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MOTOR NEGLECT: THEORETICAL AND CLINICAL ASPECTS

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ABSTRACT

Neglect is a disabling and complex neuropsychological condition, often conceived as a syndrome (Kerkhoff & Schenk, 2012). Neglect has received a considerable amount of attention in the scientific literature over the past quarter of a century (Punt & Riddoch, 2006). In humans, neglect typically affects the left side of space, opposite to right-hemispheric lesions (both cortical and subcortical). Neglect is present, on average, in 50% of cases in the acute phase following right-hemisphere stroke (Vallar & Calzolari, 2018). Behaviorally, patients fail to attend, orient, process, and respond to stimuli presented in the contralateral side of their body and fail to explore that space through body movements (Vallar & Calzolari, 2018). Neglect can affect several modalities and can be distinguished into different subtypes, resulting from a variety of ipsilesional and contralesional deficits (Vallar & Calzolari, 2018).

The motor subtype of neglect is among the most important and, probably, the least understood neuropsychological disorders of motor intention (Saevarsson, 2013). Motor neglect is very frequent after right-hemisphere injury, with a high number of patients presenting the disorder in the acute phase post stroke (Sampanis & Riddoch, 2013). Motor neglect manifests as the failure of patients to use or act with their contralesional hemibody in the absence of sensorimotor deficits (Bartolomeo, 2021a; Laplane & Degos, 1983); anosognosia is a crucial feature of these patients' behavior (Kerkhoff, 2001). Motor neglect doubly dissociates from deficits affecting motor production and deficits responsible for a directional motor bias (Bartolomeo, 2021b). Nevertheless, in severe cases, distinguishing motor neglect from these deficits becomes a problematic and challenging task (Punt & Riddoch, 2006).

The present thesis aimed to introduce the main theories and clinical aspects of motor neglect. Chapter 1 focused on the neglect syndrome, explaining its subtypes and manifestations, theoretical models, neuroanatomical correlates, assessment procedures, and rehabilitation approaches. In Chapter 2, an in-depth description of motor neglect was presented. Special efforts were made to analyze motor neglect features and related deficits, examine the underlying mechanisms, present the neuroanatomy of the disorder, and describe current therapeutic techniques. In the final chapter (i.e., Chapter 3), general comments regarding the limitations influencing the assessment and rehabilitation procedures were discussed, and future directions for research were proposed.

CHAPTER 1:

NEGLECT

1.1. Neglect definition, characteristics, and subtypes

The term neglect refers to the acquired neuropsychological disorder of contralesional spatial awareness. Across the decades, the scientific literature has extensively relied on synonyms while referring to the concept of neglect (e.g., spatial hemineglect, hemispatial neglect, hemi-inattention, hemisensory neglect, etc.), with over 200 different terms used to indicate the disorder per se or one of its subtypes. This inconsistency concerning the terminology possibly results from the heterogenous nature of the disorder in question. As a matter of fact, since the early studies on neglect in the 1970s, the complexity of the disorder and the varied pattern of impairments of the affected patients have caught the attention of the scientific field, which currently conceives neglect as a syndrome (Vallar & Calzolari, 2018). The term "syndrome" greatly anticipates the heterogeneity of this disorder, which cannot be approached or interpreted in a single manner and cannot be explained solely by a single exogenous and/or endogenous spatial orientation, sensory, or motor deficit (Rode et al., 2017).

Historically, a complete and operational definition of neglect was proposed by Kerkhoff (2001), who has described neglect, and more specifically, sensory neglect, as *"the impaired or lost ability to react to or process sensory stimuli (visual, auditory, tactile, olfactory) presented in the hemispace contralateral to a lesion of the human right or left cerebral hemisphere"*. In other terms, this syndrome is characterized by a *"behavioral bias directed ipsilaterally to the damaged hemisphere and loss of spatial awareness for the contralesional side"* (Rode et al., 2017). Consequently, patients affected by right-hemisphere damage fail to look, listen to, feel, and react to visual, auditory, and tactile events in the contralesional space, as well as to orient their attention towards them. Neglect patients also fail to perform movements directed towards the contralateral side of space and objects present in it, and they use their contralateral limbs less (Vallar & Calzolari, 2018).

From a clinical perspective, given that a variety of deficits are encountered in neglect, separating the disorder into subtypes may provide useful information (Adair et al., 1998). The existence of separable spatial neglect subtypes is not only proven by a variety of observable, concrete deficits, but it is further documented by a remarkable number of dissociations between assessment methods used to detect the disorder, which will be later described (Adair & Barrett, 2008; Buxbaum et al., 2004).

To begin with, a very first distinction differentiates the sensory modality of neglect (i.e., visual neglect, auditory neglect, olfactory neglect, somatosensory neglect), the motor modality of neglect (i.e., motor neglect), the representational modality of neglect (i.e., representational neglect), the one affecting the dimension of the spatial sector (i.e., personal neglect, peripersonal neglect, extrapersonal neglect), and finally the one concerning the dimension of reference frame (i.e., egocentric neglect and allocentric neglect; Vallar & Calzolari, 2018).

Within the affected sensory modality, visual neglect is the most frequent one. It is defined as the inability to attend stimuli presented in the contralesional space (Rode et al., 2017) and may manifest with or without associated sensory deficits. The hemianopias[1] and the quadrantanopias[2] are examples of visual sensory deficits that often co-occur with visual neglect (Vallar & Calzolari, 2018). Distinguishing visual neglect from visual sensory deficits (e.g., hemianopia, quadrantanopia) can be sometimes difficult, because neglect at times mimics the clinical picture of visual sensory disorders. Similarly, to visual neglect, somatosensory (tactile) neglect can mimic the clinical picture of hemianesthesia[3] (Rode et al., 2017). Nevertheless, the analysis of anatomical lesions and quantitative assessment methods can contribute to the differential diagnosis between neglect and sensory deficits.

As for motor disorders, motor neglect manifests with the spontaneous loss or underutilization of the contralesional limbs in the absence of primary motor or sensory deficits. Typically, the impairment is global and affects proximal/distal movements as well as voluntary gestures, even though the underlying mechanisms should still be refined. The signs of motor neglect could mimic the ones observed in hemiparesis[4] and hemiplegia[5], which may largely be manifestations of motor neglect, but never its cause (Vallar & Calzolari, 2018).

Neglect may also impact the processing of mental images, negatively affecting the patient's point of view and resulting in what has been defined as representational (or

[1]*Hemianopia (or hemianopsia)*: *"Visual field defect marked by loss of vision in half the normal visual field"* (American Psychological Association, 2022).
[2]*Quadrantanopia (or quadrantanopsia)*: *"Loss of vision in one fourth, or one quadrant, of the visual field"* (American Psychological Association, 2022).
[3]*Hemianesthesia: "Loss of sensitivity to stimuli on one side of the body"* (American Psychological Association, 2022).
[4]*Hemiparesis*: "*Partial loss of strength in one side of the* body" (Stirling & Elliott, 2008).
[5]*Hemiplegia: "Total loss of strength in one side of the body"* (Cleveland Clinic, 2023).

imaginal) neglect. This is the case of the famous Piazza del Duomo experiment (Bisiach & Luzzatti, 1978). When patients are asked to mentally visualize their main town square or a country-map, they only report ipsilesional landmarks (Rode et al., 2017). Nevertheless, when patients are asked to describe the same mental image, but from the diametrically opposite viewpoint, they ignore the originally reported landmarks, but they report the originally omitted ones. Imaginal neglect has been also reported when patients are required to recall cities from a country map, or when they have to remember specific details from their own homes (Kerkhoff, 2001).

The physical space can be affected by neglect, either in a global or a dissociated manner. Generally, space is divided into separate discrete zones (Adair & Barrett, 2008):

(a) Personal space (i.e., the space occupied by the body). Patients affected by personal neglect ignore the contralesional side of their body (e.g., they dress and groom only the ipsilesional side of their body).
(b) Peripersonal space (i.e., the space within reaching). Patients affected by peripersonal neglect ignore the contralesional side of the reaching space (e.g., they eat food only in the ipsilesional side of their plate).
(c) Extrapersonal space (i.e., the space beyond reaching). Patients affected by extrapersonal neglect ignore the contralesional side of the beyond-reaching space (e.g., they are aware only of cars in the ipsilesional side of a crossroad).

The impaired contralesional side in neglect can be defined by distinct spatial frames of reference (i.e., egocentric vs. allocentric coordinates). In egocentric neglect, errors increase as a function of stimulus position with respect to the viewer's body. Thus, if egocentric neglect patients are presented with a variety of stimuli, they will commit no errors for stimuli on the right, some errors for stimuli in the middle, and many errors for stimuli on the left side of space (Rode et al., 2017). In allocentric neglect, errors are located in the intrinsic contralesional side of the stimuli, regardless of the spatial location of the stimuli with respect to the viewer's body. In other words, allocentric neglect implies that a patient ignores the left side of a stimulus, such as an object, a word, a face, regardless of the stimulus location in space (Kerkhoff, 2001; see Figure 1A, B).

1.2. Neglect manifestations

It has been proposed that the existence of the aforementioned neglect subtypes results from different underlying deficits. More specifically, neglect can be characterized by two sets of abnormal signs, negative (i.e., defective) manifestations and positive (i.e., productive) manifestations. Those manifestations may be found together or in isolation and they have partly distinct neuropathologic correlates (Vallar & Calzolari, 2018).

When right-hemisphere-damaged patients exhibit the absence of the appropriate behavior, as required by the experimental task, or, more generally, by the activities of daily living (ADL) setting, then it is reasonable to talk about negative manifestations (Vallar & Calzolari, 2018). These may be witnessed across all processing modalities and affect a variety of dimensions of the personal, peripersonal, and extrapersonal space.

Defective manifestations of neglect may vary as a function of perceptual attentional deficits (e.g., visual neglect, auditory neglect, somatosensory neglect), representational attentional deficits (i.e., representational neglect), deviated reference frames (i.e., egocentric neglect, allocentric neglect), and finally motor/intention deficits (i.e., motor neglect; Rode et al., 2017). Except for motor neglect, these deficits are typically associated with damage to the posterior parietal cortex (Vallar & Calzolari, 2018).

Positive manifestations can concern either the ipsilesional or the contralesional space (Rode et al., 2017). The main features of positive manifestations are characterized by the production of unnecessary actions or the manifestation of delusional beliefs that are inappropriate with respect to the setting presented. Positive manifestations can be observed both in the personal and the peripersonal space, as well as in the extrapersonal space. In the personal space, a productive manifestation is somatoparaphrenia, a phenomenon defined as a diverse set of delusional bodily disorders involving the contralesional limbs. In other words, patients can experience a sense of unfamiliarity towards the contralesional body parts, a sense of separation and disownership from their contralesional body to the point of believing that the affected body parts belong to another person and not to them.

Productive manifestations in peripersonal space include three main aspects:

(a) Ipsilesional perseveration, which is characterized, for instance, by the needless multiple marking of the same target located in the right-hand side of the sheet in a target cancellation task (see Figure 1D);

(b) "Magnetic" attraction towards ipsilesional stimuli;

(c) Avoidance of stimuli occurring in the contralateral side of space.

Moreover, as opposed to defective manifestations, productive manifestations are not a correlate of posterior parietal cortex damage (Vallar & Calzolari, 2018; see Table 1).

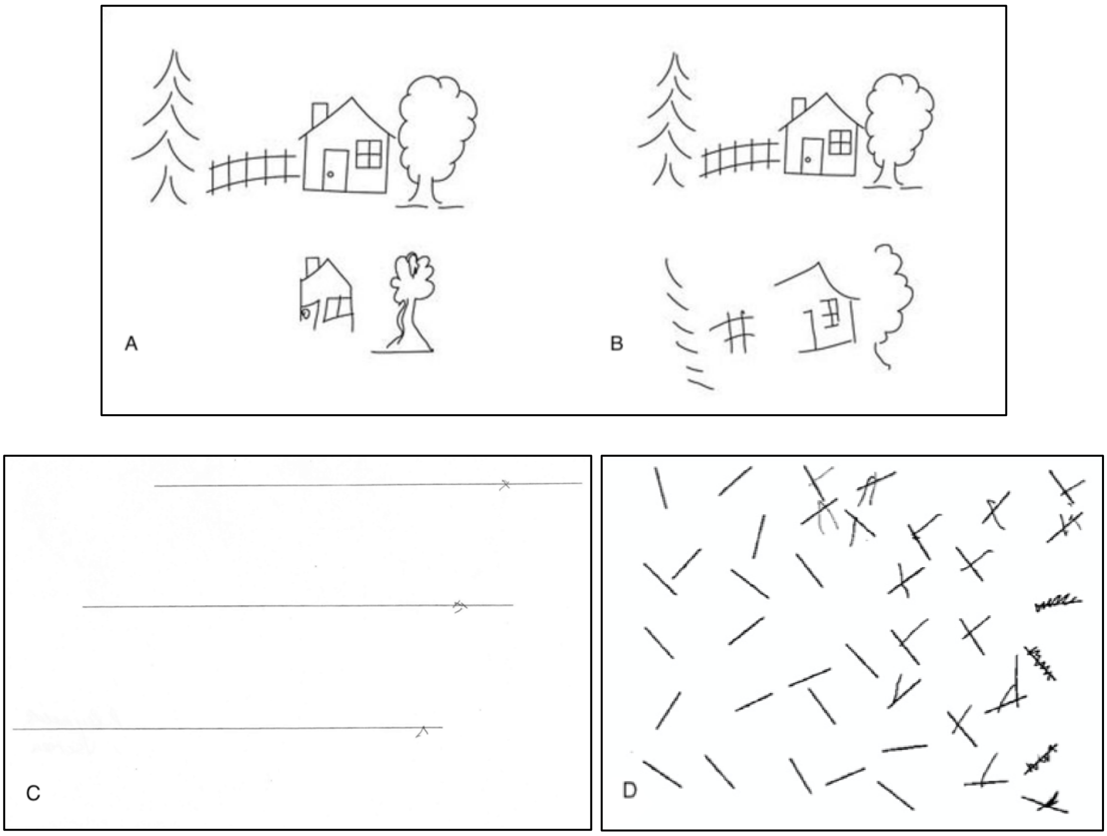

FIGURE 1. Defective and productive manifestations of left spatial neglect. (A) An example of egocentric neglect in comparison with an example of (B) allocentric neglect in a drawing task. In the first case, errors increase as a function of the stimulus position with respect to the viewer's body. In the second case, no increase of errors from right to left is detected; rather, the left side of the stimulus is totally ignored independently of its spatial position with reference to the viewer's body. (C) Example of a line bisection task. The patient failed to check the midpoint of the line, shifting it to the right end of it (Vallar & Calzolari, 2018). (D) Example of perseveration errors in a target cancellation task. The patient repeatedly canceled the same targets in the right-hand side of the sheet and selectively omitted all lines in the left-hand side (Rode et al., 2017).

TABLE 1. Neglect subtypes.

DIMENSION	TYPE OF NEGLECT	SYMPTOMS	DIFFERENTIAL DIAGNOSIS	PROCESSING MODALITY	SPACE
Sensory	Visual neglect	Omission, perseveration	Hemianopia	Sensory/attention	Peripersonal, extrapersonal
	Auditory neglect	Omission, sound localization	Deafness	Sensory/attention, representation	Peripersonal, extrapersonal
	Somatosensory neglect	Omission, tactile localization	Hemianesthesia	Sensory/attention, representation	Personal
	Olfactory neglect	Omission, olfactory localization		Sensory/attention, representation	Personal
Motor	Motor neglect	Under-utilization	Hemiplegia, motor extinction, directional hypokinesia	Motor intention	Personal
Representational	Representational neglect	Omission		Attention, representation	Personal, peripersonal, extrapersonal
Range of space	Personal neglect	Omission, distortion	Anosognosia, somatoparaphrenia	Attention, representation	Personal
	Peripersonal neglect			Attention, representation	Peripersonal
	Extrapersonal neglect			Attention, representation	Extrapersonal
Reference of frame	Allocentric neglect	Omission, perseveration, addition, allochiria	Hyperschematia	Attention	Peripersonal, extrapersonal
	Egocentric neglect	Omission, head/eye deviation		Attention, representation	Peripersonal, extrapersonal

1.3. Theoretical models to explain neglect

Theoretical models mainly vary in terms of the physiological mechanisms they propose. The majority of them focuses on specific visual aspects of neglect and analyzes the differences in the prevalence of the disorder in the right and left side of space (Zebhauser et al., 2019). Even though it is difficult to distinguish among these models, some of them claim compatible hypotheses and propose matching results. It seems unlikely, in fact, that one single theory can explain all features of spatial neglect, given both the heterogenous and dissociable phenomena of the disorder, as well as the anatomically large lesion sites so far studied in neglect patients. According to Kerkhoff (2001), the current theories can be grouped into four main categories: attentional, representational, transformational, and cerebral balance theories.

Attentional theories offer a quite acceptable explanation for neglect. Within attentional theories, Posner's spotlight-of-attention theory is one of the most influential. Together with his colleagues, Posner has proposed that the core deficit in neglect patients is the disengagement of spatial attention[6] from a current ipsilesional focus to a contralesional stimulus (Kerkhoff, 2001). Specifically, it has been assumed that orienting spatial attention occurs through three mental operations (Zebhauser et al., 2019):

1. Disengagement of spatial attention from the current stimulus location (inferior parietal lobule);
2. Movement of spatial attention to a new stimulus location (superior colliculi);
3. Engagement of spatial attention to the new stimulus location (pulvinar).

According to Posner's et al. theory, parietal lesions should result in a disengagement deficit of spatial attention, which could possibly explain why patients affected with neglect have difficulties in directing their spatial attention contralesionally. Nevertheless, this theory does not justify why patients preferentially search stimuli in their right side in situations of total darkness and in the absence of sensory stimuli (Posner et al., 1984, as cited in Kerkhoff, 2001).

Apart from Posner's theory, Kinsbourne's orienting vector model has obtained considerable support. This theory postulates that both the right and the left hemisphere contain an orienting vector specialized in directing spatial attention to the contralateral hemispace. In healthy persons, these vectors create the overall vector that coordinates spatial

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[6] *Spatial attention:* type of attention that involves directing attention to a location in space (American Psychological Association, 2022).

attention (Kinsbourne, 1987, as cited in Kerkhoff, 2001). According to the model, lesions to this attentional network will consequentially lead to a hypoactivity of the lesioned (i.e., right) hemisphere and a hyperactivity of the intact (i.e., left) hemisphere (Zebhauser et al., 2019), a phenomenon referred by Kinsbourne as "right-side hyperattention".

The activation of the intact left hemisphere, which because of the right-hemisphere lesion becomes disinhibited, automatically forces patients to orient their spatial attention towards the right side of the space (Bartolomeo, 2021b). Consequently, neglect patients become magnetically attracted by stimuli presented in their ipsilesional side of space. Interestingly, a combination of Kinsbourne's orienting vector model and Posner's spotlight-of-attention theory may explain how a hyperactivation on the left hemisphere and pathological hypoactivation of the right hemisphere can be responsible for the entire picture regarding neglect.

Heilman and Van Den Abell (1980, as cited in Kerkhoff, 2001) have suggested that a right hemisphere dominance in spatial attention could potentially explain the hemispheric asymmetry observed in the frequency and severity of spatial neglect. Mesulam (1998, as cited in Kerkhoff, 2001) has supported this idea with neuroanatomical evidence showing a neural network contained in the right hemisphere and specialized for both the left and right hemispaces. Indeed, neglect is more frequent after right-hemisphere than after left-hemisphere damage. Mesulam (1981, as cited in Zebhauser et al., 2019) has motivated this assumption by explaining that while the left hemisphere orients spatial attention only towards the right side of space, the right hemisphere orients spatial attention towards both the left and the right sides of space.

Representational theories assume that the perception of every sensory event requires, indeed, a representation. In particular, Bisiach and Luzzatti's model of topological space (1978, as cited in Kerkhoff, 2001) is based on the idea that neglect may result from an impairment in the representation of contralesional stimuli. This fact, in neglect patients, translates as an enlarged representational space in the left side and a constricted representational space in the right side. Compatible to this model is Rizzolatti and colleagues' theory (1997, as cited in Kerkhoff, 2001). They have considered the cerebral structures that represent different parts of space and explained how lesions to one of these structures -located mostly, in the premotor cortex- can cause contralesional neglect.

According to transformational theories, neglect results from an impairment in the transformation from a sensory information into a motor action. Thus, the necessary input-to-output coordinate transformation that occurs in healthy brain subjects is compromised in brain-damaged patients (Kerkhoff, 2001). According to Karnath and Vallar (2002; 1986, as cited in Zebhauser et al., 2019), these mechanisms are implemented in the parietal cortex. Lesions to the parietal cortex could cause a consistent error leading to the ipsilesional gaze-deviation and head-to-trunk-orientation, typical of neglect patients. Nevertheless, transformational theories fail to deal with allocentric and egocentric neglect and do not seem to attempt any explanation on this regard in their framework (Kerkhoff, 2001).

One last viewpoint has been advanced by supporters of the cerebral balance theories. Inspired by the imbalanced spatial attention mechanisms proposed by some of the attentional theorists, Sprague, Payne and Lomber (1966; 2002, as cited in Zebhauser et al., 2019) conducted pioneering experiments that gained support by human and animal research. Similar to Kinsbourne's theory, their model proposes that it is the relative (in)balance between cortical and subcortical structures in the lesioned and intact hemispheres to determine neglect, rather than the absolute level of neural activity within each cerebral hemisphere (Kerkhoff, 2001). As a matter of fact, cerebral balance theorists observed that cooling the superior colliculus (SC) in humans and the posterior middle-suprasylvian cortex (PmS) in cats caused a profound visual neglect of the contralesional side of space. In these cases, visual neglect could be abolished by the successive cooling of the homologue area in the other hemisphere. Interestingly, this theory has strong implications for the development of neglect treatment techniques (Kerkhoff, 2001).

As previously anticipated, some theoretical models of spatial neglect are mutually compatible for what regards proposed assumptions and reached conclusions, even though this is rarely admitted by their proponents (Kerkhoff, 2001). Regardless of the fact that the aforementioned models overall provide a detailed picture in the etiology of neglect, a comprehensive integration of the multitude of underlying symptoms and manifestations of the disorder is the next target to be reached.

1.4. Neuroanatomy of neglect

In the past 40 years of research, knowledge on the neuroanatomy and recovery of neglect has greatly progressed. Undoubtedly, strokes in the right middle cerebral artery that cause damage to the inferior parietal cortex and adjacent structures is so far the most frequent lesion site underlying the neglect syndrome (Kerkhoff, 2001). For a long time, neuroscientists have believed that damage to the posterior parietal lobe, involving the inferior parietal lobule (IPL) and the temporoparietal junction (TPJ), particularly of the right hemisphere, plausibly seemed to be responsible for the onset of neglect (Vallar & Calzolari, 2018).

In the early 1970s, however, it became clear that neglect could be associated also to lesions of the ventrolateral and dorsolateral premotor cortices, and to the dorsolateral and medial prefrontal cortices. More recently, neglect onset has been associated with lesions to the superior temporal gyrus (STG), to the thalamus, and to white-matter fiber tracts (Vallar & Calzolari, 2018).

Beyond stroke, neglect may also result after tumors, traumatic brain injury, or neurodegenerative disorders affecting the aforementioned brain areas. Neglect can be present, on average, in 33% of patients with left-hemisphere damage and more than 50% of patients with right-hemisphere damage. Thus, lesions to both hemispheres can result in neglect. Nevertheless, interhemispheric asymmetries have revealed that neglect is more severe, frequent, disabling, and permanent following right-hemisphere damage (Kerkhoff, 2001).

Within the right hemisphere, lesions responsible for neglect are typically localized in the postero-inferior portions of the parietal lobe, the frontal lobe, the cingulate gyrus, the thalamus, and the basal nuclei. It is reasonable to believe that these cerebral structures do not have a special role per se, but rather they result in network-based dysfunctions affecting the spatial attention circuits (Bartolomeo, 2021b).

The existence of a causal link between neglect in patients with right or left parietal impairments and spatial orientation/attention deficits has been positively supported by the findings of a variety of studies (Buxbaum et al., 2004; Kerkhoff & Zoelch, 1998). In addition, evidence from meta-analyses has suggested that egocentric neglect may result from damage to white-matter fiber tracts, the precentral and the postcentral gyri, the supramarginal gyrus of the inferior parietal lobule (IPL), and the superior temporal gyrus (STG). By contrast, the angular gyrus (AG) of the inferior parietal lobule (Vallar & Calzolari, 2018) and mostly, the posterior inferior temporal gyrus of the superior temporal lobe (Medina et al., 2009) are considered as the cerebral correlates responsible for allocentric neglect signs.

Recently, thanks to a voxel-based analysis, it has been possible to associate personal neglect with damage to the inferior parietal lobule (IPL), and extrapersonal neglect with damage to the temporal cortex (in particular, in the superior/middle temporal gyri), the dorsolateral prefrontal cortex, and the precentral cortex (Adair & Barrett, 2008; Vallar & Calzolari, 2018). As for motor neglect, a variety of lesion locations have been studied in both the right and left hemisphere, though, more on this will be later described.

Somatoparaphrenia and other productive manifestations have been associated with damage to the frontal lobe, right subcortical structures (i.e., basal nuclei and white matter), inferior parietal lobule (IPL), posterior parietal/temporal lobes, and to the insula (Vallar & Calzolari, 2018).

Homologue lesions to the left hemisphere rarely lead to the same defective manifestations as those following right-hemisphere damage. Signs of right neglect can be observed following bilateral hemispheric damage, indicating that some degree of right hemisphere dysfunction -potentially in the ventral branch of the superior longitudinal fasciculus (SLF III) -may be necessary for right-side neglect to manifest (Bartolomeo, 2021b). Nevertheless, little is known on the precise lesion locations concerning right neglect, as the majority of studies has focused on patients affected by left neglect (see Figure 2).

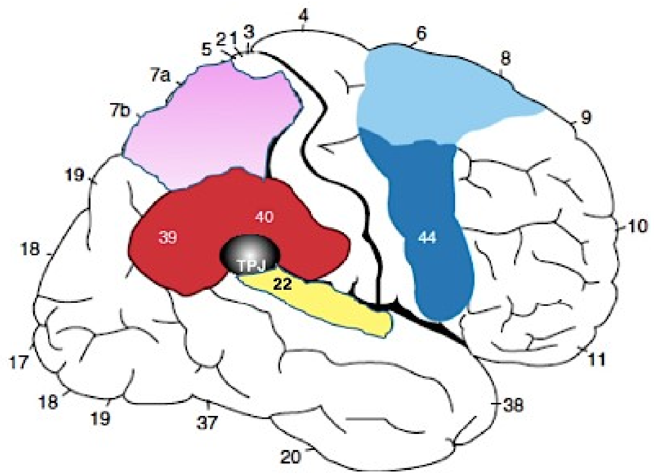

FIGURE 2. The lateral surface of the right hemisphere with most relevant regions associated with neglect highlighted in different colors. Inferior parietal lobule (IPL, red): angular gyrus (AG: Brodmann area (BA) 39), supramarginal gyrus (SMG: BA 40). Superior parietal lobule (SPL: BAs 7 and 5, pink). Posterior part of the superior temporal gyrus (STG: BA 22, yellow). Temporoparietal junction (TPJ, black). Premotor cortex (BA 44, blue; BAs 6 and 8, azure; Vallar & Calzolari, 2018).

1.5. Assessment methods

Diagnosing neglect can be sometimes challenging. The manifestations of neglect are heterogenous and currently there exists no single test that can precisely detect all types of neglect. Nevertheless, adopting a certain type of assessment method allows clinicians to distinguish between spatial neglect subtypes. Traditionally, the quantitative assessment of spatial neglect has relied on four types of tasks (Vallar & Calzolari, 2018): cancellation, line bisection, drawing by copy, and drawing from memory.

The standard version of the cancellation task requires the patient to find out and mark items presented on a certain area delimited in the paper sheet. Several other versions of the task are available (Adair & Barrett, 2008). A frequent "defective" error committed by neglect patients, on this task, is the omission of targets in the contralesional side of the display (Vallar & Calzolari, 2018).

On the line bisection task, a series of horizontal lines of varying length are presented to the patients. These lines are aligned with the midsagittal plane of the patient's body, and the main task consists of dividing the line into two equal segments (i.e., bisection). Generally, spatial neglect patients fail to mark the midpoint of the line, by subjectively shifting it towards the ipsilesional end of the line. A variant of this test, not requiring a motor response, is the landmark test. On this test, the lines are pre-bisected, and participants must judge which of the two halves of the line is longer or shorter (Vallar & Calzolari, 2018; see Figure 1C).

Another highly used task to assess neglect is drawing. Patients are asked to draw a copy of a figure they are presented with or to draw it from memory. Patients' performance is evaluated both on the number of contralesional omissions and on the asymmetry of the details in both the left and right side of the drawing. Typically, the contralesional side of copies and drawings from memory are inaccurate and incomplete (Vallar & Calzolari, 2018).

It is reasonable to acknowledge and remember that target cancellation, drawing, and line bisection tasks do not distinguish between the perceptual and intentional components of unilateral spatial neglect. Indeed, beyond perceptual awareness, these tasks also require a motor exploratory activity. From recent versions of these tests, it has become possible to conclude that impaired input (i.e., perceptual) and/or output (i.e., intentional) processes may contribute to the defective contralesional exploration (Vallar & Calzolari, 2018).

All the aforementioned assessment methods require some degree of visuomotor integration and coordination. Nevertheless, there exist tasks entailing no limb motor response which can alternatively be useful to test spatial neglect. For instance, in the Wundt-Jastrow illusion task patients are presented with two identical shapes whose configuration induces non-affected individuals to misjudge one figure and extend further to the left. Nevertheless, neglect patients tend to select the shape which extends further to the right, experiencing then the opposite illusion. The same spatial bias can also be expressed in the Landmark test. One last method for eliciting neglect without limb movement is spatial analysis of reading, where neglect patients typically fail to read words from the left side of a text (Adair & Barrett, 2008).

Not all patients show neglect on all the abovementioned tests and this is consistently motivated by the multicomponential nature of the neglect syndrome, which assumes different patterns of deficits occurring in different patients. Thus, in order for clinicians to achieve an adequate diagnostic sensitivity, it is recommended to test patients with a variety of tests (Bartolomeo, 2021b).

1.6. Rehabilitation approaches

Neglect represents a significant obstacle to successful rehabilitation outcomes, and currently no consensus exists regarding a well-established, evidence-based rehabilitation approach. Although some consensus does exist concerning recovery of the most common neglect symptoms, limited information is available about the recovery of functional activities of daily living (ADL; Adair & Barrett, 2008). Therefore, neglect can be seen as a substantial negative predictor of successful rehabilitation from brain lesions (Kerkhoff, 2001). Statistically, it has been observed that 75% of left neglect patients recover from signs of neglect within the first six months, whereas in the remaining 25% signs may last for up to 12 years from onset (Kerkhoff, 2001).

Among the early treatment approaches presented in the 1970s, visual exploration training is undoubtedly the most prominent one. This is a top-down approach which activates scanning by means of voluntary spatial attention orienting. Through operant conditioning techniques and verbal/non-verbal cues, patients are required to actively explore the contralesional side of space. The use of visual exploration training, in neglect patients, has led to improvements of spatial search strategy and speed (Kerkhoff, 2001).

Bottom-up approaches have been also used in neglect rehabilitation. These are rehabilitation techniques that require less active participation from the patient, and that capitalize on the idea that a multitude of sensorimotor processes are responsible for reducing neglect sings. These techniques include, optokinetic stimulation (OKS), caloric vestibular stimulation, and electrical stimulation, either vibratory or transcutaneous, to the left paracervical muscles (Adair & Barrett, 2008). Finally, prism adaptation (PA) has been recently employed and its benefits extends to functional activities of daily living (Serino et al., 2006). Pharmacotherapy could also be considered a type of bottom-up intervention (Adair & Barrett, 2008). Nevertheless, no firm conclusion on the benefits of pharmacotherapy is possible at present (Kerkhoff, 2001).

It is reasonable to acknowledge that in spite of the several improvements that have been made in the development of treatment techniques for neglect, several patients *"remain impaired at the end of clinical rehabilitation"*, indicating that effective treatment techniques are urgently required in this field (Kerkhoff, 2001).

CHAPTER 2:

MOTOR NEGLECT

2.1. Motor neglect definition, characteristics, and assessment

The term motor neglect, to indicate a deficit of contralesional motor awareness, has been extensively interchanged and redefined over the years to the point of misusing it to describe other similar neuropsychological disorders. The term motor neglect refers to *"the behavior of patients with unilateral brain damage, who underuse the limbs contralateral to their lesion, in the absence of sensorimotor deficits that might account for such behavior"* (Bartolomeo, 2021a). Underuse of the contralesional limbs should not be explained by defects of muscular strength, reflexes, or somatic sensibility (Laplane & Degos, 1983). Typically, patients affected by motor neglect show a consistent loss of movement of the contralesional limbs (Rode et al., 2017), but they present normal dexterity and strength when specifically solicited to move them (Toba et al., 2021).

Laplane and Degos (1983) named this deficit "motor neglect" for the first time. In their study, they involved 20 stroke patients presenting mainly right hemisphere lesions, who showed signs of pure motor neglect without basic sensori-motor deficits (Laplane & Degos, 1983). The seminal work of Laplane and Degos provided a detailed clinical description of the common behaviors observed on motor neglect patients (Punt & Riddoch, 2006). These behaviors included:

1. No or little movement of the contralesional limb while gesturing;
2. No or little involvement of the contralesional limb in activities of daily living (ADL) requiring bimanual tasks (e.g., opening a bottle, clapping hands, buttoning/unbuttoning a shirt, etc.);
3. A tendency to use the ipsilesional limb although the contralesional limb would be more convenient in a certain situation;
4. The disturbance can affect both extremities, but a predominance of the upper limb was detected;
5. While walking, the contralesional limb may fall behind the ipsilesional limb;
6. Confabulations are sometimes produced by patients to justify their limbs' underutilization;

7. Improvement of performance when attention is drawn to it;
8. Normal or relatively normal performance of the contralesional limb when the patient is actively encouraged to use it (Laplane & Degos, 1983).

Motor neglect is usually a transient and regressive deficit (Rode et al., 2017). In stroke patients, motor neglect is more common in the acute phase (12-23%) than in the chronic phase (8%; Rode et al., 2017). Motor neglect occurs after lesions either to the right or to the left hemisphere. Nonetheless, Laplane and Degos (1983) reported that cases of left-sided motor neglect after right-hemisphere damage were overall predominant (see also Kojović & Bhatia, 2019). So far, few cases of right-sided motor neglect have been reported in the literature, with only one patient still presenting the disorder after years from lesion onset (Priftis et al., 2022).

At present, it is challenging for neuropsychologists to objectively evaluate motor neglect on affected patients and its clinical diagnosis is exclusively subjective, based on the observation of spontaneous motor behavior (Bartolomeo, 2021b; Rode et al., 2017). Nevertheless, Toba et al. (2021) have recently proposed differential actigraphy as a novel technique that could objectively quantify the disorder. Patients were asked to wear wristwatch-like accelerometers, which are motion sensor detectors that record spontaneous motor activity of the patients' upper limbs in a time period of 24 hours. Motion detection sensor provide both continuous assessment of spontaneous motor movements and measures of asymmetries between right and left upper limbs. This approach to differential actigraphy offers a sensitive and automatized procedure to follow-up motor behavior in neurological patients (Toba et al., 2021).

2.2. Motor neglect and related disorders

A major distinction must be drawn between input and output neglect (Vallar & Calzolari, 2018). Spatial attention is not a unitary concept and, by considering all the types of dissociations reported in the literature, it is plausible to assume that there exist different spatial attention circuits in the human brain (Adair et al., 1998). Clinically, neglect behavior has been dichotomized into unawareness of the contralesional space (resulting in input neglect) and improper execution of movements (resulting in output neglect; Adair et al., 1998). In other words, impaired attention processing of the contralesional side of the body could impact perception, action, or both (Toba et al., 2021).

When patients fail to attend contralateral sensory stimuli (e.g., visual neglect, auditory neglect, olfactory neglect, somatosensory neglect), their condition is a result of input neglect

(Vallar & Calzolari, 2018). By contrast, when patients encounter difficulties in the execution of movements (e.g., motor neglect, directional hypokinesia), regardless of adequate perception of the contralesional personal and peripersonal space, then it is more appropriate to talk about output neglect (Adair et al., 1998).

To avoid misdiagnosis, however, it is important to differentiate motor neglect from some motor deficits that are totally independent from but could be associated with motor neglect, and can therefore resemble its clinical picture (Bartolomeo, 2021b). For simplicity, it has been suggested to classify these deficits into two categories, respectively those that affect the contralesional limb with a deficit in motor production (e.g., hemiparesis or hemiplegia, and motor extinction), and those responsible for a directional/space motor bias towards the contralesional space independently of the limb used (e.g., directional hypokinesia; Punt & Riddoch, 2006).

With respect to motor production deficits, research indicates that in many patients, following stroke, motor neglect may masquerade as hemiparesis, and, in severe cases, it can ultimately mimic hemiplegia (Punt & Riddoch, 2006; Vallar & Calzolari, 2018). At first glance, both hemiparetic/hemiplegic patients and motor neglect patients may show faulty motor execution of the contralesional limbs. Moreover, the presence of correlated signs between motor neglect and hemiparesis/hemiplegia can impact motor neglect diagnosis (Punt & Riddoch, 2006), being this merely observational. Nevertheless, the literature suggests that double dissociations exist between motor neglect, on the one hand, and hemiparesis/hemiplegia, on the other hand (Vallar & Calzolari, 2018).

As a matter of fact, hemiparesis and hemiplegia clinically differ from motor neglect (Toba et al., 2021). Hemiparesis and hemiplegia are muscle strength disorders originating from lesions to the corticospinal pathway; their difference mainly lies in the degree of impairment, which is partial in hemiparesis and total in hemiplegia (Siekierka-Kleiser et al., 2006). By contrast, motor neglect is due to damage to higher level processing underlying the intention to act with the contralesional limbs towards any side of space (Kojović & Bhatia, 2019; Siekierka-Kleiser et al., 2006).

Unlike patients with hemiparesis and hemiplegia, who present impaired muscular strength, motor neglect patients are not paralyzed or plegic and do not present pyramidal signs (Bartolomeo, 2021b; Punt & Riddoch, 2006). In addition, it has been suggested that when motor neglect patients are verbally solicited to move their contralesional limbs, their increased attention can lead to successful performance (Laplane & Degos, 1983), but this cannot be achieved by hemiparetic/hemiplegic patients, as a consequence of their disorder.

Motor extinction[7] is another deficit of contralesional motor awareness, which can either co-occur with motor neglect or appear in isolation (Kojović & Bhatia, 2019). In more general terms, sensory extinction can manifest in different sensory modalities (e.g., visual extinction, tactile extinction, acoustic extinction), that may present independently from one another (Vallar & Calzolari, 2018). Typically, sensory extinction, which double dissociates from motor extinction, is tested with both unilateral and bilateral simultaneous stimuli. Patients with sensory extinction accurately respond to unilateral stimuli but fail to detect contralesional stimuli, when simultaneously presented with ipsilesional stimuli (Punt & Riddoch, 2006). Likewise, in motor extinction, patients' ability to use contralesional limbs is intact in isolation but impaired in bimanual tasks (Kojović & Bhatia, 2019). In other words, patients with motor extinction can raise either limb alone, but when asked to raise simultaneously both limbs, they raise only the ipsilesional one (Kojović & Bhatia, 2019).

Disproportionate poor performance of the contralesional side during bimanual activity is, indeed, a clinical feature of motor neglect (Punt & Riddoch, 2006). Nevertheless, contrary to extinction, motor neglect can be observed in both unimanual (i.e., with the contralesional limb) and bimanual tasks (Kerkhoff, 2001). Moreover, as it is the case for hemiparesis/ hemiplegia, also motor extinction patients do not improve their performance in bimanual tasks when verbally solicited to do so (Kojović & Bhatia, 2019). The distinction between motor neglect and motor extinction is further strengthened by the differential lesion sites associated with the two disorders, though damage of overlapping neural circuits (e.g., in the frontal lobe) may cause motor neglect and motor extinction to occur in conjunction (Kerkhoff, 2001).

As concerns directional motor disorders, motor neglect has been frequently interchanged throughout the past decades with directional hypokinesia (i.e., *"a spatial disorder affecting movement toward the contralesional side, independent of the effector limb"*; Bartolomeo, 2021a). Regardless of their apparently similar pictures, motor neglect greatly differs from directional hypokinesia. Indeed, motor neglect selectively affects the spontaneous movement of the contralesional limbs independently of the spatial direction of the movement (i.e., ipsilesional or contralesional; Bartolomeo, 2021a; Toba et al., 2021). By contrast, directional hypokinesia affects movements towards the contralesional side of space, independently of the limb used (Bartolomeo, 2021a; Toba et al., 2021). Nonetheless, in some

[7] *Motor extinction:* inability to move the contralesional limb when two actions must be performed with both hands simultaneously (Kerkhoff, 2001).

instances motor neglect may resemble the picture of directional hypokinesia for leftward arm movements and complicate the ultimate clinical diagnosis (Vallar & Calzolari, 2018).

Even though clinicians are aware and familiar with these descriptions, developing an objective measure that can discriminate motor neglect and related deficits remains a challenging and problematic task.

2.3. Mechanisms underlying motor neglect

Right-hemisphere-damaged patients with left neglect are typically unaware of their contralateral sensory and/or motor deficits (Vallar & Calzolari, 2018). Anosognosia[8] is a very common feature in cerebral diseases (e.g., neglect, Wernicke's aphasia, dysexecutive disorders, amnesia, etc.) and this holds true especially in the acute phase of neglect and, specifically, motor neglect (Kerkhoff, 2001). Notably, anosognosic motor neglect patients are unaware of the nature and the cause of their motor abnormalities, they cannot imagine further consequences to their condition, and, consequently, they do not attempt any movement (Garbarini et al., 2013; Kerkhoff, 2001). From a clinical viewpoint, anosognosia represents a great limit in the diagnostic procedure and in the rehabilitation phase. As a matter of fact, patients cannot collaborate with the examiner and describe their impairments in detail, and this gives rise to significant obstacles to successful rehabilitation outcomes (Adair & Barrett, 2008).

To a certain extent, unawareness of the disorder in motor neglect patients is a positive predictor of their impaired motor voluntary drive. While the processes that produce a motor act may have no direct access to consciousness, people are usually aware of their motor intention and they retain motor awareness of whether they are moving or not a certain part of their body (Garbarini et al., 2012). Indeed, the majority of movements performed in daily activities require volition, movement planning, and selection of the motor program, which are all conscious mechanisms preceding the execution of the motor action (Kojović & Bhatia, 2019). Nevertheless, any disruption in one of these mechanisms may result in abnormal motor behavior, causing higher-order motor disorders. Among these, intentional disorders (which include motor neglect and motor impersistence[9]) originate from damage to those programs that provide instructions on whether and when to move, when to stop a

[8] *Anosognosia: "A condition in which a person who suffers impairment following brain damage seems unaware of or denies the existence of their handicap, even if the handicap is severe"* (Stirling & Elliott, 2008).
[9] *Motor impersistence: "Inability to sustain motor act (movement or posture), unless repeatedly prompted by examiner"* (Kojović & Bhatia, 2019).

movement, and when to persist one (Kojović & Bhatia, 2019). Intentional disorders are usually associated with right hemisphere dysfunctions (Kojović & Bhatia, 2019), and this suggests the dominant role the left hemisphere plays in performing deliberate motor activities (Laplane & Degos, 1983). Motor neglect, thus, is classified as a disorder of intention and this may justify the reason why patients lack voluntary drive, yet they retain motor abilities.

The specific mechanisms underlying motor neglect still need to be refined, but in the past decades several attempts have been made to explain the condition. Initially, Laplane and Degos (1983) proposed that motor neglect could be possibly conceived as a result of a deficit in the mechanisms controlling the preparation and programming of movement, because the cerebral structures mainly involved in motor neglect and those required in the organization of movement are, respectively, the same (Laplane & Degos, 1983).

Coulthard et al. (2008) have suggested that left motor neglect may emerge as a consequence of a lateralized deficit that fails to inhibit ipsilesional limb motor plans. Coulthard et al. carried out a study that involved right-hemisphere-damaged patients with motor neglect, right-hemisphere-damaged patients without motor neglect, and a group of healthy participants. The task aimed at measuring the reaction time of motor actions for ipsilesional and contralesional hands after the presentation of a stimulus (i.e., congruent stimulus: prime stimulus and target stimulus pointed to matched directions; incongruent stimulus: prime stimulus and target stimulus pointed to different directions; Coulthard et al., 2008). Results revealed that motor neglect patients were overall slower compared to patients without motor neglect and healthy subjects, plus their response delay consistently increased with incongruent stimuli and leftward movements (Coulthard et al., 2008; Rode et al., 2017).

In a more recent study, Garbarini et al. (2012) illustrated the inability of motor neglect patients to generate actions. Garbarini et al. proposed that motor neglect could be due to a motor intention deficit (Rode et al., 2017; Sampanis & Riddoch, 2013). They recruited a group of healthy participants, a group of motor neglect patients (i.e., these patients show lack of motor intention, but intact motor execution) and a group of hemiplegic patients with anosognosia (i.e., these patients present intact voluntary drive, but impaired motor ability; Garbarini et al., 2012).

Garbarini et al. (2012) asked participants to perform unimanual and bimanual drawing movements, while blindfolded, and then they contrasted participants' performance. Specifically, Garbarini et al. observed that bimanual spatial coupling effect (i.e., both hands move simultaneously as a consequence of the moving of the healthy hand affecting the moving of the contralesional hand) was preserved in anosognosic hemiplegic patients but was not present in healthy participants and motor neglect patients (Garbarini et al., 2012). These findings suggest the presence of specific damage to the mechanisms responsible for motor intention of the contralesional limbs in patients with motor neglect (Rode et al., 2017).

2.4. Neuroanatomy of motor neglect

The neuroanatomical correlates associated with motor neglect are still being debated. Laplane and Degos (1983) first observed that frontal, parietal, and thalamic lesions were associated with the manifestation of pure motor neglect (Laplane & Degos, 1983). Consistent with their findings, cases of left-sided motor neglect were subsequently reported after damage to the prefrontal and parietal cortices (Rode et al., 2017). Subcortical lesions (including the putamen, the thalamus, and the internal capsule) and lesions to the primary motor and premotor areas have been also associated with motor neglect. In addition, some patients with motor and visual neglect had damage to the cingulum, a bundle of fibers often associated with motor initiation and motivational aspects of action (Rode et al., 2017, see Figure 3).

Evidence suggests that neural circuits involved in spatial attention (i.e., fronto-parietal networks) are linked with those responsible for planning movements (Bartolomeo, 2021b). This finding might explain the positive relation that is thought to exist between movement and spatial attention (Punt & Riddoch, 2006).

To support the fact that motor neglect occurs in the absence of sensorimotor deficits, the results of some studies (Kojović & Bhatia, 2018) involving positron emission tomography (PET) have indicated that the primary motor cortex in motor neglect patients is intact. The real problem probably originates from lesions to the motor association areas and the connections that they share with the primary motor cortex (Kojović & Bhatia, 2019). In fact, fundamental areas associated with the motor output system (i.e., primary sensorimotor cortex, cerebellum, and basal nuclei) are not impaired and show normal metabolism. By contrast, poor glucose reuptake (i.e., hypometabolism) has been observed in the premotor, parietal, prefrontal, and cingulate cortex (Sampanis & Riddoch, 2013). This possibly explains why muscle strength, reflexes, and sensation, in motor neglect patients, are typically intact.

Studies involving stimulation to inferior parietal regions have revealed that the inferior parietal lobule (IPL) is positively linked to the desire to move, in motor neglect patients, even while no overt movement is produced (Sampanis & Riddoch, 2013). These findings indicate that intentions to move are typically generated before an action is performed (Sampanis & Riddoch, 2013).

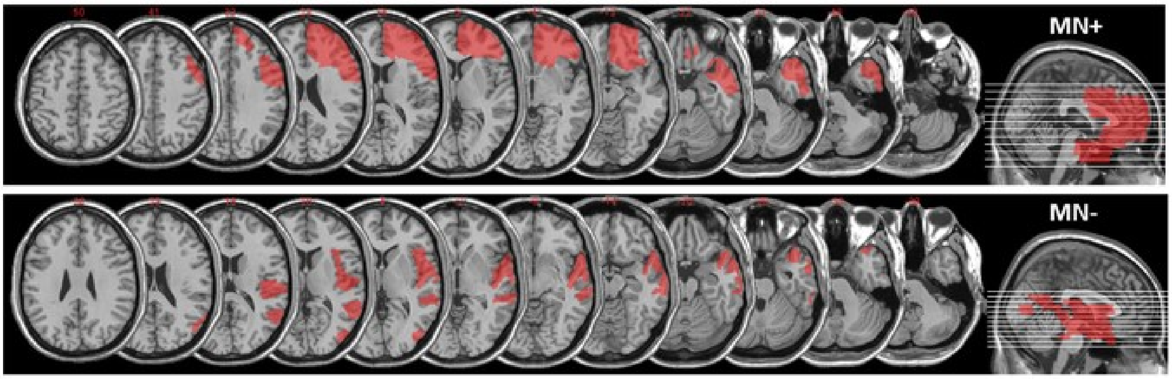

FIGURE 3. Reconstruction of the lesion sites in a patient with motor neglect (MN+) compared to those of a patient without motor neglect (MN-). Scans are obtained with a MicroN software. The scan on the top shows that the patient with motor neglect (MN+) has lesions in the right frontal and temporal lobes. The damage involves the orbital cortex; the inferior, middle, and superior frontal gyrus; the precentral gyrus; the inferior, middle, and superior temporal lobe, and the cingulum. On the bottom scan, instead, the patient without motor neglect (MN-) presents lesions in the right occipital, temporal, and parietal lobes. These impairments involve the middle occipital gyrus, middle and superior temporal gyrus, and the insula (Garbarini et al., 2015).

2.5. Rehabilitation approaches

Rehabilitation research and therapeutic interventions for motor neglect remain at an early stage of development (Punt & Riddoch, 2006). As it is the case for perceptual (i.e., input) neglect, bottom-up approaches have been used also in motor (i.e., output) neglect rehabilitation. In particular, improvements have been observed in motor neglect patients after prism adaptation (PA)[10], neck vibration[11] (Christophe et al., 2016), and caloric vestibular stimulation[12], even though the effects on motor performance may be only transitory (Rode et al., 1998). Moreover, optokinetic stimulation (OKS)[13] has proved to ameliorate motor neglect signs (Saevarsson, 2013), and, recently, noradrenergic (NA) stimulation has been proposed as the best predictor for motor neglect treatment (Sampanis

[10]Prism adaptation: rehabilitation technique involving daily visuo-motor training sessions. Patients are required to wear rightward-shifting optical prisms, which shift the visual field to the right. After the adaptation session, the direction of the performed movements is slightly deviated contralesionally, and the so-called after-effect phenomenon is observed (Christophe et al., 2016; Kerkhoff & Schenk, 2012).

[11] Neck vibration: vibration of the neck muscles is obtained by applying a stimulus to the left/right neck muscles. This technique induces the patient to constantly feel movement to the contralesional side, thus reducing motor neglect signs (Christophe et al., 2016; Kerkhoff & Schenk, 2012).

[12]Vestibular stimulation: technique that temporarily reduces manifestation of motor neglect. It is performed by using cold caloric stimulation of the left ear in right-hemisphere-damaged patients or of the right ear in left-hemisphere-damaged patients. The external ear canal is filled with cold water for some seconds (e.g., 30 sec), and during stimulation the patient is laying blindfolded (Rode et al., 1998).

[13]Optokinetic stimulation (OKS): technique that stimulates the damaged brain regions associated with motor neglect through optokinetic stimuli across repetitive sessions (Saevarsson, 2013).

& Riddoch, 2013). Particularly, by modulating the pathologically altered motor network in stroke patients, NA stimulation can result in improvement of motor function. Future research might show NA stimulation to be a promising tool for facilitating spontaneous recovery in the weeks post-stroke in those motor neglect patients that show impaired attention and visuomotor intention (Sampanis & Riddoch, 2013).

Enhancing the patient's motor awareness, by means of symmetric movements, may be helpful in the recovery of contralesional motor functions (Garbarini et al., 2013). In line with this, recent studies (e.g., de Villiers et al., 2021) have proposed that using virtual environments (VE) to improve motor function (i.e., mobility, balance, and speed) may be particularly beneficial in patients with motor neglect. According to this novel technique, patients are instructed to walk on a treadmill, following a path displayed on a screen in front of them. Simultaneously, an avatar-like projection mimics all the movements performed in real time, providing the patients with constant biofeedback on the screen (de Villiers et al., 2021). It seems that *"visual feedback from seeing the avatar move in the virtual environment helps to produce change through interoceptive neuroplastic mechanisms"*, reducing the severity of the disorder and improving the patient's motivation (de Villiers et al., 2021).

In summary, although new approaches for treating motor neglect are available, the current data are not sufficient to support or refute their efficacy to reduce motor neglect signs (Adair & Barret, 2008). Hence, it is very soon to draw solid conclusions on the most effective rehabilitation approaches for motor neglect (Saevarsson, 2013; Siekierka-Kleiser et al., 2006). Finally, for the clinicians working in rehabilitation, distinguishing motor neglect from related deficits (e.g., hemiparesis and hemiplegia, extinction, directional hypokinesia) remains a challenging and uncertain task (Punt & Riddoch, 2006).

CHAPTER 3:

LIMITATIONS AND TOPICS FOR FUTURE RESEARCH

3.1. Limitations in the diagnostic procedure

The clinical impact of motor neglect is indisputable (Saevarsson, 2013). While being an extremely disabling condition for the patients and a great burden for their caregivers, the motor subtype of the neglect syndrome posits considerable limitations for those working in the field of cognitive and clinical neuropsychology (Adair & Barrett, 2008). One of the greatest limitations regards the assessment procedure for the diagnosis of the disorder (Adair & Barrett, 2008; Saevarsson, 2013).

The current diagnostic criteria for motor neglect are confusing and complicated (Saevarsson, 2013). A lot of this confusion originates from the terminology of motor neglect itself, which is relatively extensive and complicated compared to that of other motor and sensory neuropsychological disorders (Mark, 1996). Across the decades, many scholars have often used the term "motor neglect" to describe other deficits affecting movement following stroke (Saevarsson, 2013), generating further confusion and misunderstandings. To aggravate the picture, a good variety of motor deficits totally independent from but associated with motor neglect (e.g., hemiparesis and hemiplegia, motor extinction, directional hypokinesia, etc.) are also diverse, and their taxonomy has rarely served to clarify the clinical picture of motor neglect (Mark, 1996; Saevarsson, 2013). All these facts result in diagnostic issues and controversial findings (Saevarsson, 2013).

Several attempts have been made to overcome assessment shortcomings (Saevarsson, 2013). One major difficulty regards the manifestation of symptoms (Rode et al., 2017). In the application of clinical assessment, motor neglect symptoms and related disorders may be covered differently between studies, and at times some motor neglect signs relevant for the final diagnosis are erroneously excluded (Saevarsson, 2013). Moreover, the quantification of pure motor neglect behaviors represents another difficult task. Modern technologies have gradually introduced novel techniques to assess motor neglect signs. Nevertheless, these expensive and complicated methodologies (e.g., see Toba et al., 2021) may not always suit normal clinical settings (Adair & Barrett, 2008; Saevarsson, 2013).

These limitations call for more detailed and standardized assessment procedures (Saevarsson, 2013). Future studies addressing motor neglect should therefore compare motor neglect and related deficits in a more systematic way (Bartolomeo, 2021b; Saevarsson, 2013).

3.2. Limitations in the rehabilitation phase

A confused and complicated diagnostic procedure can negatively affect the development of an effective therapeutic program. To date, as previously described, few studies have evaluated rehabilitation methods for the neglect syndrome, and research selectively addressing therapeutic techniques for motor neglect is still a work in progress (Saevarsson, 2013; Sampanis & Riddoch, 2013).

Regardless of the advancements in neuroimaging technology that progressively provide new insights into the neurobiology concerning the neglect syndrome, some limitations should be kept in mind in the process of drawing conclusions (Adair & Barrett, 2008). As a matter of fact, differences in the selection of patients, time between injury onset and imaging application, and methods used for identifying specific regions or localizing structures of interest vary across studies (Adair & Barrett, 2008). Such variations can potentially compromise comparisons between research groups and undermine the integration of observations into a cohesive evaluation of the scrutinized data (Adair & Barrett, 2008).

The deterrent effect of time is also to take into consideration, as rehabilitation programs need extensive research evidence before being approved as reliable. Limited knowledge on treatment approaches that reach a maximal outcome remains an unsolved issue (Adair & Barrett, 2008). Thus far, only a minor portion of motor neglect patients recover spontaneously within the first weeks from lesion onset (Adair & Barrett, 2008), but the specific way this process occurs has yet to be discovered (Sampanis & Riddoch, 2013). It would be useful for researchers to know which mechanisms lead to spontaneous recovery and facilitate improvements during rehabilitation (Kerkhoff, 2001).

As a final note, exhaustive knowledge of the disorder is key for a successful diagnosis and an effective rehabilitation outcome. Different assessment issues need to be addressed systematically in future research in light of current findings to increase our awareness and understanding of motor neglect (Saevarsson, 2013). Ideally, *"an improved and systematic motor neglect assessment is likely to clarify our current understanding, increase the number of diagnosed patients, and improve the likelihood of developing a relevant therapy and understanding"* (Saevarsson, 2013).

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