Twenty neglect patients was pseudorandomly subdivided into 2 groups and assigned to either PA or NG treatment. Both treatments consisted of 10 daily sessions (5 session per week). Each session comprised 90 pointing movements towards toward a visual target presented in a variety of positions on the right, left, and the centre of the visual field. Throughout the sessions, patients in the PA group wore prismatic goggles deviating the visual field 10° degrees to the right, whereas patients in the NG group wore goggles with lenses inducing no deviation. At the end of treatment with neutral

goggles, patients in the NG group underwent an additional two-week treatment with prismatic goggles. To test long-term effects of prism adaptation, a follow-up evaluation was performed one month after the last treatment session. Unilateral left neglect was assessed with the Behavioural Inattention Test (BIT; Wilson et al., 1987) and with the Bell Cancellation Test (Gauthier et al., 1989). Neglect dyslexia was also evaluated by using the reading test described by Làdavas et al. (1997). The results showed that the repetition of pointing movements toward visual stimuli improved visuo-spatial performance in both patients treated with PA and with neutral goggles. However, the improvement was significantly stronger when the pointing was performed under the exposure to prismatic goggles: neglect improved more in patients treated with PA than in those treated with neutral goggles. In addiction, the improvement of neglect signs was maintained at least one month after the end of the treatment in both groups of patients, confirming the long-lasting beneficial effects of PA described in previous studies.

Taken together, the aforementioned results undoubtedly support the positive and long-lasting effects of PA on unilateral neglect patients in several paper-and-pencil and more ecological tasks. However, some patients described (Dijkerman et al., 2003; Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003; Frassinetti et al., 2002; Pisella, Rode, Farnè, Boisson, & Rossetti, 2002) do not benefit from PA treatment or the improvement is limited only to some aspects of the syndrome. Moreover, other authors did not find effects of prism adaptation on spatial attention tasks (Morris, Kritikos, Berberovic, Pisella, Chambers, & Mattingley, 2004), and on cancellation and reading tasks (Rousseaux, Bernati, Saj, & Kozlowski, 2006). Finally, at least two studies (Nys et al., 2008; Serino et al., 2009) reported no clinically relevant results about the real effectiveness of PA treatment compared with visuo-motor task treatment without prismatic goggles. Thus, based on this evidence, it is too early to conclude that PA may be the elective treatment in rehabilitation of patients with unilateral neglect (Mattingley, 2002).

In the light of these findings, the present study aimed to consider the evidence of effective cognitive rehabilitation in spatial neglect patients, with a quasi-randomized clinical trial study of cathegory II-1. This study is the first that directly compares three neglect treatments and which evaluates the effectiveness (or the ineffectiveness, or the absence of any effect) of these treatments. Every treatment was guided by the major

neuropsychological neglect theories. Our approach was based on the study of the functioning and disfunctioning mechanisms in neglect patients, to deeply and better understand if a treatment is effective or not, and consequently why. In fact, according to Robertson & Murre (1999), "without understanding how rehabilitation works, the refinement and improvement of rehabilitation methods on scientific principles will be difficult, if not possible".

2. METHOD

2.1 Participants

Twenty-one patients (9 F; mean age = 68.4 years, SD = 11.5; mean education = 8.1 years, SD = 4.1) with right brain damage with left unilateral neglect participated in the study. Patients gave their informed consent according to the Declaration of Helsinki and the hospital ethical committee. Inclusion criteria comprised absence of dementia, substance abuse, and psychiatric disorders. All patients had unilateral lesions due to a cerebrovascular accident, confirmed by Computerised Tomography (CT) or Magnetic Resonance Imaging (MRI) scan. In addition, the presence of visual field deficits was evaluated by means of visual perimetry test. Gender, age, education, length of illness, lesion site, and presence of left visual field deficits are provided in Table 1. All patients were right-handed and had normal or corrected-to-normal vision.

2.3 Neuropsychological assessment

All patients were assessed through a standardised battery of tests for visuo-spatial deficits (BIT; Wilson et al., 1987), the Bell Cancellation Test (Gauthier et al., 1989), a room description test, the Fluff Test (Cocchini et al., 2001), a semi-structured scale for evaluating the patient's ability in situations similar to those of every day life (Zoccolotti & Judica, 1990), and a revised version of the Comb and Razor test (McIntosh et al., 2000). Moreover, a test for motor functions (Motricity Index; Demeurisse et al., 1980) and a the mental number bisection task to assess the representational neglect (Zorzi et al., 2002) were made. In addiction, neuropsychological tests for memory, general cognitive functions, and language were administered: the Mini Mental State Examination (MMSE; Folstein et al., 1975), the test of Verbal Judgements (Spinnler & Tognoni, 1987), the Digit Span (from WAIS-R; Wechsler, 1981), an italian version of the Rey Auditory Verbal Learning Test

(RAVLT; Carlesimo et al., 1996), and the italian version of the Verbal Fluency test (phonemic and semantic parts; Novelli et al., 1986).

Patient	Gender	Age (years)	Education (years)	Onset of illness (months)	Lesion site	Left visual field deficits
LAT1	M	75.3	5	7.1	P	-
LAT2	F	80.1	13	1.6	P-BN	-
LAT3	M	54.7	17	3.2	TPO	+
LAT4	M	39.0	8	3.8	FTP	-
LAT5	F	81.4	17	2.3	----NA----	-
LAT6	F	50.5	8	1.0	CN	+
LAT7	M	72.9	5	2.7	TPO	-
Mean (SD)		**64.8 (16.6)**	**10.4 (5.2)**	**3.1 (2.0)**		
PA1	M	57.3	8	2.4	T-BN	-
PA2	F	74.9	8	1.5	P	-
PA3	M	62.3	5	11.8	FP	-
PA4	M	69.3	8	1.6	FTP	-
PA5	M	69.3	5	2.4	FP	-
PA6	F	58.7	5	7.1	P	-
PA7	F	72.0	5	2.3	TP	+
Mean (SD)		**66.3 (6.8)**	**6.3 (1.6)**	**4.1 (3.9)**		
VS1	M	69.5	13	3.3	BN	-
VS2	M	85.6	5	4.9	FTP	-
VS3	M	60.6	13	1.6	P-LV	-
VS4	F	79.2	3	3.4	TP	-
VS5	F	71.9	5	7.7	BN-LV	-
VS6	F	77.9	8	2.0	MCA	-
VS7	M	74.0	6	2.8	FTP	+
Mean (SD)		**74.1 (8.0)**	**7.6 (4.0)**	**3.7 (2.1)**		

Table 1. Lesion site column reports the cortical and sub-cortical structures involved by the lesion. F = Frontal; T = Temporal; P = Parietal; O = Occipital; BN = Basal Nuclei; CN = Capsular Nucleus; LV = Lateral Ventriculus; MCA = Medial Cerebral Artery. The last column indicates the presence of left hemianopia (+ presence, - absence of hemianopia); NA = data not available.

The neuropsychological evaluation was performed four times (see Fig. 1). The first screening assessment (A1) was to verify the presence and amount of neglect-related deficits and the other cognitive functions; the second assessment (A2, pre-treatment assessment) was carried out to verify the effects of spontaneous neuro reorganization and the effects of the other therapies (e.g., physiotherapy); the third assessment was made 2 weeks after the second assessment (A3, post-treatment) to compare the effectiveness of the treatments (LAT, PA, and VS) each other; and at 2 weeks after the end of treatment (A4, follow-up) served to evaluate the long-lasting effects of rehabilitation treatments.

```
A1                    A2                    A3                    A4
        2 weeks               2 weeks               2 weeks
      pre-treatment          treatment          post-treatment

                              Time
```

Figure 1. Experimental design.

Patients were assessed and performed the rehabilitation treatment at the Neuropsychology Department of IRCCS San Camillo Hospital (Venice-Lido), and were selected on the basis of their defective performance in at least one visuo-spatial neglect score of the BIT (Wilson et al., 1987). Patients were assigned to the rehabilitation group (LAT, PA, or VS group) on the basis of the order of intake in the hospital. A randomized sequence with the order of treatments was made; the sequence remained the same and it was repeated in blokcs (e.g., one block consisted of a fixed sequence: PA, LAT, and VS; the first patient was assigned to the PA group, the second patients to the LAT group, the third patient to the VS group, and so on). Therefore, this is a quasi-randomized controlled trial. All patients of the three groups (LAT, PA, and VS) received the same neurological and neuropsychological assessment according to the rehabilitation protocol. The 2-weeks rehabilitation programme consisted of 20 sessions of 20 minutes each, held 2 times a day, for five days per week.

2.3 LIMB ACTIVATION TREATMENT (LAT)

2.3.1 Apparatus and stimuli

Stimuli comprised printed draws with black lines on a white sheet of paper. The draws were divided in multiple parts, with or without a little black point inside. The task was to colour only the draw's parts with the black point inside. The draws were placed horizontally at the centre of the patient's body midline, one at a time. The draws were presented with the same order for each patient.

2.3.2 Rehabilitation procedure

Training involved the use of a Limb Activation Training Device (LAT-D), a modified version of the original "Neglect Alert Device" (NAD; Robertson et al., 2002). The device consists of a small metal box, roughly 11×6×3 cm, with a switch attached via a

cable. The device can be set such that it emits aloud buzzing noise if the switch is not pressed within a predetermined time interval. A red light is also mounted on the box, which remains on as long as the buzzer is not activated. Patients were required to press the switch to turn off the buzzer during the performance of the draw completion which constituted the rehabilitation programme. This procedure remained equal through all phases of the rehabilitation treatment. The LAT-D was placed on the left side of the table, and the switch was inserted between the left arm and the left side of the patient's trunk. In the first week of treatment, the device was set to emit the buzzing at a fixed interval of 120 sec, whereas in the second week of treatment the device was set at a variable time interval between 5 and 20 sec. When a movement was made, the buzzing stopped, and the LAT-D resetted the timer. If patients did not move within 30 sec during the buzzing, the examiner reminded them to end the buzzing by the arm movement; no other verbal cues was made by the examiner The time interval used was identical from patient to patient. All patients who completed the treatment had sufficient movement of the left arm to start and terminate the rehabilitation protocol. The treatment's duration was fixed in 20 min per session, one in the morning and one in the evening at the same time, when possible.

2.4 PRISM ADAPTATION (PA)

2.4.1 Apparatus, stimuli, and procedure

The procedure was the same used by Frassinetti et al. (2002). Patients performed the task wearing prismatic goggles (Julbo Inc., Williston-USA). The googles were fitted with wide-field, prismatic lenses, inducing a 10° shift of the visual field to the right. Patients were seated at a table and in front of them there was a wooden box (height 30 cm, width 75 cm, depth 34 cm at the centre in front of patient and 18 cm at the periphery). The box was open on the side facing the patient and on the opposite side, facing the examiner. A visual target (a pen) was presented manually by the examiner at the distal edge of the top face of the box. The visual target was presented randomly in one of three possible positions: a central position, straight ahead in front of the patient (0°), and in a lateral position to the left or right of the patient's body midline (−21° and +21°, respectively). The examiner recorded patients' pointing as the distance between the central position of the box (0°) and the final position of the patient finger. A graduated scale (in cm) was used to assess pointing deviation and was recorded manually by the experimenter. Patients were asked to keep their right

ipsilesional hand on their chest, at the level of the sternum (hand starting position) and to point with the index finger towards the pen, without hesitation to obtain a psudo-ballistic movement. No verbal cues about the performance was made by the examiner. The pointing task was performed in three experimental conditions: Pre-exposure (visible and invisible pointing), exposure (visible pointing) and post-exposure (invisible pointing).

2.4.1.1 Pre-exposure condition

Patients were required to point with their right index finger 30 targets randomly presented at one of three possible positions (10 targets in the centre, 10 on the right, and 10 on the left) with visible pointing (i.e., pre-exposure with visible pointing condition, which was the baseline for the exposure condition). Subsequently, patients were required to point with their right index finger other 30 targets randomly presented at one of three possible positions (10 targets in the centre, 10 on the right, and 10 on the left) with invisible pointing (i.e., pre-exposure with invisible pointing condition, which was the baseline for the post-exposure condition).

2.4.1.2 Exposure condition

Patients performed the same task wearing the prismatic goggles (Optique Peter, Lyon). The goggles were fitted with wide-field prismatic lenses inducing a 10° shift of the visual field to the right. Patients were asked to point with their right finger without hesitation to 90 targets presented in a random order in each of the three possible positions (30 targets in the centre, 30 on the right, and 30 on the left). During the exposure condition, the pointing movement was hidden below the top face of the box, apart from the final part of the movement where the index finger emerged beyond the distal edge of the top face of the box (visible pointing) to permit the patient to see his/her finger.

2.4.1.3 Post-exposure condition

Immediately after removal of the prism, patients were required to point towards 30 targets (10 in the centre, 10 on the right, and 10 on the left). The pointing movement was performed entirely below the top face of the box, so that the index finger was not visible at any stage (invisible pointing). All conditions were ran in each session, one

in the morning and one in the evening at the same time, when possible. The treatment's duration was about 20 min per session.

2.5 VISUAL SCANNING (VS)

2.5.1 Apparatus and stimuli

Stimuli were identical to those presented to the LAT group.

2.5.2 Rehabilitation procedure

Patients were required to look at a vertical wide pink strip placed on the left side of the space, exactly on the left edge of the stimulus, before starting the task. During the performance of the draw completion, patients were verbally instructed and encouraged to look at the pink strip every time before to start again a new visual scanning procedure. This verbal cues remained equal through all the phases of the rehabilitation treatment; no other verbal cues was made by the examiner. The treatment's duration was fixed in 20 min per session, one in the morning and one in the evening at the same time, when possible.

3. RESULTS

The results and the statistical analyses of the data are reported test by test, both for groups and single cases. For all neuropsychological tests, a mixed ANOVA was conducted, with assessment (A1, A2, A3, A4) as the within-subjects factor and group (LAT, PA, VS) as between-subjects factors. The dependent variable was the score on each neuropsychological test. The repeated contrast was carried out, to follow-up significant differences. Whenever, the Mauchly's test indicated that the assumption of sphericity had been violated, degrees of freedom were reported using the appropriate test. Single case data were analyzed through the revised standardized difference test (RSDT; Crawford & Garthwite, 2005) that controls for a significant difference between two measures by comparing a control sample and the single patient's performance. In the case of the present study, the "control" group changed analysis by analysis depending on the comparison considered.

A three-way ANOVA was performed to test the homogeneity of clinical and demographic data among the three groups of patients. The assumption of homogeneity of variance was violated for the age and education variables; therefore, the Welch F-ratio is reported. There were no significant effects of age, $F(2, 11.164) =$

2.081, $p = .171$, education, $F(2, 9.658) = 2.036$, $p = .183$, and months since the lesion, $F(2, 18) = 0.243$, $p = .787$, among the three groups.

3.1 Neglect tests for peripersonal space

3.1.1 BIT Conventional (Wilson et al., 1987)

The dependent variable was the total score of the BIT. Mauchly's test indicated that the assumption of sphericity was violated (W = .304, $\chi^2(5) = 19.894$, p < .05), therefore degrees of freedom were corrected using Huynh-Feldt estimates of sphericity ($\varepsilon = 0.772$). The results of the mixed ANOVA revealed a main effect of assessment, $F(2.316, 41.695) = 11.513$, $p < .001$, $\eta_p^2 = .390$, observed power = .995, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 0.944$, $p = .407$, $\eta_p^2 = .095$, observed power = .188, suggesting no difference between the three treatments. Finally, the interaction between the assessment and the group was not significant, $F(4.633, 41.695) = 1.246$, $p = .306$, $\eta_p^2 = .122$, observed power = .382. The repeated contrast for the main effect of assessment indicated a significant difference ($p < .05$) between levels 1 and 2 (A1 and A2, pre-treatment changing), and bwtween levels 2 and 3 (A2 and A3, effect of treatment), but not between levels 3 and 4 (A3 and A4, long-lasting effects). This seems to indicate that patients' condition significantly changed in the period between the first assessment and the second assessment before the treatment. Moreover, there was also a specific effect of the treatment on the patients' performance.
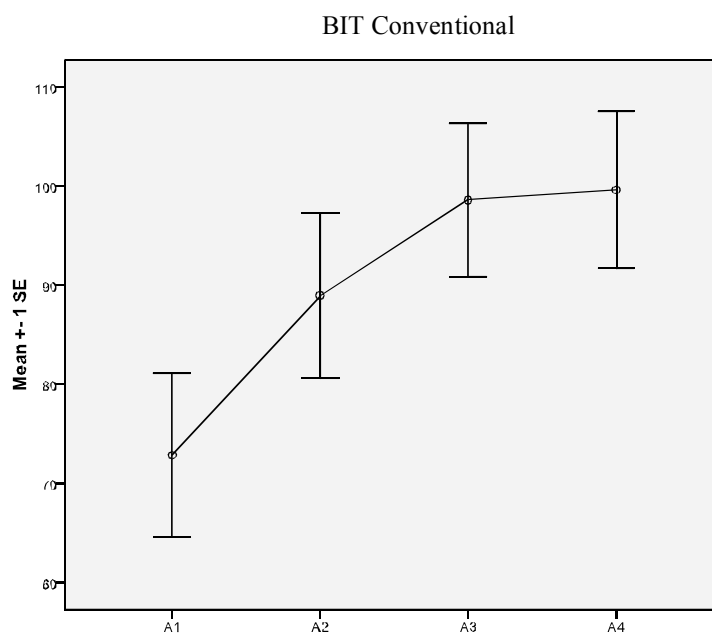
Figure 2a. BIT Conventional score in neglect patients. The graph shows the trend of the mean score throughout the assessments.

The individual analyses showed that in the pre-treatment condition (A2-A1) only one patient (LAT6) improve with respect to the control groups, indicating a personal positive change before the treatment. The comparison between the pre- and post-treatment assessments showed a significant positive difference (improving) for five patients (PA6, VS2, VS6, VS7, LAT3) whereas the performance of three patients declined (VS4, LAT1, LAT7), suggesting that treatments may influence the patients' performance, both in positive or negative ways. Finally, two patients (V2 and VS4) improved in the two weeks after the treatment, compared to both PA and LAT groups, whereas one patient (VS6) worsened, suggesting no lasting effects of treatment.

	BIT CONVENTIONAL								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-	CONTROL GROUP (n=7)			-	$t(6)=4.17$ $p = .006$ (-11)*	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	$t(6)=3.06$ $p = .022$ (+1)	-
LAT4	-	-	-				-	-	-
LAT5	-	-	-				-	-	-
LAT6	$t(6)=2.97$ $p = .025$ (+79)	-	-				$t(6)=2.84$ $p = .029$ (+79)	-	-
LAT7	-	-	-				-	$t(6)=2.76$ $p = .033$ (-4)*	-
PA1	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-			
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1	CONTROL GROUP (n=7)			-	-	-	-	-	-
VS2				-	-	$t(6)=3.95$ $p = .008$ (+25)	-	$t(6)=2.97$ $p = .025$ (+7)	$t(6)=2.69$ $p = .036$ (+25)
VS3				-	-	-	-	-	-
VS4				-	$t(6)=4.38$ $p = .005$ (-56)*	$t(6)=5.52$ $p = .001$ (+42)	-	$t(6)=5.78$ $p = .001$ (-56)*	$t(6)=3.59$ $p = .012$ (+42)
VS5				-	-	-	-	-	-
VS6				-	$t(6)=3.25$ $p = .018$ (+45)	$t(6)=3.46$ $p = .013$ (-27)*	-	-	-
VS7				-	-	-	-	$t(6)=2.96$ $p = .025$ (+15)	-

Table 3. BIT Conventional individual score of neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.2 Line crossing (BIT-C)

The dependent variable was the total score of the line crossing sub-test of BIT-C. The results of the mixed ANOVA revealed a main effect of assessment, $F(3, 54) = 4.470$, $p = .007$, $\eta_p^2 = .199$, observed power $= .855$, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 1.442$, $p = .263$, $\eta_p^2 = .138$, observed power $= .268$, suggesting no difference between the three treatments. Finally, the interaction between the assessment and the group was not significant, $F(6, 54) = 0.299$, $p = .935$, $\eta_p^2 = .032$, observed power $= .124$. The repeated contrasts for the main effect of assessment indicated that there was no significant difference (all $ps > .05$). This seems to indicate that the patients' performance did not significantly change among the assessments.
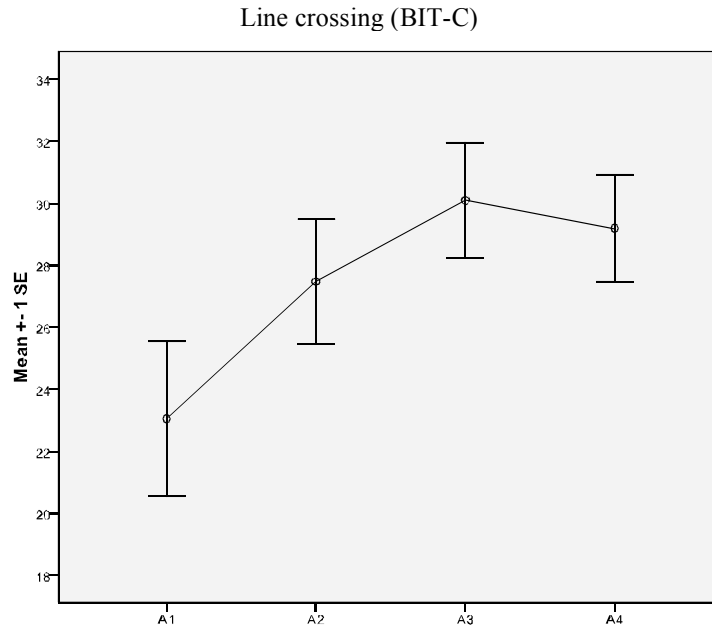
Line crossing (BIT-C)

Figure 3. Line crossing sub-test of the BIT-C score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that in the pre-treatment condition there was no significant difference of the single patients' performance with respect to that of the control groups. The comparison between the pre- and post-treatment assessments showed a significant positive difference (improving) for four patients treated with VS (VS2, VS5, VS6, VS7) and one patient treted with LAT (LAT4) with respect to the PA group, whereas the performance of one patient treated with VS (VS4) and three patients treated with LAT (LAT1, LAT3, LAT7) declined with respect to the PA group, suggesting that VS treatment may influence positively the patients' performance in the line crossing task, whereas the LAT induced a worsening of patients' performance in this task. Finally, two patients (PA4 and VS2) improved the in the two weeks after the treatment, both compared to the LAT group, whereas one patient (PA7) got worse.

	LINE CROSSING (BIT-C)								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	$t(6)=6.88$ $p < .001$ **(-6)***	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-		CONTROL GROUP (n=7)		-	$t(6)=5.94$ $p = .001$ **(-5)***	-
LAT4	-	-	-				-	$t(6)=4.37$ $p = .005$ **(+12)**	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	-				-	$t(6)=5.54$ $p = .001$ **(-7)***	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	$t(6)=3.03$ $p = .023$ **(+11)**		CONTROL GROUP (n=7)	
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	$t(6)=4.27$ $p = .005$ **(-18)***			
VS1				-	-	-	-	-	-
VS2				-	-	$t(6)=3.15$ $p = .020$ **(+13)**	-	$t(6)=3.44$ $p = .014$ **(+3)**	-
VS3				-	-	-	-	-	-
VS4		CONTROL GROUP (n=7)		-	-	-	-	$t(6)=4.54$ $p = .004$ **(-7)**	-
VS5				-	-	-	-	$t(6)=5.61$ $p = .001$ **(+17)**	-
VS6				-	-	-	-	$t(6)=6.01$ $p = .001$ **(+18)**	-
VS7				-	-	-	-	$t(6)=3.08$ $p = .022$ **(+7)**	-

Table 4. Line crossing sub-test of the BIT-C score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.3 Letter cancellation (BIT-C)

The dependent variable was the total score of the letter cancellation sub-test of BIT-C. Mauchly's test indicated that the assumption of sphericity was violated (W = 0.457, $\chi^2(5) = 13.109$, p < .05); therefore degrees of freedom were corrected using the Huynh-Feldt estimates of sphericity (ε = 0.812). The results of the mixed ANOVA revealed a main effect of assessment, $F(2.437, 43.861) = 6.536$, $p = .002$, $\eta_p^2 = .266$, observed power = .927, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 0.954$, $p = .404$, $\eta_p^2 = .096$, observed power = .189, suggesting no difference between the three treatments. Finally, the interaction between the assessment and the group was not

significant, $F(4.873, 43.861) = 1.410$, $p = .240$, $\eta_p^2 = .135$, observed power $= .443$. The repeated contrasts for the main effect of assessment indicate that there was no significant difference ($p > .05$) among the levels. This seems to indicate that patients' performance did not significantly changed among assessments.

Figure 4. Letter cancellation sub-test of the BIT-C score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that in the pre-treatment condition (A1-A2) two patients (PA2 and VS5) worsened respect to the LAT group, indicating a personal negative change before the treatment. On the contrary, one patient (LAT6) improved. The comparison between the pre- and post-treatment assessments (A2-A3) showed a significant positive difference (improving) for only one patient treated with VS (VS7) with respect to the PA group, whereas the performance of two patients treated with LAT (LAT1 and LAT3) and three patients treated with VS (VS2, VS4, VS5) declined with respect to the control groups, suggesting that both LAT and VS treatments may influence negatively the patients' performance in line crossing task, whereas the VS induced an improvement in the performance on this task, only for one patient. Finally, one patient (PA7) improved in the two weeks after the treatment compared to the LAT group.

LETTER CANCELLATION (BIT-C)									
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	t(6)=3.51 p = .013 (-3)*	-				-	t(6)=3.51 p = .013 (-3)*	-
LAT2	-	-	-				-	-	-
LAT3	-	t(6)=4.53 p = .004 (-6)*	-		CONTROL GROUP (n=7)		-	t(6)=4.53 p = .004 (-6)*	-
LAT4	-	-	-				-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				t(6)=2.77 p = .032 (+26)	-	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	t(6)=2.71 p = .035 (-5)*	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-		CONTROL GROUP (n=7)	
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	t(6)=2.66 p = .037 (+15)			
VS1				-	-	-	-	-	-
VS2				-	-	-	-	t(6)=3.19 p = .019 (-1)*	-
VS3				-	-	-	-	-	-
VS4		CONTROL GROUP (n=7)		-	t(6)=3.29 p = .017 (-15)*	-	-	t(6)=5.90 p = .001 (-15)*	-
VS5				t(6)=2.51 p = .046 (-5)*	-	-	-	t(6)=2.74 p = .034 (-3)*	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	t(6)=2.97 p = .025 (+1)	-

Table 5. Letter cancellation sub-test of the BIT-C score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.4 Star cancellation (BIT-C)

The dependent variable was the total score in the star cancellation sub-test of BIT-C. Mauchly's test indicated that the assumption of sphericity was violated (W = 0.471, $\chi^2(5) = 12.577$, p < .05), therefore degrees of freedom were corrected using the Huynh-Feldt estimates of sphericity ($\varepsilon = .933$). The results of the mixed ANOVA revealed a main effect of assessment, $F(2.800, 50.398) = 10.356$, $p < .001$, $\eta_p^2 = .365$, observed power = .996, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 0.754$, $p = .485$, $\eta_p^2 = .077$, observed power = .158, suggesting no difference between the three treatments. Finally, the interaction between the assessment and the group was not significant, $F(5.600, 50.398) = 1.796$, $p = .123$, $\eta_p^2 = .166$, observed power = .600.

The repeated contrasts for the main effect of assessment indicated that there was a significant difference ($p < .05$) only between levels 1 and 2 (A1 and A2, pre-treatment). This seems to indicate that patients' performance significantly changed in the period between the first assessment and the second assessment before the treatment, and that there was no specific effect of treatment on the patients' performance.
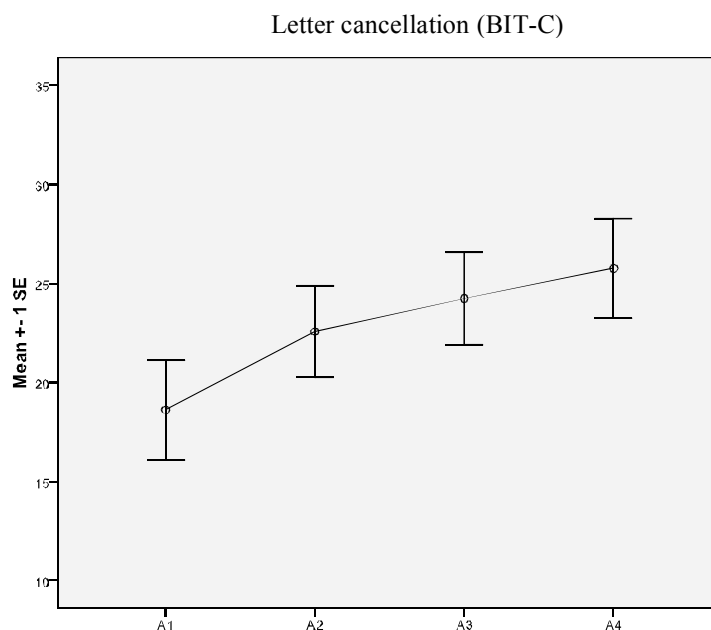
Star cancellation (BIT-C)

Figure 5. Star cancellation sub-test of the BIT-C score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that, in the pre-treatment condition (A1-A2), six patients (LAT2, LAT4, LAT6, LAT and PA2, PA7) improved with respect to the VS group, indicating a positive change before the treatment. Moreover, the performance of one patient (LAT1) declined. The comparison between the pre- and post-treatment assessments (A2-A3) showed a significant positive difference (improving) for two patients (PA6 and VS7) with respect to the LAT and the PA groups, respectively. On the contrary, the performance of one patient treated with LAT (LAT1) and one patient treated with VS (V4) declined with respect to the control groups, suggesting that both LAT and VS treatments may influence negatively the patients' performance in the cancellation, task, whereas PA and VS induced an improvement in the performance on this task only for one patient, respectively. Finally, the performance of two patients (VS4 and VS2) improved in the two weeks after the treatment compared both to the LAT and the PA groups, whereas two patients (LAT1 and PA6) worsened.

Patient	STAR CANCELLATION (BIT-C)								
	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	$t(6)=2.58$ $p = .042$ (-15)*	-	-				-	$t(6)=3.39$ $p = .015$ (-4)*	$t(6)=2.58$ $p = .042$ (-1)*
LAT2	$t(6)=2.83$ $p = .030$ (+13)	-	-				-	-	-
LAT3	-	-	-				-	-	-
LAT4	$t(6)=5.26$ $p = .002$ (+32)	-	-	CONTROL GROUP (n=7)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	$t(6)=4.66$ $p = .003$ (+26)	-	-				-	-	-
LAT7	$t(6)=2.54$ $p = .044$ (+12)	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	$t(6)=4.48$ $p = .004$ (+26)	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-			
PA5	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA6	-	-	-	-	$t(6)=2.84$ $p = .030$ (+23)	$t(6)=2.74$ $p = .034$ (-19)*			
PA7	$t(6)=5.90$ $p = .001$ (+37)	-	-	-	-	-			
VS1				-	-	-	-	-	-
VS2				-	-	-	-	-	$t(6)=2.68$ $p = .037$ (+6)
VS3				-	-	-	-	-	-
VS4	CONTROL GROUP (n=7)			-	$t(6)=4.93$ $p = .003$ (-29)*	$t(6)=4.10$ $p = .006$ (+29)	-	$t(6)=4.43$ $p = .004$ (-29)*	$t(6)=4.58$ $p = .004$ (+29)
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	$t(6)=2.67$ $p = .037$ (+5)	-

Table 6. Star cancellation sub-test of the BIT-C score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.5 Line bisection (BIT-C)

The dependent variable was the total score in the line bisection sub-test of BIT-C. The results of the mixed ANOVA revealed a main effect of assessment, $F(3, 54) = 2.863$, $p = .045$, $\eta_p^2 = .137$, observed power = .653, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 0.236$, $p = .792$, $\eta_p^2 = .026$, observed power = .082, suggesting no difference between the three treatments. Finally, the interaction between the assessment and the group was not significant, $F(6, 54) = 1.792$, $p = .118$, $\eta_p^2 = .166$, observed power =

.622. The repeated contrasts for the main effect of assessment indicated that there was no significant difference ($p > .05$) among the levels. This seems to indicate that patients' performance did not significantly change among the assessments.

Line bisection (BIT-C)

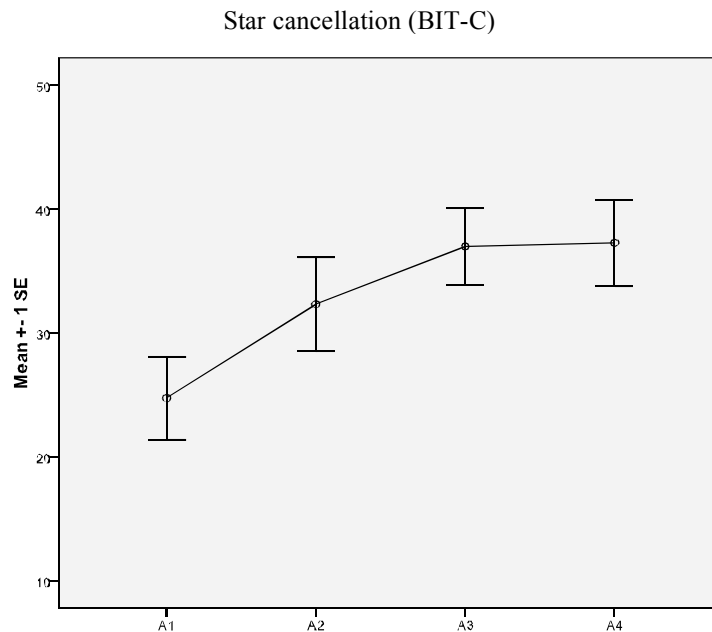**Figure 7**. Line bisection sub-test of the BIT-C score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that in the pre-treatment condition (A1-A2) the performance of one patient (LAT2) improved with respect to both the VS and PA groups, indicating a personal positive change before the treatment. Moreover, the performance of two patients (VS4 and VS6) declined compared to that of the PA group. The comparison between the pre- and post-treatment assessments (A2-A3) showed only a significant negative difference (worsening) for patient VS2 with respect to the PA group.

	LINE BISECTION (BIT-C)								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	*t*(6)=2.53 *p* = .045 **(+6)**	-	-				*t*(6)=4.76 *p* = .003 **(+6)**	-	-
LAT3	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT4	-	-	-				-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1				-	-	-	-	-	-
VS2				-	-	-	-	*t*(6)=2.78 *p* = .032 **(-2)***	-
VS3				-	-	-	-	-	-
VS4	CONTROL GROUP (n=7)			-	-	-	*t*(6)=3.91 *p* = .008 **(-4)***	-	-
VS5				-	-	-	-	-	-
VS6				-	-	-	*t*(6)=4.63 *p* = .004 **(-5)***	-	-
VS7				-	-	-	-	-	-

Table 7. Line bisection sub-test of the BIT-C score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.6 BIT Behavioural

The dependent variable was the total score in the BIT Behavioural. The results of the mixed ANOVA revealed a main effect of assessment, $F(3, 51) = 7.986$, $p < .001$, $\eta_p^2 = .320$, observed power = .986, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 17) = 0.311$, $p = .737$, $\eta_p^2 = .035$, observed power = .092, suggesting no difference among the three treatments. Finally, the interaction between the assessment and the group was not significant, $F(6, 51) = 1.101$, $p = .374$, $\eta_p^2 = .115$, observed power = .394. The repeated contrast for the main effect of assessment indicated that there was a significant difference ($p < .05$) only between levels 1 and 2 (A1 and A2, pre-treatment). This seems to indicate that patients' condition significantly changed in the period between the first assessment and the second assessment before the treatment, and that there was no specific effect of treatment on the patients' performance.

BIT Behavioural

Figure 8. BIT Behavioural score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that in the pre-treatment condition (A1-A2) the performance of two patients (LAT6 and VS7) was improved with respect to that of the control groups, indicating a personal positive change before the treatment. In contrast, the performance of two patients (LAT3 and VS2) declined compared to that of the PA group. The comparison between the pre- and post-treatment assessments (A2-A3) showed only a significant negative difference (worsening) for patient VS4 with respect to both the LAT and the PA groups.

	BIT BEHAVIOURAL								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-		CONTROL GROUP (n=6)		$t(6)=3.27$ $p = .017$ (-8)*	-	-
LAT4	-	-	-				-	-	-
LAT5	-	-	-				-	-	-
LAT6	$t(6)=2.97$ $p = .025$ (+32)	-	-				$t(6)=2.50$ $p = .047$ (+32)	-	-
LAT7	NA	NA	NA				NA	NA	NA
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-		CONTROL GROUP (n=7)	
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
							-	-	-
VS1				-	-	-	-	-	-
VS2				-	-	-	$t(6)=3.00$ $p = .024$ (-8)*	-	-
VS3				-	-	-	-	-	-
VS4		CONTROL GROUP (n=7)		-	$t(5)=2.71$ $p = .042$ (-30)*	-	-	$t(6)=2.50$ $p = .046$ (-30)*	-
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	$t(6)=2.68$ $p = .037$ (+1)	-	-

Table 8. BIT Behavioural score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.7 Picture scanning (BIT-B)

The dependent variable was the total score in the picture scanning sub-test of BIT-B. Mauchly's test indicated that the assumption of sphericity was violated ($W = 0.383$, $\chi^2(5) = 16.067$, $p < .05$); therefore, degrees of freedom were corrected using the Huynh-Feldt estimates of sphericity ($\varepsilon = .892$). The results of the mixed ANOVA revealed a main effect of assessment, $F(2.667, 48.184) = 5.155$, $p = .005$, $\eta_p^2 = .223$, observed power $= .877$, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 1.130$, $p = .345$, $\eta_p^2 = .112$, observed power $= .218$, suggesting no difference between the three treatments. Finally, the interaction between the assessment and the group was not significant, $F(5.354, 48.184) = 1.086$, $p = .382$, $\eta_p^2 = .108$, observed power $= .364$. The repeated contrasts for the main effect of assessment indicated that there was no significant difference between the four levels (all $p > .05$). This seems to indicate that patients' performance did not significantly changed among assessments.
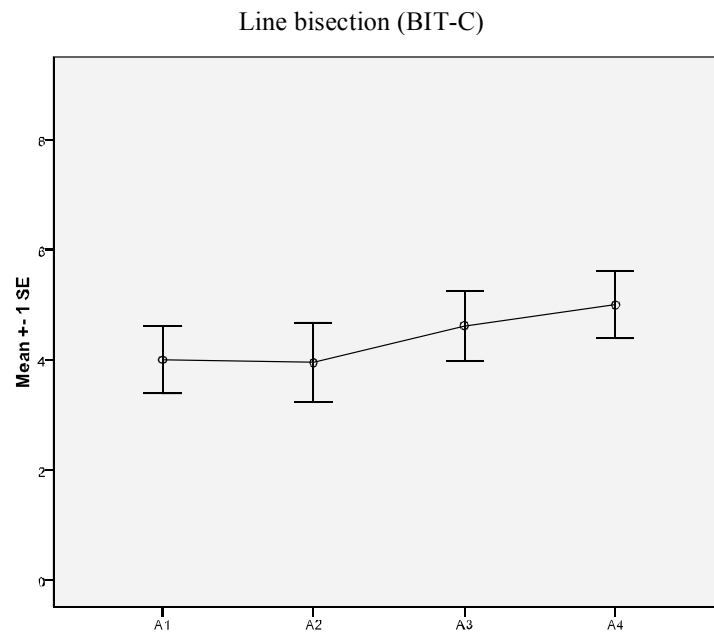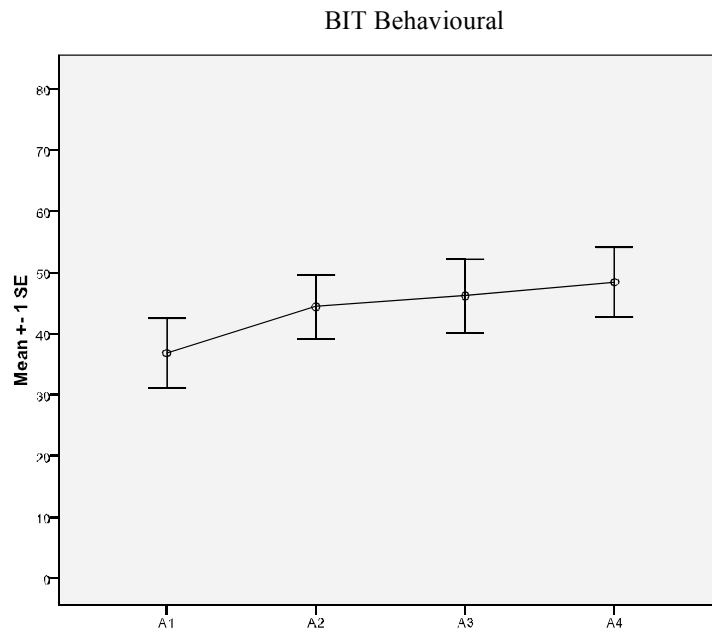
Picture scanning (BIT-B)

Figure 9. Picture scanning sub-test of the BIT-B score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that in the pre-treatment condition (A1-A2) the performance of five patients (PA1, PA2, PA4, PA5, and VS4) declined with respect to that of the LAT group, indicating a personal negative change before the treatment. The performance of one patient (VS3) improved compared to that of the LAT group. The comparison between the pre- and post-treatment assessments (A2-A3) showed two significant positive differences in performance for patient LAT6 and PA2 with respect to the performance of the the control groups. Finally, the performance of two patients (PA1 and VS4) in the two weeks after the treatment compared to that of the control groups, whereas the performance of one patient (VS3) declined.

PICTURE SCANNING (BIT-B)									
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	-	-
LAT4	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	$t(6)=3.43$ $p = .014$ (+7)	-				-	$t(6)=3.14$ $p = .020$ (+7)	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	$t(6)=6.53$ $p = .001$ (-2)*	-	-			
PA2	-	-	-	$t(6)=6.47$ $p = .001$ (-1)*	$t(6)=2.46$ $p = .049$ (+1)	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	$t(6)=4.63$ $p = .004$ (-1)*	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	$t(6)=2.88$ $p = .028$ (-1)*	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1				-	-	-	-	-	-
VS2				-	-	-	-	-	-
VS3				$t(6)=3.34$ $p = .016$ (+1)	-	-	-	-	$t(6)=2.80$ $p = .031$ (-4)*
VS4	CONTROL GROUP (n=7)			$t(6)=6.11$ $p = .001$ (-2)*	-	$t(6)=3.38$ $p = .015$ (+6)	-	-	$t(6)=2.89$ $p = .028$ (+6)
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 9. BIT Behavioural score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.8 Menu reading (BIT-B)

The dependent variable was the total score in the menu reading sub-test of BIT-B. The results of the mixed ANOVA revealed a main effect of assessment, $F(3, 54) = 4.694$, $p = .006$, $\eta_p^2 = .207$, observed power = .873, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 0.755$, $p = .484$, $\eta_p^2 = .077$, observed power = .158, suggesting no difference between the three treatments each other. Finally, the interaction between the assessment and the group was not significant, $F(6, 54) = 0.284$, $p = .942$, $\eta_p^2 = .031$, observed power = .120. The repeated contrasts for the main effect of assessment indicate that there was no significant difference among the four levels($p > .05$). This seems to indicate that patients' performance did not significantly change among assessments.
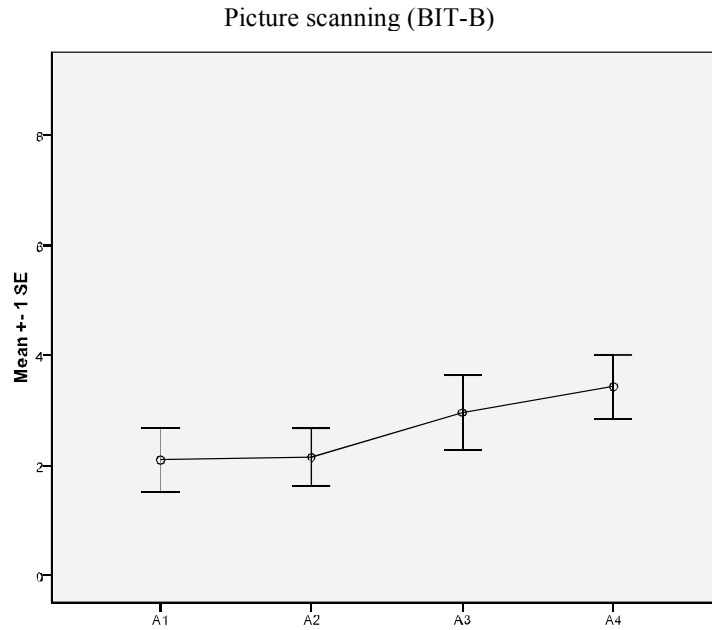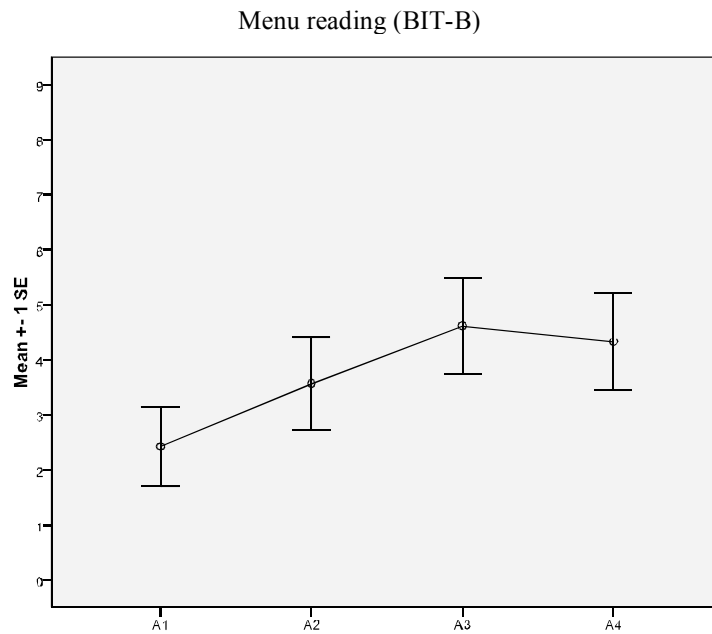
Menu reading (BIT-B)

Figure 10. Menu reading sub-test of the BIT-B score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that in the pre-treatment condition (A1-A2) that the performance of one patient (VS5) declined with respect to that of the LAT group, indicating a personal negative change before the treatment. The comparison between the pre- and post-treatment assessments (A2-A3) showed no significant differencies. Finally, the performance of one patient (VS4) improved in the two weeks after the treatment compared to that of the LAT group.

MENU READING (BIT-B)									
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	-	-
LAT4	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
							-	-	-
VS1				-	-	-	-	-	-
VS2				-	-	-	-	-	-
VS3				-	-	-	-	-	-
VS4	CONTROL GROUP (n=7)			-	-	$t(6)=2.50$ $p = .047$ (+6)	-	-	-
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 10. Menu reading sub-test of the BIT-B score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.9 Coin sorting (BIT-B)

The depemdent variable was the total score in the coin sorting sub-test of BIT-B. The results of the mixed ANOVA revealed no main effect of assessment, $F(3, 54) = 1.759$, $p = .166$, $\eta_p^2 = .089$, observed power = .433, showing no differencies of the patients' scores through the assessments. There was no significant main effect of group, $F(2, 18) = 1.158$, $p = .337$, $\eta_p^2 = .114$, observed power = .222, suggesting no difference between the three treatments. Finally, also the interaction between the assessment and the group was not significant, $F(6, 54) = 1.316$, $p = .266$, $\eta_p^2 = .128$, observed power = .471.

Single case analyses showed that in the pre-treatment condition (A1-A2) the performance of three patients (LAT7, VS2, VS5) declined with respect to that of the PA group, indicating a personal negative change before the treatment, whereas the performance of patient LAT6 improved with respect to that of the PA group. The comparison between the pre- and post-treatment assessments (A2-A3) showed no significant difference. Finally, the performance of one patient (VS4) improved in the two weeks after the treatment compared to that of both the LAT and the PA groups.

	COIN SORTING (BIT-B)								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				$t(6)=2.55$ $p = .043$ (0)	-	-
LAT4	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	$t(6)=2.91$ $p = .027$ (+9)	-	-				$t(6)=3.36$ $p = .015$ (+9)	-	-
LAT7	-	-	-				$t(6)=2.66$ $p = .037$ (-2)*	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1				-	-	-	-	-	-
VS2				-	-	-	$t(6)=4.30$ $p = .005$ (-5)*	-	-
VS3	CONTROL GROUP (n=7)			-	-	-	-	-	-
VS4				-	-	$t(6)=2.66$ $p = .038$ (+6)	-	-	$t(6)=2.48$ $p = .048$ (+6)
VS5				-	-	-	$t(6)=2.98$ $p = .025$ (-4)*	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	$t(6)=2.55$ $p = .043$ (0)	-	-

Table 11. Coin sorting sub-test of the BIT-B score in neglect patients. The graph shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.10 Card sorting (BIT-B)

The dependent variable was the total score in the card sorting sub-test of the BIT-B. The results of mixed ANOVA revealed no main effect of assessment, $F(3, 54) = 0.057$, $p = .982$, $\eta_p^2 = .003$, observed power $= .059$, showing no differencies of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 1.208$, $p = .322$, $\eta_p^2 = .118$, observed power $= .230$. Finally, also the interaction between the assessment and the group was not significant, $F(6, 54) = 2.116$, $p = .066$, $\eta_p^2 = .190$, observed power $= .709$. Single case analyses showed that in the pre-treatment condition (A1-A2) the performance of two patients (LAT5 and VS5) declined with respect to that of the PA group, indicating a personal negative change before the treatment. The comparison between the pre- and post-treatment assessments (A2-A3) showed no significant difference. Finally, in the 2 weeks after the treatment, the performance of patient PA4 declined with respect to that of both the

VS and the LAT groups, whereas the performance of one patient (VS1) improved with respect to that of the LAT group.

	COIN SORTING (BIT-B)								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				$t(6)=2.55$ $p = .043$ (0)	-	-
LAT4	-	-	-				-	-	-
LAT5	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT6	$t(6)=2.91$ $p = .027$ (+9)	-	-				$t(6)=3.36$ $p = .015$ (+9)	-	-
LAT7	-	-	-				$t(6)=2.66$ $p = .037$ (-2)*	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1				-	-	-	-	-	-
VS2				-	-	-	$t(6)=4.30$ $p = .005$ (-5)*	-	-
VS3	CONTROL GROUP (n=7)			-	-	-	-	-	-
VS4				-	-	$t(6)=2.66$ $p = .038$ (+6)	-	-	$t(6)=2.48$ $p = .048$ (+6)
VS5				-	-	-	$t(6)=2.98$ $p = .025$ (-4)*	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	$t(6)=2.55$ $p = .043$ (0)	-	-

Table 12. Card sorting sub-test of the BIT-B score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.1.11 Bells test (Gauthier et al., 1989)

The dependent variable was the total score in the test. Mauchly's test indicated that the assumption of sphericity was violated (W = 0.379, $\chi^2(5) = 16.234$, p < .05); therefore degrees of freedom were corrected using the Huynh-Feldt estimates of sphericity ($\varepsilon = .750$). The results of the mixed ANOVA revealed a main effect of assessment, $F(2.249, 40.479) = 5.074$, $p = .009$, $\eta_p^2 = .220$, observed power = .822, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 1.674$, $p = .215$, $\eta_p^2 = .157$, observed power = .306. Finally, the interaction between the assessment and the group was not significant, $F(4.498, 40.479) = 0.676$, $p = .629$, $\eta_p^2 = .070$, observed power = .210.

The repeated contrasts for the main effect of assessment indicated that there was a significant difference ($p < .05$) only between levels 1 and 2 (A1 and A2, pre-treatment). This seems to indicate that patients' performance significantly changed in the period between the first assessment and the second assessment before the treatment, and that there was no specific effect of treatment on the patients' performance.

Bells test

Figure 11. Bells test score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

Single case analyses showed that in the pre-treatment condition (A1-A2) the performance of one patient (PA7) improved with respect to that of the VS group, indicating a personal positive change before the treatment. The comparison between the pre- and post-treatment assessments (A2-A3) showed a significant negative difference (worsening) f the performance of patient VS4 with respect to that of both the LAT and the PA groups.

	BELLS TEST								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	-	-
LAT4	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-			
PA5	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA6	-	-	-	-	-	-			
PA7	$t(6)=3.34$ $p = .016$ (+18)	-	-	-	-	-			
							-	-	-
VS1				-	-	-	-	-	-
VS2				-	-	-	-	-	-
VS3				-	-	-	-	-	-
VS4	CONTROL GROUP (n=7)			-	$t(6)=2.70$ $p = .036$ (-22)*	-	-	$t(6)=3.68$ $p = .010$ (-22)*	-
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 13. Bells test score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.2 Neglect tests for personal space

3.2.1 Comb and Razor test (Beschin & Robertson, 1997)

The dependent variable was the bias score calculated with the formula of McIntosh et al. (2000). The results of the mixed ANOVA revealed no main effect of assessment, $F(3, 54) = 0.468$, $p = .706$, $\eta_p^2 = .025$, observed power $= .138$, showing no differencies of the patients' score through the assessments. There was a significant main effect of group, $F(2, 18) = 4.948$, $p = .019$, $\eta_p^2 = .355$, observed power $= .737$, suggesting a difference between the three groups. Note, however, that for this test the three groups were not homogenei, $F(2, 18) = 4.252$, $p = .031$. Finally, the interaction between the assessment and the group was not significant, $F(6, 54) = 1.830$, $p = .111$, $\eta_p^2 = .169$, observed power $= .633$.

COMB AND RAZOR TEST: LAT

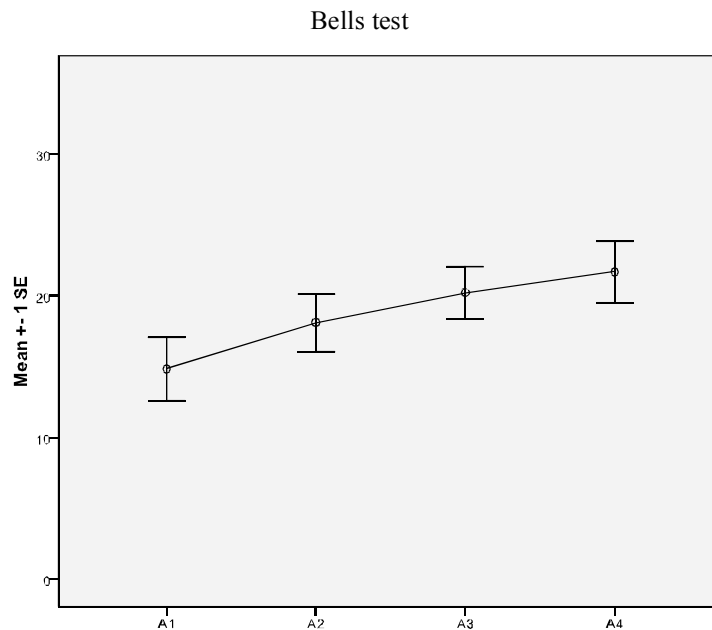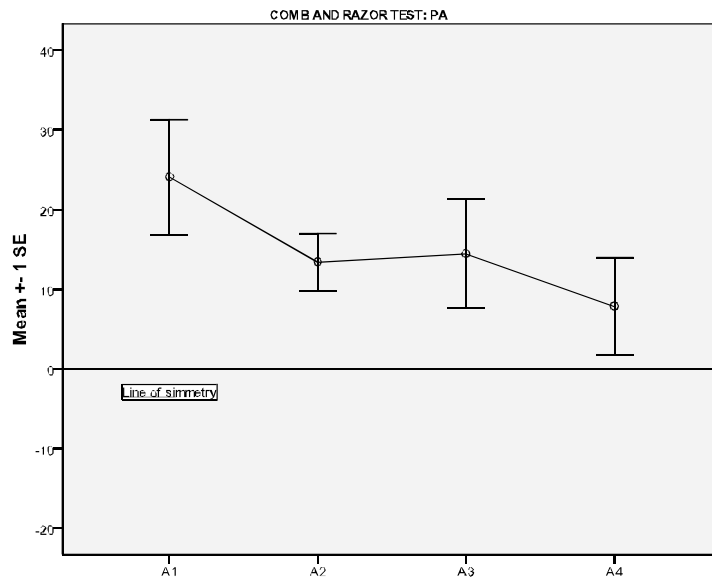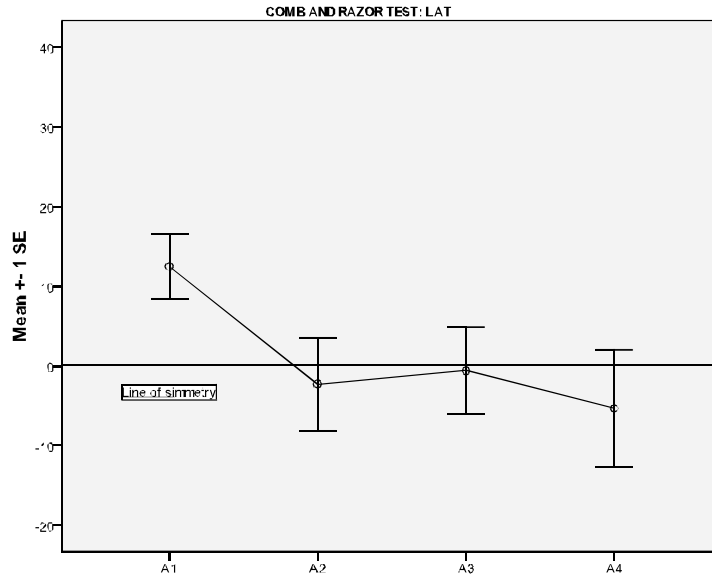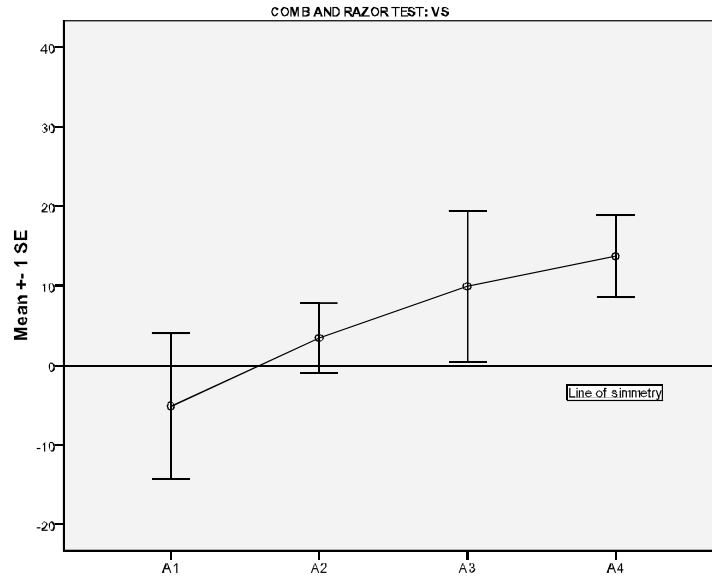COMB AND RAZOR TEST: PA

Figure 12. Comb and Razor test bias score in neglect patients. The graphs show the trend of the mean score throughout the assessments for each group.

Single case analyses showed in the pre-treatment condition (A1-A2) one the performance of one patient (VS2) improved with respect to that of the LAT group. All other comparisons were not significant.

COMB AND RAZOR TEST									
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	-	-
LAT4	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
							-	-	-
VS1				-	-	-	-	-	-
VS2				$t(6)=3.73$ $p = .010$ **(+48.6)**	-	-	-	-	-
VS3				-	-	-	-	-	-
VS4	CONTROL GROUP (n=7)			-	-	-	-	-	-
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 14. Comb and Razor test bias score in neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

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3.2.2 Fluff test (Cocchini et al., 2001)

The dependent variable was the total number of left omissions. The results of the mixed ANOVA revealed a main effect of assessment, $F(3, 54) = 3.834$, $p = .015$, $\eta_p^2 = .176$, observed power $= .792$, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 1.669$, $p = .216$, $\eta_p^2 = .156$, observed power $= .305$. Finally, the interaction between the assessment and the group was not significant, $F(6, 54) = 0.871$, $p = .522$, $\eta_p^2 = .088$, observed power $= .314$. The repeated contrasts for the main effect of assessment indicated that there was no significant difference ($p > .05$) between the four levels. This seems to indicate that patients' condition did not significantly changed among assessments.
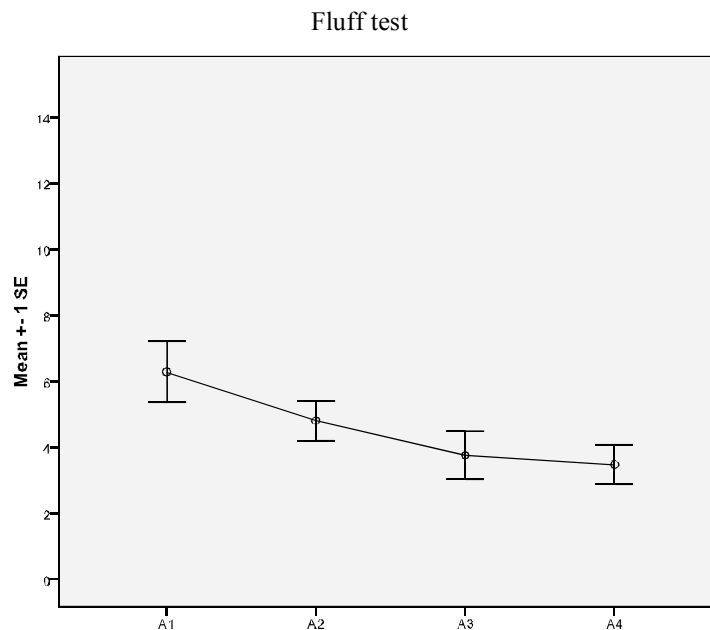
Figure 13. Number of omissions in the Fluff test of neglect patients. The graph shoes the trend of the mean of omissions throughout the assessments.

Single case analyses showed that in the pre-treatment condition (A1-A2) the performance of two patients (PA4 and VS2) improved with respect to that of the LAT group, whereas the performance of other two patients (VS3 and VS5) declined with respect to that of the LAT group. The comparison between the pre- and post-treatment assessments (A2-A3) showed no significant differencies. Finally, in the two weeks after the treatment, the performance of patient PA7 declined with respect to that of the LAT group.

			FLUFF TEST						
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT4	-	-	-				-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	*t*(6)=4.11 *p* = .006 **(-14)**	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	*t*(6)=2.76 *p* = .033 **(+7)***			
VS1				-	-	-	-	-	-
VS2				*t*(6)=2.74 *p* = .034 **(-9)**	-	-	-	-	-
VS3				*t*(6)=2.80 *p* = .032 **(+5)***	-	-	-	-	-
VS4	CONTROL GROUP (n=7)			-	-	-	-	-	-
VS5				*t*(6)=2.67 *p* = .037 **(+5)***	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 14. Number of omissions in the Fluff test of neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.3 Neglect tests for extrapersonal space

3.3.1 Room description

The dependent variable was the total number of targets detected. The results of the mixed ANOVA revealed no main effect of assessment, $F(3, 54) = 1.455$, $p = .237$, $\eta_p^2 = .075$, observed power = .364. There was no significant main effect of group, $F(2, 18) = 1.517$, $p = .246$, $\eta_p^2 = .144$, observed power = .280. Finally, also the interaction between the assessment and the group was not significant, $F(6, 54) = 0.583$, $p = .742$, $\eta_p^2 = .061$, observed power = .214.

The individual analyses showed that in the pre- and post-treatment assessments (A2-A3) the performance of one patient (PA4) declined compared to that of the LAT group. There was no other significant effect.

	ROOM DESCRIPTION								
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	-	-
LAT4	-	-	-	CONTROL GROUP (n=7)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	$t(6)=2.98$ $p = .025$ **(-11)***	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
							-	-	-
VS1				-	-	-	-	-	-
VS2				-	-	-	-	-	-
VS3				-	-	-	-	-	-
VS4	CONTROL GROUP (n=7)			-	-	-	-	-	-
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 15. Room description test scores of neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.3.2 Semi-structured ecological scale (Zoccolotti & Judica, 1991)

The dependent variable was the score assigned by three independent examiners. The results of the mixed ANOVA revealed no main effect of assessment, $F(3, 54) = 1.154$, $p = .336$, $\eta_p^2 = .060$, observed power = .293. There was no significant main effect of group, $F(2, 18) = 0.663$, $p = .528$, $\eta_p^2 = .069$, observed power = .144. Finally, also the interaction between the assessment and the group was not significant, $F(6, 54) = 1.683$, $p = .143$, $\eta_p^2 = .158$, observed power = .590.

The analyses of single cases showed that in the pre-treatment condition (A1-A2) the performance of two patients (LAT1 and PA6) declined with respect to that of the VS group, whereas the performance of one patient (VS5) improved with respect to that of both the VS and the PA groups. The comparison between the pre- and post-treatment assessments (A2-A3) showed no significant differencies. Finally, in the two weeks after the treatment, the performance of patient LAT6 declined with respect to that of the PA group, whereas the performance of patients VS4 and VS was improved.

SEMI-STRUCTURED ECOLOGICAL SCALE									
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	$t(6)=2.47$ $p = .048$ (+1)*	-	-	CONTROL GROUP (n=7)			-	-	-
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	-	-
LAT4	$t(6)=4.87$ $p = .003$ (-3)	-	-				$t(6)=3.68$ $p = .010$ (-3)	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	$t(6)=3.21$ $p = .018$ (+1.5)*
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-			
PA5	-	-	-	-	-	-			
PA6	$t(6)=2.47$ $p = .048$ (+1)*	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1	CONTROL GROUP (n=7)			-	-	-	-	-	-
VS2				-	-	-	-	-	-
VS3				-	-	-	-	-	-
VS4				-	-	-	-	-	$t(6)=2.66$ $p = .038$ (-1.5)
VS5				-	-	$t(6)=2.64$ $p = .039$ (-2)	-	-	$t(6)=3.45$ $p = .014$ (-2)
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 16. Semi-structured ecological battery scores of neglect patients. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.4 Neglect test for representational space

3.4.1 Mental number bisection task (Zorzi et al., 2002)

For each patient, the mean difference between observed (O) and correct (C) responses (dO - C) was computed for every number interval length. Individual data were analyzed through a regression procedure for repeated measures designs (Method 3; Lorch & Myers, 1990). For each participant, we performed a regression analysis, with length of the interval as the predictor variable, to calculate individual regression slopes. Then, for the analysis we considered the B index of the regression of each patient. Mauchly's test indicated that the assumption of sphericity was violated (W = 0.489, $\chi^2(5) = 11.243$, p < .05); therefore, degrees of freedom were corrected using the Huynh-Feldt estimates of sphericity ($\varepsilon = .885$). The results of the mixed ANOVA revealed no main effect of assessment, $F(3, 51) = 1.130$, $p = .346$, $\eta_p^2 = .062$, observed power = .287. There was no significant main effect of group, $F(2, 17) = 1.226$, $p = .318$, $\eta_p^2 = .126$, observed power = .231. Finally, also the interaction

between the assessment and the group was not significant, $F(6, 51) = 1.428$, $p = .222$, $\eta_p^2 = .144$, observed power = .506.

In the single case analyses, the comparison between the pre- and post-treatment assessments (A2-A3) showed that the performance of patients VS1 and VS5 was improved. In the two weeks after the treatment, the performance of four patients (LAT3, LAT7, VS1, and VS2) declined with respect to that of the control group, whereas the performance of patient VS7 was improved.

MENTAL NUMBER BISECTION TASK									
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	NA	NA	NA				NA	NA	NA
LAT2	-	-	-				-	-	-
LAT3	-	-	-				-	-	t(6)=4.24 p = .005 (+0.183)*
LAT4	-	-	-	CONTROL GROUP (n=6)			-	-	-
LAT5	-	-	-				-	-	-
LAT6	-	-	-				-	-	-
LAT7	-	-	t(6)=3.38 p = .015 (+0.68)*				-	-	t(6)=10.6 p < .001 (+0.684)*
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA5	-	-	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1	CONTROL GROUP (n=7)			-	t(5)=3.55 p = .016 (-0.221)	-	-	-	t(6)=3.31 p = .016 (+0.148)*
VS2				-	-	-	-	-	t(6)=4.96 p = .003 (+0.214)*
VS3				-	-	-	-	-	-
VS4				-	t(5)=4.55 p = .006 (-0.306)	-	-	-	-
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	t(6)=5.08 p = .002 (-0.225)

Table 17. Score of neglect patients in the mental number bisection task. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

3.5 Motor functions

3.5.1 Motricity Index and trunk control test (Demeurisse et al., 1980)

The dependent variable was the total score of the Motricity Index test. Mauchly's test indicated that the assumption of sphericity was violated (W = 0.215, $\chi^2(5) = 25.713$, p < .05); therefore, degrees of freedom were corrected using the Huynh-Feldt estimates of sphericity ($\varepsilon = .608$). The results of the mixed ANOVA revealed a main effect of

assessment, $F(1.825, 32.849) = 25.856$, $p < .001$, $\eta_p^2 = .590$, observed power = 1.0, showing an increase of the patients' score through the assessments. There was no significant main effect of group, $F(2, 18) = 0.370$, $p = .696$, $\eta_p^2 = .039$, observed power = .10. Finally, the interaction between the assessment and the group was not significant, $F(3.650, 32.849) = 1.453$, $p = .241$, $\eta_p^2 = .139$, observed power = .382. The repeated contrasts for the main effect of assessment indicated that there was a significant difference ($p < .05$) between levels 1 and 2 (A1 and A2, pre-treatment changing), and between levels 2 and 3 (A2 and A3, effect of treatment), but not between levels 3 and 4 (A3 and A4, long-lasting effects). This seems to indicate that patients' performance significantly changed in the period between the first assessment and the second assessment before the treatment, but also that there was a specific effect of treatment on the patients' performance.
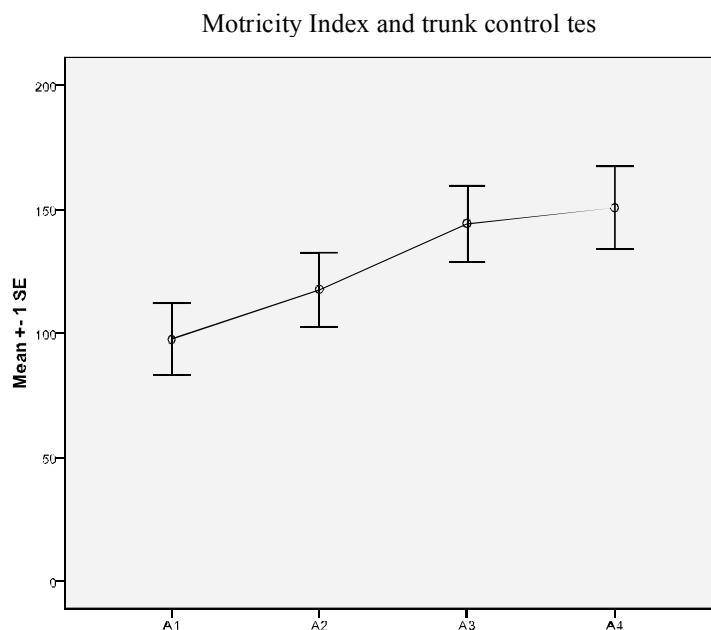

Figure 14. Motricity Index and trunk control test score in neglect patients. The graph shoes the trend of the mean score throughout the assessments.

The single case analyses showed that in the pre-treatment condition (A1-A2) none of the patients was improved with respect to the control groups. On the contrary, the comparison between the pre- and post-treatment assessments (A2-A3) showed that the performance of four patients of the LAT group (LAT2, LAT3, LAT4, LAT6) was improved with respect to that of both to the VS and the PA groups. Also the performance of one patient treated with VS (VS1) was improved with respect to that of the PA group, suggesting a strong effect of LAT in patients' performance, whereas

the PA and the VS had no significant effect on motor performance. Finally, the performance of one patient (VS2) improved in the two weeks after the VS treatment compared to that of the PA group.

MOTRICITY INDEX AND TRUNK CONTROL TEST									
Patient	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3	A2-A1	A3-A2	A4-A3
LAT1	-	-	-				-	-	-
LAT2	-	$t(6)=2.69$ $p = .036$ (+88)	-	CONTROL GROUP (n=7)			-	$t(6)=4.56$ $p = .004$ (+88)	-
LAT3	-	-	-				-	$t(6)=2.54$ $p = .044$ (+49)	-
LAT4	-	-	-				-	$t(6)=3.06$ $p = .022$ (+59)	-
LAT5	-	-	-				-	-	-
LAT6	-	$t(6)=4.55$ $p = .004$ (+119)	-				-	$t(6)=5.79$ $p = .001$ (+119)	-
LAT7	-	-	-				-	-	-
PA1	-	-	-	-	-	-			
PA2	-	-	-	-	-	-			
PA3	-	-	-	-	-	-			
PA4	-	-	-	-	-	-	CONTROL GROUP (n=7)		
PA5	-	$t(6)=2.51$ $p = .046$ (0)	-	-	-	-			
PA6	-	-	-	-	-	-			
PA7	-	-	-	-	-	-			
VS1	CONTROL GROUP (n=7)			-	-	-	-	$t(6)=3.18$ $p = .021$ (+59)	-
VS2				-	-	-	-	-	$t(6)=3.72$ $p = .010$ (+59)
VS3				-	-	-	-	-	-
VS4				-	-	-	-	-	-
VS5				-	-	-	-	-	-
VS6				-	-	-	-	-	-
VS7				-	-	-	-	-	-

Table 18. Score of neglect patients in the Motricity Index and in the trunk control test. The table shoes the difference between the indivual patients' score compared with the control groups, related to the assessments.

4. DISCUSSION

The present study investigated the role of different rehabilitation treatments of patients with unilateral left neglect, checking the role of behavioural/cognitive changes (e.g., spontaneous recovery, non-cognitive rehabilitation treatments, and all the other situations which were not directly implied in the cognitive rehabilitation treatments). In fact, previous rehabilitation studies (e.g., Frassinetti et al., 2002; Serino et al., 2007, 2009; Robertson et al., 2002) did not control for the effect of these other variables, leaving some important opened questions. Moreover, our purpose was

to study the rehabilitation effects on the several space domains (i.e., personal, peripersonal, extrapersonal, and representational). To achieve this goal, 21 patients with unilateral left neglect, after right-hemisphere lesion, were assigned to the treatments in a quasi-random order. At the end of the protocol, each group was composed by seven patients. Each of the three groups of patients was treated two times a day, over a period of two weeks, with the Limb Activation Treatment (LAT; Robertson et al., 2002), with Prism Adaptation (PA; Serino et al., 2007), and with a Visual Scanning training (VS; Antonucci et al., 1995), respectively. To check for the interference of external variables, after the first assessment (A1) elapsed a period of 2 weeks in which no cognitive rehabilitation was made. At the end of these two-weeks baseline, a second assessment (A2) was carried out at the beginning of the treatment (i.e., pre-treatment assessment). A third assessment (A3) was made at the end of the treatment (i.e., post-treatment assessment) to evaluate the effectiveness (or the ineffectiveness) of the treatment. Finally, we evaluated the long-term post-treatment changes carrying out a fourth assessment (A4), two weeks after the end of the treatment.

Given that unilateral neglect is a complex syndrome, the data were analysed both at a group and at a single case levels, to better and deeply understand the real effects of rehabilitation in the several space domains.

The results will be discussed in separate sessions, based on the spatial domain investigated.

4.1 Peripersonal space

All together, the tests used to assess the peripersonal spatial abilities of neglect patients show that there is no significant difference between groups, suggesting that the three treatments do not differ each other. Nevertheless, the analyses of the individual data show that (1) there are 11 patients of the LAT group who significantly differ respect to both the PA and VS groups together, after the rehabilitation treatment; (2) there are only 2 patients of the PA group who significantly differ with respect to both the LAT and the VS groups together, after the rehabilitation treatment; and (3) there were 18 patients of the VS group who significantly differ with respect to both the PA and the LAT groups together, after the rehabilitation treatment. This data suggest the existence of a difference between the groups, detectable only with the analysis of each single patient, with respect to a control group. In this case, it seems

that both the LAT and the VS treatments have a stronger effect as than the PA treatment. However, note that changing in performance can stand for both improving or worsening. In fact, taken the LAT, the PA, and the VS together, 16 patients improved their performance after the treatment, whereas 15 patients got worse. The present data suggest that, in rehabilitation studies, the patients' performance should be investigate both at a group and at individual levels; in fact, these levels of analysis can be successfully integrated each other.

The main effect of assessment was reported almost for all the tests used (with the exception of the subtests Coin sorting and Card sorting of the BIT; Wilson et al., 1987). That suggests that the patients' performance changed significantly throughout the time, between the assessments. Specifically, the repeated contrasts showed a significant difference between the first and the second assessments (A1 and A2) in the BIT Conventional (Wilson et al., 1987), in the star cancellation subtest of the BIT Conventional (Wilson et al., 1987), in the BIT Behavioural (Wilson et al., 1987), and in the Bells Cancellation test (Gauthier et al., 1989). That difference between A1 and A2 show the effect of external variables (e.g., spontaneous recovery, worsening of clinical conditions, pharmacological effects, physiotherapy treatment, etc.) which, could interfere with the rehabilitation treatments. The individual analysis shows that 15 patients improved, whereas 18 patients declined.

The only test in which there is a significant difference between the second and the third assessments (A2 and A3) is the BIT Conventional (Wilson et al., 1987); this difference is directing ascribing to the effect of treatment. Nevertheless, the single case analysis shows that four patients improved, whereas three patients got worse after the treatment.

In line with the group results, the present data suggest that, in rehabilitation studies, the patients' performance should be investigate both at a group and at individual levels; in fact, only the single case analysis can show what is the direction (improving or worsening) of the changing directly ascribing to the effect of the treatment.

Finally, no difference was found between the third (A3, post treatment) and the fourth (A4, follow-up) assessments at the group level. The single case analysis shows, however, that 11 patients improved, whereas five patients got worse during the two weeks after the treatment.

To summarise, the data show that the LAT, the PA, and the VS are treatments that can modulate the peripersonal space domain in unilateral neglect patients, in the sense of an improving or a worsening of the patients' performance.

4.2 Personal space

The tests used to assess the peripersonal neglect, i.e. the Comb and Razor test (Beschin & Robertson, 1997) and the Fluff test (Cocchini et al., 2001) show that there is a significant difference between groups only in the Comb and Razor test (Beschin & Robertson, 1997), suggesting an effect of the group. Nevertheless, the analyses of the single cases show that there is no individual difference between each patient and the control groups. The existence of the difference between the groups is still not detectable with the analysis of each individual patient, with respect to the assigned control group. In this case, it seems that none of the treatments has an effect.

In the Fluff test (Cocchini et al., 2001) there is no significant difference between groups. Neither the analysis of the single cases show any difference between the treatments. The present data suggest again that, in rehabilitation studies, the patients' performance should be investigate both at a group and at individual levels; in fact, these levels of analysis can be successfully integrated each other.

The main effect of assessment was reported only for the Fluff test (Cocchini et al., 2001). That suggests that, in this test, the patients' performance changed significantly throughout the time, between the assessments. The repeated contrasts showed no significant difference between all assessments. However, in the single cases analysis, there is a difference between A1 and A2: four patients clearly show the effect of some external variables (e.g., spontaneous recovery, worsening of clinical conditions, pharmacological effects, physiotherapy treatment, etc.). Two of these patients improved, whereas the other two of the patients got worse.

Finally, no difference was found between the third (A3, post treatment) and the fourth (A4, follow-up) assessments at the group level. The single case analysis is in line with the group analysis.

To summarise, it seems that the LAT, the PA, and the VS are treatments who cannot effectively modulate the personal space domain in unilateral neglect patients.

4.3 Extrapersonal space

The test used to assess the peripersonal neglect is the room description test. This test show that there is neither significant difference between groups, neither between each patient and the control groups. Neither the main effect of assessment was reported, even if one patient got worse after the PA treatment.

It seems, therefore, that the LAT, the PA, and the VS are treatments that do not modulate the extrapersonal space domain in unilateral neglect patients, suggesting no generalization effect of the treatments in all spatial domains.

4.4 Representational space

In 2002, Zorzi et al. reported the effects of the mental number bisection task in negelct patients. According to the authors, this task is appropriate for assessing the representational space, frequently impaired in neglect patients. We used the same task to test the effect of the LAT, the PA, and the VS on the representational space.

This test show that there is no significant difference between groups, suggesting that the three treatments do not differ each other.

There is no main effect of assessment. That suggests that the patients' performance did not change significantly throughout the time, between the assessments. However, the single case analysis shows that one patient improved, whereas four patients got worse during the two weeks after the treatment.

4.5 Motor functions

The Motricity Index and the trunk control test (Demeurisse et al., 1980) were used to assess motor functions. The data show that there is no main effect of group, suggesting that the three treatments do not differ each other. Nevertheless, the analyses of the individual data show that (1) there are four patients of the LAT group who significantly differ respect to both the PA and VS groups together, after the rehabilitation treatment; and (2) there is 1 patient of the VS group who significantly differ respect to both the LAT and VS groups together, after the rehabilitation treatment These data clearly suggest the existence of a difference between the groups, detectable only with the analysis of each single patient, respect to a control group. In this case, it is clear that the LAT have a stronger effect as regards both the PA and the VS treatment. However, it is to note that, in this test, changing in performance stand only for improving. The present data confirm that, in rehabilitation studies, the

patients' performance should be investigate both at a group and at individual levels; in fact, these levels of analysis can be successfully integrated each other.

The main effect of assessment was found. That suggests that the patients' performance changed significantly throughout the time, between the assessments. Specifically, the repeated contrasts showed a significant difference between the first and the second assessments (A1 and A2). That difference between A1 and A2 show the effect of external variables (e.g., spontaneous recovery, worsening of clinical conditions, pharmacological effects, physiotherapy treatment, etc.) which could interfere with the rehabilitation treatments.

The repeated contrasts also showed a significant difference between the second and the third assessments (A2 and A3). The single case analysis revealed that 5 patients improved in the performance, whereas no patients made worse the performance after the treatment. Four patients out of the five were treated with the LAT, whereas one patient was treated with the VS. These data suggest a very positive effect of LAT treatment on motor functions.

In line with the group results, the present data suggest that, in rehabilitation studies, the patients' performance should be investigated both at the group and at the single case levels; in fact, only the single case analysis can show what is the direction (improving or worsening) of the changing directly ascribing to the effect of the treatment.

Finally, no difference was found between the third (A3, post treatment) and the fourth (A4, follow-up) assessments at the group level. The single case analysis shows that one patient improved in the performance during the two weeks after the treatment.

To summarise, the data show that the LAT is the most appropriate rehabilitation treatment to induce a strong amelioration of motor functions in unilateral neglect patients.

4.6 General conclusions

Taken together, both the group and the single case analysis show a double contrary effect of the treatment, that is an improving or a worsening. Based on these data, we can conclude that the cognitive treatments for unilateral spatial neglect, per se, have the power to interfere with the cognitive processing of space, but it is not yet clear in which way. Therefore, on the base of the effects reported in this study, we

cannot generalize and reduce the terminology in "effective" or "ineffective" terms. Probably, it would be more correct thinking about cognitive rehabilitation in terms of what is the best way to treat a person with a specific cognitive deficit. More specific is the cognitive deficit, more specific should be the cognitive intervention. The present study is the first which goes to this direction.

<center>**APPENDIX**</center>

<center>*Description of the neuropsychological tests*</center>

Tests to assess peripersonal neglect

Behavioural Inattention Test (BIT; Wilson et al., 1987)

The Behavioural Inattention Test (BIT; Wilson, Cockburn, & Halligan, 1987) is a standardized battery specifically designed to evaluate visuo-spatial neglect in peripersonal space. There are two parallel versions of the BIT (versions A and B), each comprising six "conventional" subtests and nine "behavioural" subtests. The conventional subtests have commonly been used to evaluate visuo-spatial deficits in neglect patients, whereas the nine behavioural subtests were developed to simulate activities of daily living.

The six conventional subtests are: line crossing, letter cancellation, star cancellation, figure and shape copying, line bisection, and drawing by request.

- *Line crossing*: this test requires the patient to detect and cross out all the target lines on a A4 sheet of paper. The examiner demonstrates the required response by crossing out two of the four lines located in the central column, and then instructs the patient to cross out all the lines he/she can see on the page. The maximum score is 36 (the subtest cut-off score is ≤ 34).

- *Letter cancellation*: this test requires the patient to detect and mark all the letters E and R among other alphabet letters. The letters are set in 5 parallel horizontal lines. The examiner demonstrates the required response by crossing out two example E and R letters located out of the letter lines, and then instructs the patient to mark all the E and R letters he/she can see on the page. The maximum score is 40 (the subtest cut-off score is ≤ 32).

- *Star cancellation*: this test consists of a page containing a random array of verbal and non-verbal stimuli (i.e., english letter strings), among small and big stars. The patient is instructed to mark all the small stars from this array. Before starting, two examples of the small stars are pointed out to the patient. The maximum score is 54 (the subtest cut-off score is ≤ 51).

- *Figure and shape copying*: the patient is instructed to copy three shapes from the left side of the page. The three drawings, a four-pointed star, a cube, and a daisy, are arranged vertically and are clearly indicated to the patient. The second part of the test requires the patient to copy three geometric shapes

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presented on a separate sheet. Unlike the previous items, the geometric shapes are not pointed out to the patient. The total score comprised of the first part score (i.e., score of the three drawing = 3) and the second part score (i.e., score of the geometric shapes copy = 1), with a maximum score of 4 (the subtest cut-off score is ≤ 3).

- *Line bisection*: this test consists of a page containing three horizontal lines, equal in length, each positioned relatevely on the right, centre, and left of the central point of the paper. The patient is instructed to make a sign in the centre of each line. No examples are given to the patient. The maximum score is 9 (the subtest cut-off score is ≤ 7).

- *Drawing by request*: in this test patient is instructed to draw a clock, a human figure (man or woman), and a butterfly, in three separate sheets. The score is assigned for each draw, with respect to the symmetry and the presence of all part of the figures drew. The maximum score is 3 (the subtest cut-off score is ≤ 2).

The six subtests of the BIT have all been shown to intercorrelate highly. However, subsequent research has indicated that while it is clinically meaningful to cluster the impairments as a common deficit, the underlying mechanisms impaired may be far from unitary (Halligan, Marshall, & Wade, 1989). Scores from the BIT conventional subtests can be used to calculate an aggregate score for the six subtests. Points are given for correct performance, thus higher scores indicate better performance. A score at or below 129 (0-146, maximum score 146) on the aggregate score of the six conventional subtests is considered as a sign of deficit. An alternative way of scoring, which has the advantage of providing specific information about the potential different types of negelct involved, is to note the number of tests (using the individual test cut-off) on which the pathological score is present.

Instead, the nine behavioural subtests of the BIT include the following: picture scanning, telephone dialling, menu reading, article reading, telling and setting the time, coin sorting, address and sentence copying, map navigation, and card sorting.

- *Picture scanning*: in this test three large photographs are presented one at a time and depict: a meal, a wash basin and toiletries, and a large room flanked by various pieces of furniture and hospital aids. The patient is instructed to name and/or point to the items in the picture. Each photograph is placed in front of the seated patient who is not permitted to move it. Omissions are

scored, although errors of identification are noted. The scoring of this and all subsequent tests is out of a total of nine. Points are subtracted from this maximum score from errors and is calculated from the total number of omissions recorded. The cut-off score of this subtest is ≤ 5.

- *Telephone dialling*: in this test patient is instructed to read three number sequences, one at a time, and then to digit them on a touch-tone telephone placed in front of him/her. The performance is considered correct only if patient read and then digit the phone numbers without errors. The cut-off score of this subtest is ≤ 7.

- *Menu reading*: this task consists of an "open-out" page containing 18 common food items arranged in 4 adjacent columns (2 on the left and 2 on the right). Each of the 18 items is scored as correct or incorrect. Incorrect responses refer to partial/whole word substitutions or omissions. The cut-off score of this subtest is ≤ 8.

- *Article reading*: in this test patient is required to read a story or an article, divided in three columns (left, central, and right). The examiner notes all reading errors (substitutions and omissions). The cut-off score of this subtest is ≤ 8.

- *Telling and setting the time*: this test is composed by three parts. The first requires the patient to read the time from photographed settings on a digital clock face. Secondly, the patient is required to read the time from three settings on an analogue clock face. Finally, the patient is required to set times on the same analogue clock face moving both the minute and hour hands. The cut-off score of this subtest is ≤ 8.

- *Coin sorting*: in this test patient have to indicate coins of different value as requested by the experimenter. There are 3 coins each value, for a total of 15 coins arranged on a board placed in front of patient. The examiner notes the omissions. The cut-off score of this subtest is ≤ 8.

- *Address and sentence copying*: this test is composed by two parts. The first requires the patient to copy an address on a sheet of paper; the second requires the patient to copy a brief sentence. The total number of characters copied is noted. The cut-off score of this subtest is ≤ 7.

- *Map navigation*: this task consists of a board containing 9 alphabet letters connected by lines. The letters are arranged like the white stripes of the British

flag. The experimenter says patient the letter to indicate with the finger, without raise it from the board, like following the route of a map. The cut-off score of this subtest is ≤ 8.

- ***Card sorting***: in this test patient have to indicate the cards that represent the kings, the queens, the tens, and the sixes, in a fixed sequence. The cards are placed in front of patient in 4 columns. The examiner notes the cards omitted. The cut-off score of this subtest is ≤ 8.

As the conventional subtests, both the overall behavioural score and the individual subtests scores can be considered. A total score at or below 67 (0-81, maximum score 81), or scores at or below the cut-off on one or more individual subtests, may suggest a deficit in visuo-spatial abilities. Among the BIT subtests, it is not uncommon to find differences both within and between patients.

Bells Cancellation Test (Gauthier et al., 1989)

Patients were asked to cross out bells printed, along with other objects, on a sheet of A4 paper (17 targets on the left and 17 on the right side of the paper); the number of correct responses was recorded. Gauthier et al. (1989) recommended scoring only the errors in the right and left sides of the visual field, and scoring omissions in the centre separately. For this type of scoring, the test sheet is divided lengthwise into 7 sectors (3 left, 3 right, 1 centre). The total correct is 30 (omitting the central column). The total time for completion of the test is irrelevant. On the other side, Rousseaux et al. (2002) considered a difference of 1 omission between the right and the left side as normal (95th percentile), and a difference of 5 as pathologic (5th percentile).

Test to assess extrapersonal neglect

Room description test

There are not yet standardised measures of unilateral neglect for far space. However, Stone et al. (1991b) described a simple bedside task to assess the patient's ability to detect objects in far space. In their test, they asked patients to point or name all the objects they could see on both sides of the hospital room. After to have checked that the distribution of objects on the left and right side of space was roughly the same, the examiner noted which objects were situated at 0, 45, 90, 135, and 180° landmarks. As the patient named and/or pointed the objects in the room, the examiner marked their approximate location and number of degrees. In a similar way, this test have been

used both by Frassinetti et al. (2002) and Serino et al. (2007, 2009) to test neglect in far space. In the same way, we tested patients in a room (7 x 4 m) provided with various objects arranged simmetrically (10 on the left and 10 on the right) respect of the room's midline. Patients sat on the wheelchair in the central longer side of the room. The objects were two chairs, two tables, a wastepaper basket, a dresser, a radiator, a window, a bookcase, and a low shelf. Patients were asked to name and/or indicate the objects seen in the room, without a time limit. The correct responses was recorded by the examiner. The maximum score is 20.

Semi-structured ecological scale (Zoccolotti & Judica, 1991)

This semi-structured scale was developed to assess the qualitative/quantitative asymmetries present in the exploration of space in neglect patients, in situations similar to those of everyday life. In the present study, we used only the subtest A (serve the tea) and C (deal the cards). Both the sub-tests has been recorded with a camcorder and the patient's performance was evaluated off-line by three examiners.

- **Sub-test A**: the patient is seated on a table, which is set for the tea. On the table there are 4 cups, 4 napkins, 4 teaspoon, 1 teapot, and 1 sugar bowl. The examiner is seated in front of the patient, and 2 other people are seated one on the left and one on the right side of the table, respect to the patient. Patient is asked by the examiner to serve the tea. The score is based on a three-level scale, which evaluates qualitatively how the patient serves the tea; the maximum score is 0, whereas the worst score is 3. There are no time limit to perform the test.

- **Sub-test C**: the patient is seated on a table. The examiner is seated in front of the patient, and 2 other people are seated one on the left and one on the right side of the table, respect to the patient. Patient is asked by the examiner to deal the cards as playing "broom". In this card-play, each player must have 3 cards. The score is based on a three-level scale, which evaluates qualitatively how the patient serves the tea; the maximum score is 0, whereas the worst score is 3. There are no time limit to perform the test.

Tests to assess personal neglect

Comb and Razor test (Beschin & Robertson, 1997)

This test was based on Beschin and Robertson (1997) test, using a more sensitive formula which characterises personal neglect as a lateral bias of behaviour rather than as a lateralised deficit (McIntosh et al., 2000). The equipment consists of one comb, one razor with shield on and one powder compact. The experimenter sat opposite to the patient and held up the combs saying: "I would like you to comb your hair, and continue combing until I tell you to stop". The experimenter activates the stopwatch as soon as the person takes the combs, and categories each stroke of the comb according to whether it is on the left of the head, or on the right of the head or ambiguous (i.e., not clearly on the right, not clearly on the left, or in the centre of the head). At the end of 30 seconds, the examiner tells the patient to stop. The entire test was videotaped and then the number of strokes of the comb in each of the three categories was analysed off-line. Instead, in the razor condition, which is used with men, the patient is told: "I am going to give you a razor (with shield on), and I would like you to use it like you are shaving. Continue shaving until I tell you stop". Timing begins as soon as the patient takes the razor, and the scoring is in the same format as for the comb task, namely number of stroke on the left, right and ambiguous. In the powder compact case, which is applied to women, the instructions are exactly equal to those for the razor test; the number of touches of the compact on the left or right side of the face, together with ambiguous responses have been recorded.

The formula to calculate the lateral bias of patients' behaviour is:

$$\%\text{bias} = \frac{\text{right} - \text{left strokes}}{\text{left} + \text{ambiguous} + \text{right strokes}} \times 100$$

Rightward bias yields a positive percentage score, whereas leftward bias yields a negative percentage score.

Fluff test (Cocchini et al., 2001)

The test required patients to remove all the targets attached to the front of their clothes (see Figure). The stimuli consisted of 24 identical circles (2 cm in diameter) made of white cardboard. The circles had velcro on one side to make it easy to attach them to clothes using little pressure. There were three stickers on the right (A–C) and three on the left (D–F) of the central body midline area, six stickers along the subject's left

arm (G–L), six along the right leg (M–R), and six along the left leg (S–Y). No targets were placed on the right arm as the task was performed using this arm. Each subject was blindfolded and seated whilst the targets were attached and he or she was not informed how many targets were present. Patients were distracted by engaging them in a conversation while the examiner attached each sticker, to avoid a bias on the results due to patients counting the stimuli. When the examiner finished attaching the targets, patients were asked to remove them while still blindfolded. There was no time restriction for the response and the test finished when the patient says that had collected all the stickers. Only the left omissions are considered to determine the cut-off score of 13 stickers detached out of 15 (86.7%).

Task to assess representational neglect

Mental number bisection task (Zorzi et al., 2002)

Stimuli consisted of pairs of numbers (e.g., 1-3, 1-5, 1-9, etc.). Each pair defined a number interval with an integer number in the middle (e.g., 1–5, midpoint = 3). Each number pair had a length of three (e.g., 1–3), five (e.g., 1–5), seven (e.g., 1–7), or nine (e.g., 1–9). The same number intervals were repeated within the units (i.e., numbers from 1 to 9; e.g., 1–7), the teens (i.e., numbers from 11 to 19; e.g., 11–17), and the twenties (i.e., numbers from 21 to 29; e.g., 21–27). The final set of stimuli comprised 48 number pairs subdivided into 16 pairs within the units, 16 pairs within the teens, and 16 pairs within the twenties. Each number pairs were presented aloud to the patients. Patients were asked to say what was the number halfway between each number interval, without making calculation (e.g., the examiner asked: "What number is halfway between 1 and 9"? Correct answer: "5"). There was no time limit to perform the task and stimuli were repeated to the participants if required. The examiner registered the patient's response; afterward, for each patient, the mean difference between observed (O) and correct (C) responses (dO-C) was computed for every number interval.

Test to assess motor functions

Motricity Index and trunk control test (Demeurisse et al., 1980)

The Motricity Index is a neurological scale to measure the motor impairment of a patient who suffered from a stroke or from other neurological disease. The scale provides a separate measure of the upper and lower limb, and of the movements of the

trunk. When the patient is seated, the movements of the superior limb are assessed with the pinch grip, the elbow flexion, and the shoulder abduction (maximum score = 100), whereas the movements of the inferior limbs are assessed with the ankle dorsiflexion, the knee extension, and the hip flexion (maximum score = 100). When the patient is on the bed, the examiner evaluates the trunk control asking patient to roll to the weak side, to roll to the strong side, to sit up from lying down, and to balance in sitting position on the side of the bed (maximum score = 100). The total score (i.e., 300) is considered for the statistical analysis.

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