Neuroanatomy, Assessment, and Therapy of Premotor Neglect

Diploma thesis
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Neuro-Reha Team Pasing
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Abstract

Background
Unilateral Neglect impairs the patients’ ability to attend to the contralesional hemispace, or also to act with their body to or in this space. This study focuses on one subtype of neglect, known as premotor neglect (PMN); an intentional motor deficit, which shows in aggravated, less efficient, and slower movements into the contralesional hemispace. The major aim of this study was to verify whether patients with premotor neglect (PMN+) suffer from different neuroanatomical lesions and behavioral deficits than neglect patients without premotor neglect (PMN-). Theories about previous research on PMN are presented and the implemented study is explained. Its results are presented and conclusions are drawn.

Methods
A total sample of 13 chronic neglect patients (7 PMN+, 6 PMN-) from the City Clinic Bogenhausen, Munich and the Schön Clinic Schwabing, Munich participated in the period from October 2013 to November 2014. All patients underwent neglect specific tests such as the modified landmark task (LM). Demographic data and medical history were gathered and the patients were pre-assessed by neuropsychologists. The testing over 4 sessions lasted approximately 1,5 hours per session respectively and was split into a general assessment, an experimental assessment and an intervention part. This information completes the behavioral observation. Further, the provided brain scans of the patients were used for a voxel-based lesion-symptom mapping analysis (VLSM) to investigate the neuroanatomical cause of PMN.

Results
Both groups were equivalent in their age ($p \geq .05$). The study showed that there is no significant group difference concerning in perceptual ($p = .929$) and motor related tasks ($p = .953$) across sessions following prism adaptation treatment. Therefore, hypothesis 1 was not confirmed. With regard to hypothesis 2, no statistical differences between groups can be found according the improvement in the modified landmark manual task (LMM) ($p = .887$). However, PMN+ achieved the highest overall numerical score ($M = 90.58$, $SD = 31.71$) in the fourth session. Further, concerning the neuroanatomy, the VLSM and the continuous analysis showed statistically significant differences between PMN+ and PMN- ($p \leq .05$). For instance, putamen was found to predict PMN+. Consequently, Hypothesis 3 can be confirmed.

Discussion
PMN as a severe neuropsychological disorder is difficult to differentiate from accompanying symptoms and not thoroughly researched. In future, larger samples with equal test methods and patient criteria should be analyzed to improve the diagnosis and therapy of PMN. In particular, larger samples could empower already existing statistical trends in this study. Unfortunately, the current study suffers from a lack of patients, as well as other methodological issues. Further, it seems advisable to formulate a standard operational definition of PMN, to avoid confusion about the term and the belonging symptoms.
Abstract

Theoretischer Hintergrund
Unilateraler Neglect beeinträchtigt die Fähigkeit der Patienten den kontraläsionalen Halbraum zu beachten, oder auch mit ihrem Körper in Richtung oder in diesem Raum zu handeln. Diese Arbeit legt den Schwerpunkt auf einen Untertyp von Neglect, der als prämotorischer Neglect (PMN) bekannt ist; ein intentionales motorisches Defizit, welches sich durch erschwerte, weniger effiziente und langsameren Bewegungen in den kontraläsionalen Halbraum auszeichnet. Das Hauptziel dieser Studie war es die Hypothese zu überprüfen, ob Patienten mit prämotorischer Neglect (PMN+) an anderen neuroanatomischen Läsionen und Verhaltensdefiziten leiden als Patienten ohne prämotorischer Neglect (PMN-). In dieser Arbeit werden sowohl Theorien und die bisherige Forschung über PMN vorgestellt, als auch die durchgeführte Studie erläutert. Die Ergebnisse werden präsentiert und Schlussfolgerungen werden gezogen.

Methoden

Ergebnisse

Diskussion
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<tr>
<td>PMN</td>
<td>premotor neglect</td>
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<tr>
<td>PMN+</td>
<td>patients with premotor neglect</td>
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<td>PMN-</td>
<td>patients without premotor neglect</td>
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<td>LM</td>
<td>modified landmark task in this study</td>
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<td>VLSM</td>
<td>voxel-based lesion-symptom mapping</td>
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<td>p</td>
<td>level of significance</td>
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<td>LMM</td>
<td>modified landmark task manual in this study</td>
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<td>M</td>
<td>mean</td>
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<td>SD</td>
<td>standard deviation</td>
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<td>ICD-10-GM</td>
<td>International Classification of Diseases 10 - German Modification</td>
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<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders 5</td>
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<tr>
<td>RHD</td>
<td>right hemispheric (brain) damage</td>
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<tr>
<td>LHD</td>
<td>left hemispheric (brain) damage</td>
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<td>VN</td>
<td>visual neglect</td>
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<td>MN</td>
<td>motor neglect</td>
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<td>STC</td>
<td>superior temporal cortex</td>
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<td>TPJ</td>
<td>temporo-parietal junction</td>
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<td>LB</td>
<td>line bisection task</td>
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<td>PB</td>
<td>perceptual bias/ visual neglect</td>
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<td>RB</td>
<td>response bias/ premotor neglect</td>
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<td>LANDMARK-V</td>
<td>verbal response version of the Bisiach landmark task</td>
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<td>LANDMARK-M</td>
<td>manual response version of the Bisiach landmark task</td>
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<tr>
<td>IPL</td>
<td>inferior parietal lobe</td>
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<td>STG</td>
<td>superior temporal gyrus</td>
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<td>IFL</td>
<td>inferior frontal lobe</td>
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<tr>
<td>VOSP</td>
<td>Visual Object and Space Perception Battery</td>
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<td>BORB</td>
<td>Birmingham Object Recognition Battery</td>
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<td>BIT</td>
<td>Behavioral Inattention Test</td>
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<td>LMV</td>
<td>modified landmark task verbal in this study</td>
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<td>PA</td>
<td>prism adaptation therapy</td>
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<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
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<td>ANOVA</td>
<td>Analysis of variance</td>
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<td>SE</td>
<td>standard error</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>FLAIR</td>
<td>Fluid Attenuated Inversion Recovery</td>
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<td>cCT</td>
<td>Cranial computed Tomography</td>
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<tr>
<td>DICOM</td>
<td>Digital Imaging and Communications in Medicine</td>
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<tr>
<td>NIfTI</td>
<td>Neuroimaging informatics Technology Initiative</td>
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<tr>
<td>SPM8</td>
<td>Statistical Parametric mapping software version 8</td>
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<tr>
<td>VOI</td>
<td>voxel of interest</td>
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<td>NPM</td>
<td>Non-parametric Mapping software</td>
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<tr>
<td>L+FDR</td>
<td>Liebermeister False Discovery Rate</td>
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<tr>
<td>MNI</td>
<td>Montreal Neurological Institute</td>
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<td>.aal</td>
<td>automated anatomical labeling</td>
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1. The human brain and attention: foundation of neglect

The human brain is a complex entity and many attempts have been made to split it into specific functional areas (e.g. Broca, 1861; Springer & Deutsch, 1997). It is divided into two hemispheres, the left and the right, which are anatomically and functionally different. Over the last centuries, different theories and assumptions were developed concerning the organization of the brain. Out of this variety of different explanations, three major theories emerged: the Equipotentiality theory, the Localization theory, and the Interaction theory. Flourens (1823) assumed in her Equipotentiality theory, that in general, all parts of the brain are involved equally in brain tasks. Later on, Lashley (1929) used this as a base for his theory of mass action of the brain, in which the mass or weight and not separate parts of the brain are important for functionality and for predicting subsequent deficits. This was disproved, as the weight of the brain has no influence on human intelligence. Representatives of the Localization theory assume that specific definable brain areas have specific functions and specific functional limitations occur due to local damages in the brain. In these theories, the brain was mapped functionally, which leads from Hippokrates and Descartes over Gall to Brodmann and Vogt (in Clarke & Dewhurst, 1973). For instance, Broca (1861) found that speech production is influenced by the inferior frontal gyrus (IFG), and Wernicke (1874) that comprehension problems emerge due to lesions in the posterior temporal cortex. More recent connectome research doubt localization and function exists within connected neurons. Popper and Eccles (1982) took up previous thoughts of Descartes’ dualistic interaction theory, and stated that spirit and matter are different substances, which affect each other. Certainly, Popper stated, that spirit and physical functions should not be seen in isolation. Sperry (1984) agreed with this in his split-brain experiments and his emergentistic interaction theory. There is a causal efficacy of the spirit on all processes in the brain and vice versa. In sum, the functions and networks of the brain are very complex, the neuroanatomy of this high functioning human organ is not fully understood, and requires further scientific investigation. Attention counts to the basic performance of our brain and can be affected or impaired by various brain injuries (Sturm, 2004). One of the most important deficits of human attention and awareness is the failure to attend or to
The human brain and attention: foundation of neglect respond to the contralesional side of the environment (Vuilleumier, 2013). This deficit is also known as ‘neuropsychological neglect’. Figure 1 shows both the hemispheres with their different tasks and cortex.

![Cerebral hemispheres](image)

**Figure 1. Cerebral hemispheres:** Each of the two hemispheres is dominant for different skills and lesions. One of the hemispheres can cause problems in the other half (image taken from "Pinterest", 2013).

Hughlings Jackson in 1876 and Holmes in 1918 (in Robertson & Marshall, 1993) presumably described neglect the first time, when he reported patients with impaired visual orientation from bilateral lesions; Riddoch (1935) was the first who investigated patients without this impairment, but visual disorientation to homonymous half-fields. Further, Brain, 1941 found these results and first regarded it as a specific syndrome after lesions to the right parietal lobe, called unilateral neglect. Sir John Lubbock explained: “What we do see depends mainly on what we look for” (1892, p.3); but patients suffering from this disorder have difficulties to react to their environment on the side opposite to their brain damage or to shift their attention to this side. Heilman, Watson, and Valenstein (1993) explain:
A patient with sensory (attentional) neglect may fail to report, respond, or orient to novel or meaningful stimuli presented contralateral to a hemispheric lesion [....] Hemispatial sensory neglect then refers to the failure to respond to stimuli (e.g. visual, auditory) that are presented in a visual half field or in head or body hemispace. (Heilman, Watson, & Valenstein, 1993, p.279).

Patients with neglect explore the space around them, but they do not systematically explore the space beyond their body midline to the left (e.g. Karnath, 1997; Saevvarsson, Eger, & Gutierrez-Herrera, 2014). Some authors claim for lateralization, which means in particular, that the left hemisphere is dominant for language and arithmetic skills, and the right hemisphere for spatial skills (Karnath & Rorden, 2012; Sperry, Gazzaniga, & Bogen, 1969). This theory might explain the common phenomenon that neglect is mostly due to right hemispheric lesions and only right brain damage leads to persistent deficits (Stone, Halligan, & Greenwood, 1993). A further explanation is a reduced cognitive capacity after right brain lesions, which leads in combination with right spatial attention preferences of both hemispheres to impaired alertness and attention as well as to left neglect (Heilman & Valenstein, 2003; Heilman & Van Den Abell, 1980; Mesulam, 1981). Heilman and Van den Abell proposed in 1980: “Spatial neglect is a complex disorder, and at least three neuropsychological mechanisms have been proposed to account for it: attentional disorder, intentional or motor activation and representational disorder” (Davidson & Hugdahl, 1996, p. 220).

Taken together, neglect is an important neuropsychological syndrome affecting animals such as dogs as well as humans (e.g. De Renzi, 1982; Heilman, Bowers, Valenstein, & Watson, 1987) and impairs many functions such as visual perception, motor activation and reaction, mental representation, or even the olfactory perception. Since neglect follows in large part right brain lesions, the current study focus on left neglect due to right hemispheric lesions. It is not clear whether there are different ‘pure’ or isolated forms of neglect and which test method is the best to differentiate between modalities. Therefore, the aim of the thesis is to study the neglect subtype premotor neglect (PMN). The patients are differentiated with the aid of the modified landmark task (LM; see section 2.2.4 for description) in this work into patients with premotor neglect (PMN+) and patients without premotor neglect (PMN-) (see section
1. The human brain and attention: foundation of neglect

2.1 for operational definition). In a second step, the behavior for both groups is explained with respect to neuroanatomical findings.

1.1 Clinical symptomatology of neglect

According to *ICD-10-GM Version 2014*, Neurological Neglect is listed in R00-99 (chapter XVII) under the category of ‘symptoms and abnormal clinical and test results, which are not classified elsewhere’. Furthermore, neglect is listed in R25-29: ‘Symptoms that affect the nervous system and the musculoskeletal system’ (“DIMDI,” 2013), where neurological neglect (R29.5) includes the following: asomatognosia, hemineglect, hemiakinesia, left neglect, sensory extinction, sensory neglect, and visual-spatial neglect. No criteria or entries for neurological neglect were found in the *DSM-5* or older versions. The clinical impact of neglect is undeniable and it is considered to be one of the most difficult-to-treat deficits (e.g. Kerkhoff, 2004; Saevarsson, Halsband, & Kristjánsson, 2011), since it is commonly accompanied by anosognosia; a deficit in which patients ignore the presence of disease (Maxton, Dineen, Padamsey, & Munshi, 2013). Patients suffering from neglect hassle in daily life, as they ignore the contralesional space. They may have bruises, forget one half of their meal on the plate, shave only one side of their face or even forget to dress one side of their body (e.g. André, Beis, Morin, & Paysant, 2000; Chen, Henderson, & Cermak, 1993; Denny-Brown & Banker, 1954; Fink & Marshall, 2005; McFie, Piercy, & Zangwill, 1950; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002). This disorder is a major focus of clinical neuropsychology, as there are approximately three to five million new neglect patients per year (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005); but as usual the incidence is coherent with enquiry period and the tests used for detection (Saevarsson, 2009). The incidence of acute neglect in right hemisphere damaged patients (*RHD*) differs due to different factors, like the used test methods. Buxbaum and colleagues (2004) found that 48% of 166 rehabilitation in- and outpatients with *RHD* suffered from left neglect. Stone and colleagues (1991) used a neglect test battery and detected that 72% of 18 *RHD* patients and only 62% of 26 left hemispheric damaged (*LHD*) patients showed neglect. A bigger study of Pedersen, Jørgensen, Nakayama, Raaschou, and Olsen (1997) revealed, that 138 of 602 stroke patients suffered from neglect, 85% of those had *RHD*. This shows a
bigger association of RHD and hemineglect, as only 39% without neglect had right brain damage.

Two month after the lesion around 27-52% of 104 patients showed neglect symptoms (Zoccolotti et al., 1989). Neglect occurs in 60-80% after a stroke in the arteria cerebri media, a right-hemispheric stroke lesion (e.g. Cherney & Halper, 2001; Hoffmann et al., 2011; Lezak, Howieson, & Loring, 2004; Maguire & Ogden, 2002; Stone et al., 1993; Vallar, Bottini, Rusconi, & Sterzi, 1993), a cerebrovascular accident, or less frequent tumors and epileptic seizures (Prilipko, Seeck, Mermillod, Landis, & Pegna, 2006). The visual inattention (or attentional neglect) does not count as a primary movement or visual field deficit (e.g. Hoffmann et al., 2011; Vuilleumier & Driver, 2002; Vuilleumier, 2013). However, hemiparesis or hemianopia does accompany neglect in many cases (Halligan, Cockburn, & Wilson, 1991; Mesulam, 2000). Patients with visual inattention have difficulties to turn to the side of the room or of the body that is opposite to the lesion location side. Stimuli or persons within this space can be ignored alone or in combination (e.g. Heilman, Watson, & Valenstein, 2012; Sturm, Herrmann, & Münte, 2009). Patients with intentional neglect (PMN) have problems to initiate movements in a specific spatial direction, to use a body part or to act in specific space areas (e.g. Heilman et al., 2012; Sævarsson, 2013). From all acute patients, about 65 % recover spontaneously within three months (e.g. Hoffmann et al., 2011; Kerkhoff, 2004), whereas about one out of ten patients develops chronic neglect (e.g. Karnath, Rennig, Johannsen, & Rorden, 2011; Ogden, 1985; Paolucci et al., 1998; Ringman, Saver, Woolson, Clarke, & Adams, 2004; Samuelsson, Jensen, Ekholm, Naver, & Blomstrand, 1997; Stone, Patel, Greenwood, & Halligan, 1992). Even if patients with a less common left neglect recover better and faster (e.g. Samuelsson et al., 1997; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994), neglect in general leads to longer rehabilitation time and hospitalization (e.g. Denes, Semenza, Stoppa, & Lis, 1982; Gillen, Tennen, & McKee, 2005; Katz, Hartman-Maeir, Ring, & Soroker, 1999). Figure 2 shows four well-known paintings of a neglect patient. The portraits show his recovery progresses over a period of 8 month after the diagnosis, where a reduction of the left neglect symptoms can be seen.
Patients with neglect show impairments in different domains and reference systems for spatial acting and sensing. Relative to the body distance, suffering from ‘body-neglect’ (Glocker, Faber, & Kerkhoff, 2008, p. 10) or neglect in personal space (e.g. Beschin & Robertson, 1997; Bisiach, Perani, Vallar, & Berti, 1986; Zoccolotti & Judica, 1991) may cause that one half of the own body (contralesional) is ignored or forgotten (e.g. André et al., 2000, Bisiach et al., 1986). This deficit occurs in about 1% of 166 patients (Buxbaum et al., 2004). In 27% of these patients, peripersonal neglect emerges, which concerns the reaching space, where most of the neglect tests are done. Extrapersonal neglect acts out in the space beyond the normal reaching (e.g. Umarova, 2010, p. 1442; Vuilleumier, Valenza, Mayer, Reverdin, & Landis, 1998). Representational neglect counts, when patients cannot imagine contralesional details of the room or space around them (I. H. Robertson & Halligan, 1999). Further, neglect can be allo-, ego-, or object-centered. Allocentric neglect describes the observation that the contralesional stimuli is perceived more closer to the right than it
Clinical symptomatology of neglect

is actually and can be seen in line bisection tasks. Egocentric refers to the sagittal midplane of the patient’s body and can be affected in pointing forward tasks. Patients with object-centered neglect can have difficulties in, for instance, copy drawings as they miss contralesional details of an object (Kerkhoff, 2001). “The deficit therefore is not one of seeing, hearing, feeling, or moving but one of looking, listening, touching, and exploring” (Mesulam, 1981, p. 318).

1.1.1 Perceptual neglect

Around 21% of 166 neglect patients show pure perceptual neglect in the acute phase (Buxbaum et al., 2004). Fullerton, McSherry, & Stout (1986) used only the Albert’s task and observed that 49% of 205 stroke patients showed perceptual neglect after RHD and only 25% after LHD. Patients with acute spatial neglect or the main type of perceptual neglect- visual neglect (VN)- often indicate shifted alignment of their attention, eye and head to their ipsilesional space (mostly the right); moreover, they bisect objects too far on the right (e.g. Heilman et al., 1993; Kerkhoff, 2004). Patients with VN are so to speak, magnetically drawn to ipsilesional stimuli; it is hard for them to turn their attention to the contralesional space. The core deficit is, that the body midline of these patients is not straight ahead (e.g. Kapoor, Ciuffreda, & Suchoff, 2001) and even if no visual stimuli are present, they are deviated to the right up to 30° (e.g. Fruhmann-Berger & Karnath, 2005; Hornak, 1992; Karnath & Fetter, 1995). Figure 3 illustrates the deviated view of neglect patients very distinct and shows not only the visual deficit, but also the affection of the head and eye movement caused by PMN (e.g. Saevarsson et al., 2014; C. L. Striemer & Danckert, 2013).
1.1.1 Perceptual neglect

![Figure 3. Spontaneous eye and head orientation of neglect patients: a) Spontaneous eye and head orientation of patients with spatial neglect following a right hemispheric stroke when no visual stimuli is presented. The eyes and head are typically oriented toward the ipsilesional, right side (e.g. Saevarsson et al., 2014; Modified from Fruhmann-Berger & Karnath, 2005). b) This deviation is also seen on brain scans, when the patient is asked to remain still. (Modified from Becker & Karnath, 2010). c) Visual scan paths of 12 neglect patients during active visual search (black lines) as well as at rest (gray lines) as compared with a group of 12 control patients without neglect. Neglect patients show a marked bias of their active and their passive behavior toward the ipsilesional, right side. (Modified from Fruhmann-Berger, Johannsen, & Karnath, 2008). (Image modified from Karnath & Rorden, 2012).](image)

Experimental data of Vossel, Eschenbeck, Weiss and Fink (2010) revealed, that patients who leave left items in cancellation tasks unmarked also have considerable problems with judging the middle of lines accurately. In cancellation tasks, patients partly have much longer search times and revisit already-targeted stimuli, when more ipsilesional distractors are on the paper (e.g. Behrmann, Ebert, & Black, 2004; Mannan et al., 2005; Posner, Walker, Friedrich, & Rafal, 1984). Further, when patients suffer from ‘neglect paralexia’, they have difficulties to read and to understand a text. Visual input from the contralesional side is not taken into account and therefore parts of words or sentences are missed (e.g. Behrmann, Black, McKeeff, & Barton, 2002; Benson & Geschwind, 1969; Heilman, Watson, et al., 1993; Mesulam, 1985; Parton, Malhotra, & Husain, 2004). When patients with spatial neglect cannot write in a proper way it is called ‘neglect dysgraphia’ (Baxter & Warrington, 1983). Another grave problem of VN is that it commonly goes hand in hand with hemianopia (explained in chapter 1.3), even though it is an independent
1.1.1 Perceptual neglect disorder (e.g. Mark, 1995; Weiskrantz, Warrington, Sanders, & Marshall, 1974). In this thesis, $PMN$ is equal to patients with $VN$.

### 1.1.2 Response neglect deficits

Neglect not only affects the perceptual, conceptual and visual modality, although it presents as a perceptual or attentional disorder in many cases. The motor components play an enormous role in this disorder and these two modalities are closely linked. Attending to space means also preparing to act in that space or direction (see in Heilman et al., 2012). Affected motor modalities may also be referred as “output” disorders (Brain, 1941), can be divided into $MN$ and $PMN$ (e.g. Saevarsson, 2013). These deficits affect spatial planning and execution of movements (e.g. Adair & Barrett, 2008; Bisiach, Geminiani, Berti, & Rusconi, 1990). Around one third of all stroke patients and approximately 17% of acute neglect patients suffer of $MN$ (Buxbaum et al., 2004; Laplane & Degos, 1983; Saevarsson, 2013; Siekierka-Kleiser, Kleiser, Wohlschläger, Freund, & Seitz, 2006). The motor behavior of one half of the space or body is affected (Mark, 1996) and was first described as a deficit by Castaigne, Laplane, and Degos (1970). They explained it as abnormal motor behavior with a reduced spontaneous use of the contralesional arm or leg without this being fully explained by “(…) defects of strength, reflexes or sensibility or a hemiparesis” (see in Laplane & Degos, 1983, p. 152; see also in Classen et al., 1997; Fink & Marshall, 2005; Vallar, Bottini, & Sterzi, 2003). This impairment mainly takes place in the personal space of the affected body side. $MN$ can be differentiated from hemiparesis or hemiplegia by, for instance, leading the patient’s attention to their neglected body part. It is also possible to strongly motivating them to move their arm or present them prominent stimuli (e.g. De la Sayette et al., 1989; Ghika, Ghika-Schmid, & Bogousslavsky, 1998; M. J. Riddoch & Humphreys, 1983; Robertson, Mattingley, Rorden, & Driver, 1998; Robertson, Tegnér, Tham, Lo, & Nimmo-Smith, 1995). According to Classen and colleagues (1997), the pathophysiological basis of $MN$ is a dysfunctional glucose metabolism, which leads to an inhibition of the intact primary motor cortex.

Another motor form is $PMN$, which is present in approximately 45% of $VN$ patients (Saevarsson et al., 2014) and is claimed not to be particularly an aspect of the neglect
1.1.2 Response neglect deficits

syndrome per se, because right-sided lesions lead to impaired reaching (Himmelbach, Karnath, & Perenin, 2007; Himmelbach & Karnath, 2003; Kim et al., 2013; Rossit et al., 2009; Striemer & Danckert, 2013). But as mentioned in other publications (e.g. Konczak & Karnath, 1998; Mattingley & Driver, 1997; Saevarsson, Eger, & Gutierrez-Herrera, 2014; Vossel et al., 2010), PMN actually is one syndrome of the neglect symptomatic or at least an important aspect of it. The pioneering steps and foundation for PMN in humans came from Watson, Miller and Heilman (1978), who found after different previous studies (e.g. Bianchi, 1895; Heilman & Valenstein, 1972; Kennard & Ectors, 1938; Welch & Stuteville, 1958), that monkeys with frontal lesions show response deficits and sensory neglect. These monkeys were trained to respond with their contralesional/ left hand to ipsilesional/ right tactile stimuli on their right leg, and further to respond with the right hand to a left- sided tactile stimuli. These monkeys behaved normally with their ipsilesional limb, but did not respond with their contralesional limb when stimulated ipsilesional. As this phenomenon cannot be explained by any of the previous explanatory models, this might be due to a failure of motor intention into the contralesional space or with the contralesional limb. In addition to these findings, Heilman and Howell (1980) also suggested, “(...) that some of the behavior seen in the neglect syndrome, such as hemispatial neglect, may be induced by an intentional defect [.... and], that attentional and intentional defects are dissociable” (p. 1035). Thereupon, this intentional defect was called ‘unilateral directional hypokinesia’ (Heilman, Bowers, Coslett, Whelan, & Watson, 1985) and described the impaired movement towards the contralesional side. This term was followed by many different others and led to confusion amongst experts. Some examples for these terms are: directional action neglect (e.g. Saevarsson et al., 2014), directional hypokinesia (e.g. Hoffmann et al., 2011; Mark, 1996; Robertson & Halligan, 1999), directional motor neglect (e.g. Umiltà, 1995), and directional akinesia (Fink & Marshall, 2005). These terms describe the abnormally long delay, slow performance or a lack of movement initiation to the contralesional space (Heilman et al., 2012). However, Bisiach and colleagues (1990) were the first to divide VN from PMN in a meaningful and systematic way and to call this impairment premotor neglect (see however Halligan & Marshall, 1989; Harvey, 2004). PMN is defined and described in the action- intention hypothesis of neglect:
The action-intention hypothesis of hemispatial neglect states that, although patients may be aware of stimuli in contralateral hemispace, they fail to act on these stimuli because they have either a reduced ability to act (or sustain action) in contralesional hemispace or they have an action-intentional bias to act ipsilesionally (Heilman et al., 2012 in Heilman & Valenstein, 2012, p. 325).

In addition to the action-intention deficit, patients suffering from PMN exhibit a tendency for right-biased motor actions (Heilman, Bowers, & Watson, 1983) and to prefer their ipsilesional side (in most of the cases the right side). This tendency is attributable to a deficit in the spontaneous execution of targeted motor movements from the ipsi- to the contralateral side (e.g. Coulthard, Parton, & Husain, 2006; Heilman et al., 1985; Heilman, Valenstein, & Watson, 2000; Vossel et al., 2010). Further, it becomes apparent in slower movements into and reduced spontaneous head- and eye movements (exploration) towards the opposite of the damaged hemisphere (e.g. Bisiach & Vallar, 1988; Fruhmann-Berger & Karnath, 2005; Howes & Boller, 1975; Husain, Mattingley, Rorden, & Driver, 2000; Karnath, Niemeier, & Dichgans, 1998; Parton et al., 2004; Saevarsson, 2013; Umiltà, 1995). PMN takes place largely in the reaching space of the patient and depends on the movement direction (e.g. Azouvi et al., 2004; Fink & Marshall, 2005; Saevarsson, 2013), which is seen when patients may not grasp coins in the left hemispace (Stone et al., 1991).

In summary, Table 1 visualizes the main types of neglect and exemplary expressions in daily life. It is important not only focusing on the different affected modalities separately and to follow the premotor activation theory of Rizzolatti and Berti (1990) that explains “…” that attention [/vision] and motor preparation are closely linked, and therefore activation of one system leads to recruitment of the other.” (Lin, 1996, p. 507). Furthermore, previous publications suggested, that active usage of affected extremities in the contralesional space decreases errors and symptoms of visual spatial neglect (Herman, 1992; Robertson & North, 1992, 1993; in Freeman, 2001). Indeed, it is important to mention for clarity’s sake that (P-) MN and VN are seldom independent from each other and in most cases a patient with mainly PMN also shows VN symptoms, too.
1.1.2 Response neglect deficits

<table>
<thead>
<tr>
<th>Visual neglect</th>
<th>Motor neglect</th>
<th>Premotor neglect</th>
</tr>
</thead>
<tbody>
<tr>
<td>• shifted, ipsilesional orientation of eyes and trunk</td>
<td>• Reduced spontaneous use of the contralesional extremities</td>
<td>• Directional motor bias or reaching deficit to the contralesional space</td>
</tr>
<tr>
<td>• 'ignore' contralesional space</td>
<td>• not fully explained by hemiparesis or -plegia (e.g. patient can be motivated to move the arm)</td>
<td>• slower movements to the contralesional side</td>
</tr>
<tr>
<td>• e.g. forget meal on the left, problems in reading, leave left items unmarked in cancellation tasks</td>
<td>• e.g. do not use the left hand to open a jar with both hands</td>
<td>• e.g. do not grasp coins on the left in the open-loop box tasks</td>
</tr>
</tbody>
</table>

*Table 1*

Schematic overview of the main neglect types: VN, MN, and PMN (see also (Saevarsson, 2013))

### 1.1.3 Neglect in other modalities

There have been various studies on neglect in other modalities, although they are not as relevant in daily life as the main forms of neglect (VN, MN, PMN) due to the lack of specification for one region or spatial process (e.g. Kobal, Van Toller, & Hummel, 1989). The most tedious relevant disorder in this content is the somatosensory or tactile neglect: patients do not react to touch on their contralesional side, locate it wrong (allaesthesia) and/or explore the contralesional space less (e.g. Karnath & Perenin, 1998). **Representational neglect** (sometimes called conceptual neglect as well): About 25% of patients with VN suffer from representational neglect, too, where they cannot access contralesional information in their imagined space (e.g. Bartolomeo, D’Erme, & Gainotti, 1994). In a famous experiment carried out by Bisiach and Luzzatti (1978), it was observed that a native Milanese could only describe details from the right side of the cathedral square. This indicates representational neglect. **Auditory neglect:** Patients with auditory neglect are unable to locate sound (e.g. Kerkhoff, 2004; Pavani, Làdavas, & Driver, 2002) or locate sound in the most ipsilesional side (e.g. Tanaka, Hachisuka, & Ogata, 1999), which is more pronounced on the contralesional ear (e.g. S. Clarke & Thiran, 2004; De Renzi, Gentilini, & Barbieri, 1989), and could cause problems in traffic situations. **Olfactory neglect:** Patients with olfactory neglect (without anosmia), cannot locate
smells correctly; this is less relevant for daily life as usually odours spread quickly in the room and can be smelled through both nostrils (e.g. Bellas, Novelty, Eskenazi, & Wasserstein, 1988). Following, Table 2 illustrates different sub-forms of neglect.

Table 2
Schematic overview of different subtypes of neglect: tactile neglect, representational neglect, auditory neglect, and olfactory neglect (see also Buxbaum et al., 2004).

1.2 Explanatory models

It is debatable whether one single theory of development can explain the multimodal syndrome of neglect, as it can occur after large various lesions and concerns many different areas of the patients’ life and behavior. Nonetheless, the major existing theories, which could explain features of neglect but not all of them, are explained briefly in this paragraph.

1.2.1 Attentional and arousal theories of neglect

Proponents of the attentional theory emerge from human data and assume different attentional problems in unilateral neglect. Some authors claim, that there are two attention vectors produced by both hemispheres and that they inhibit each other. In this case, the left hemisphere is responsible for attention to the right and the right hemisphere is responsible for attention to the left (e.g. Kinsbourne, 1970b, 1993; Smania et al., 1998). As the left hemisphere generates a stronger vector (Kinsbourne,
1970a) the orientation to the ipsilesional side is stronger than to the contralesional space. In this case, right lesions lead to hypoattention of the left side (neglect) and hyperattention of the right side (see also Karnath & Thier, 2012). This also could be an explanation for left-sided pseudoneglect in normal subjects in a tactile line-bisection task (Bowers & Heilman, 1980), as the right hemisphere plays a bigger role in processing tactile information, which results in a bigger attention for the left side. A few years later Kinsbourne (1994) assumed an attention gradient, which is always drawn to the most ipsilesional stimulus but then every lesion would lead to neglect, which is not the case (e.g. Karnath, Berger, Küker, & Rorden, 2004; Karnath, Ferber, & Himmelbach, 2001; Karnath, Himmelbach, & Rorden, 2002; Mort et al., 2003). Valenstein and Heilman (1979) suggested an attention-arousal theory, which suggests that unilateral neglect can be caused by reduced attention to the contralateral side. This lack of response to the contralateral space (Heilman et al., 1987) is due to an impaired “(…) arousal and transmission of sensory information to the cortex” (in Freeman, 2001, p. 402). Further, Kinsbourne (1987) founded the theory of interhemispheric interaction and inhibition and assumes that the left hemisphere is accountable for language and the right hemisphere for spatial functions. If one hemisphere is injured, the interhemispheric balance will be disturbed. Likewise, Heilman and Watson (1978) found, that activating the right hemisphere with spatial tasks reduced the severity of left neglect, whereas activating the left hemisphere with language tasks even worsen the symptoms. Furthermore, Heilman and colleagues (1985, 1987) claimed for this hemispheric specialization and that both hemispheres use a specific attention system with a complex loop. The right hemisphere is dominant for ‘alertness’ and spatial attention and handles/covers attention processes for the right and the left hemispace. Contrary to this, the left hemisphere is only responsible for the right hemispace. Referred to the neglect symptomatology, this means that lesions in the left hemisphere can be compensated by the right but not vice versa (I. H. Robertson et al., 1995).

Posner and colleagues (1984) found three subsystems in the process of attention. At first, attention has to be disengaged from a current ipsilesional stimulus (e.g. Losier & Klein, 2001; Posner & Petersen, 1990) to then shift it to a new contralesional point (e.g. Bartolomeo & Chokron, 2002; Posner, Walker, Friedrich, & Rafal, 1987), and at the end engage it to this new focus. Mostly, patients with parietal brain injury and visual neglect had problems to disengage their focus. It was found that even in
1.2.1 Attention and arousal theories of neglect

Complete darkness, patients with neglect turned their attention to the ipsilesional side (Hornak, 1992). It is also possible, that ipsilesional stimuli catch the attention more than contralesional targets and thus will be selected more often, which also leads to difficulties in disengaging and shifting attention (e.g. Duncan, Humphreys, & Ward, 1997).

Mesulam (1981) developed one very popular attentional theory of neglect (see also Mesulam, 1998; Weintraub & Mesulam, 1987) and claimed that a neuronal network of parietal, cingulate, premotor, frontal, and thalamic structures and also parts of the basal ganglia controls attention. Neglect can be caused by damages within these structures and mostly the left space is affected because difficulties after right lesions cannot be compensated by the left hemisphere (e.g. Heilman et al., 1987; Rengachary, He, Shulman, & Corbetta, 2011). An illustration of this ‘failure’ is given in Figure 4. Also, Heilman and Van den Abell (1979) found, that persons without neglect showed faster reaction times to the left, which also provides the hemispheric specialization theory. Models that are more recent focus on neuroanatomical structures and emphasize the importance of a neuronal network for attention.

Figure 4. Parietal lobes and hemispheres: The picture on the left shows that control patients attend to both hemispheres. Patients suffering from right hemisphere lesions only show attention for the right hemispace, cannot compensate for it and exhibit a severe left neglect. The picture on the right makes clear, that left hemisphere lesions do not lead to a loss of attention for the right side, can be compensated by the right hemisphere and lead to milder right neglect. Patients with parietal bilateral lesions suffer from severe right neglect (images taken from: “Studyblue,” 2012).
1.2.2 Representational theories

Representational theories expand other theories in the assumption that neglect manifests not only on sensory, but also on mental levels. Bisiach and colleagues (Bisiach, Capitani, Luzatti, & Perani, 1981; Bisiach & Luzzatti, 1978) stated, that a mental representation of sensory impressions is preceding every conscious perception. This means that neglect is attributable to an impaired mental representation of the contralesional space or half of the body (e.g. Karnath, 1997) or the failure of “(...) a representational map reduced to one half (...)” (Bisiach et al., 1981, p. 549). This theory is corroborated by findings that patients poorly delineate the left space of their description of the Milanese cathedral square in their native city and also omit details on the left when they draw objects (e.g. Bisiach & Luzzatti, 1978; Kerkhoff & Schindler, 1997). According to other experiments (e.g. Harvey, Milner, & Roberts, 1995a; Milner, 1987) horizontal segments in the left space are perceived as shorter than identical segments on the right. This is also attributable to the problem that their representation is stretched on the contralesional side and compressed on the ipsilesional. In Doricchis and Angelellis work (1999) only patients with left neglect and hemianopia showed this behavior, which leads to the conclusion that an interaction of both cognitive and sensory disorders is accountable for this deficit. Halligan and Marshall (1991) discovered in their work, that a RHD patient with visual neglect and hemianopia suffers from a compression of their left space rightwards (see also Karnath & Thier, 2012; Werth & Pöppel, 1988). Patients had to name the number in a row of 15 numbers, which was marked with an arrow. Patients with right brain damage, left neglect and hemianopia often named a number rightwards of the target. Rizzolatti and colleagues (Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Rizzolatti, Matelli, & Pavesi, 1983) assume, that premotor cortical structures are involved in attention processes and every movement and body part is represented in a neural network. In their opinion, injuries in premotor areas and dysfunctions in one of these structures lead to neglect (Rizzolatti et al., 1997, 1983).
1.2.3 Transformation theories

These theories emanate from the idea that any sensory information from periphery organs (eyes, ears, body, skin, and nose) has to be transformed into motor coordinates. In this process are parts of the vestibular system involved, which are also crucial for spatial neglect: the superior temporal cortex (STC), the temporo-parietal junction (TPJ), and the insula (Karnath & Dieterich, 2006). Jeannerod and Biguer (1987) assume that patients with neglect error to the ipsilesional side and cannot transform the information.

Karnath (1997) reported that neglect is attributable to a rotation of the vertical body axis to the ipsilesional space and the following generation of a flawed egocentric coordinate system. In contrast to this, Vallar postulated (1997, 1998) a (concordant) translation of space to the ipsilesional side about $0^\circ$ to $+20^\circ$. Transformation theories are a good foundation for neglect treatment such as optokinetic stimulation or proprioceptive neck muscle vibration (e.g. McIntyre & Seizova-Cajic, 2007).

1.2.4 Cerebral imbalance theories

Opposing theories are based on findings in animal studies and come from the idea that not only functional damage from the lesions lead to neglect (Payne, Lomber, Rushmore, & Pascual-Leone, 2003) but also there is an impaired interhemispheric balance. In earlier animal studies of Watson, Miller and Heilman (1978) it was shown that monkeys showed an impaired movement initiation after unilateral lesions to the prefrontal cortex, wherefore it is assumed, that neglect is conditioned by the (in)-balance of parts of a cortical and subcortical network within and across both hemispheres. This assumption was affirmed by earlier cat studies (e.g. Lomber & Payne, 1996; Saevrsson, 2009). As the two hemispheres have inhibiting and activating cerebral structures, more recent experiments (e.g. Shindo et al., 2006) stimulate the parietal cortex with transcranial magnetic stimulation to inhibit the healthy side.
1.3 Associated disorders to neglect

One common concomitant of neglect is extinction, which is also included in the neglect definition of the ICD-10-GM. Vallar and Perani (1986) ascertained, that 16 of 17 patients with neglect exhibit extinction. This deficit describes the phenomenon, that contralateral stimuli are not recognized if an ipsilateral stimulus is presented simultaneously (e.g. Driver & Vuilleumier, 2001; Ticini, de Haan, Klose, Nägele, & Karnath, 2010). Often, it appears due to lesions of the temporal parietal lobe (e.g. Karnath, Himmelbach, & Küker, 2003; Meister et al., 2006; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010), and more likely with larger lesions in adjacent areas. Posner’s disengagement theory (Posner et al., 1984) could be one possible explanation for extinction, when patients cannot detach their attention of the ipsilesional stimuli. There are different modules, which can be influenced by extinction, for instance, the tactile, the visual, and the auditory. Interestingly, attention is also controlled by affective factors and symptoms of extinction can be reduced when emotional cues are used, like spiders or faces (e.g. Domínguez-Borràs, Saj, Armony, & Vuilleumier, 2012). So it could be possible to reduce extinction with Pavlovian conditioning when a visual target on the left is linked to an aversive stimulus (Domínguez-Borràs & Vuilleumier, 2013). Further, extinction is more likely when the ipsi- and contralateral stimuli are very similar, which is called simultaneous stimulation (Rafal, 1994). When bi-manual actions are required and the contralesional hand does not work accurately, the patient suffers from motor extinction.

Asomatognosia (sometimes referred to as personal and body neglect) is another common disorder associated with neglect. Affected patients are not aware of parts of their own body. In an earlier study (Adair, Gilmore, Fennell, Gold, & Heilman, 1995) some patients could not differentiate between the examiners’ hand and their own hand when moved into their viewing space. Another disturbance that often accompanies neglect is anosognosia, the unawareness of ones own deficits. Babinski (1914) first described it as the lack of recognition or awareness of a hemiplegia or sensory experience. Patients do not recognize their reduced ability in spatial orientation due to brain lesions and their missing of information (Vocat, Staub, Stroppini, & Vuilleumier, 2010). The unawareness of the own deficits can worsen the neglect symptoms (Appelros, Karlsson, Seiger, & Nydevik, 2003), reduce the ability to
1.3 Associated disorders to neglect

compensate for deficits (Bisiach & Geminiani, 1991), and/or improve within rehabilitation (McGlynn & Schacter, 1989). It shows up in 73% of 138 patients with neglect and in 6% of 464 patients without neglect (Pedersen et al., 1997). It is, indeed, mainly seen combined with neglect (Baier & Karnath, 2005), but not causally linked to it (Kerkhoff, 2001). This deficit fades with time and is usually getting better from 3 months upwards after the lesion (Kerkhoff, 2004). These phases go from global unawareness (up to three month), over informal awareness (deficits can be described), over emerging awareness (deficits are recognized in moments of failure), to anticipatory awareness (patient knows about the symptoms). A prestige or milder form of anosognosia is *anosodiaphoria* (Critchley, 1953), when patients can verbally report their deficits, but seemingly due to being told that they suffer a disorder and not due to their own feeling (Heilman, Bowers, & Valenstein, 1993). Different theories and hypotheses have been developed to explain anosognosia. Weinstein and Kahn (1955), for instance, postulate that this deficit is some kind of defense mechanism which proceeds unconscious. *Figure 5* shows on the left the view of a healthy person, while the right picture shows the view of a patient with neglect and anosognosia.

![Figure 5. Normal and neglect perspective: A patient with left neglect and anosognosia misses or ignores the visual information coming from the left (image taken from: “Stroke4Carers,” 2014).](image)

Neglect also has to be dissociated from primary and voluntary motor, sensory, and spatial deficits, which are shown in this section. In 80% of 144 RHD patients (Sterzi et al., 1993) and 87% of 47 RHD neglect patients (Vallar & Perani, 1986) left hemianopia or homonymous visual field deficits go along with neglect and are difficult to dissociate from each other. Indeed, when patients with these deficits are asked to describe 10 things from the room they also search in the left space unlike
1.3 Associated disorders to neglect

neglect patients (e.g. Parton et al., 2004) and they will bisect lines too far to the left (e.g. Binder, Marshall, Lazar, Benjamin, & Mohr, 1992). Although Hemianopia causes a shift of the subjective middle to the contralesional side (e.g. Barton & Black, 1998), both neglect and hemianopia patients show more deviation to the ipsilesional side and line bisection performance is more affected by neglect. Another feature of hemianopia is, that even with the aid of cueing or strong motivation it is not surmountable, but the patients show an efficient search strategy. To sum, most of the patients with neglect also suffer from hemianopia (e.g. Hécaen, 1962; Vallar & Perani, 1986).

Hemiparesis or Hemiplegia accompany neglect in about 96% of 144 RHD patients (Sterzi et al., 1993) and describe a motor deficit, when patients are slightly/ partial (Hemiparesis) or fully paretic (Hemiplegia) on their contralesional body side. Hemianaesthesia is also a common companion of neglect in about 60% (Vallar, Guariglia, & Rusconi, 1997), when patients cannot feel one side of their body.

Further, the Balint Syndrome (Balint, 1909) is a symptom complex, consisting of simultaneous Agnosia (the inability to perceive more than one object at the same time; e.g. Luria, 1959), Optic ataxia (inability for goal-directed grasps), and disorders of spatial processing and movement. There are many other disorders, which can co-appear with neglect such as apraxia. However, this topic is not discussed in this work due to lack of space and the focus of the thesis.

Further, there are some attention disorders, which may be present next to neglect and are explained briefly in this paragraph. As seen at the beginning in paragraph 1.2.1 attention plays a big role in the neglect symptomatic and deficits also can be seen in test situations, when the patients cannot sustain attention or focus their attention, and show fatigability (e.g. Knight, Richard Staines, Swick, & Chao, 1999; Robertson et al., 1997). Furthermore, patients display deficits in temporal and spatial attention (e.g. Arend, Rafal, & Ward, 2008; Husain, Shapiro, Martin, & Kennard, 1997; Roberts, Lau, Chechlacz, & Humphreys, 2012) or also a bias to local features in the scene (e.g. Rafal, 1994; L. C. Robertson, Lamb, & Knight, 1988). Duncan, Emslie, Williams, Johnson & Freer (1996) found another impairment, which they called ‘goal- neglect’, when attraction to stimuli interrupt or cancel a targeted action. Further, an impaired spatial working memory could also contribute to neglect (Husain et al., 2001) and could be accountable for the patients problems in coin flipping tasks.
1.4 Theoretical bases of the line bisection task and the landmark task

1.4.1 Line bisection

As the line bisection task is the foundation for the landmark task, it is also important to illustrate briefly its history and development. In 1980, Schenkenberg, Bradford and Ajax proposed first the line bisection task (LB) with 20 lines of various lengths, which the patients were asked to bisect in the middle. In 1990, different authors tried to improve the task, as it could not differentiate between motor and perceptual biases (e.g. directional hypokinesia vs. visual neglect). Many attempts have been made to solve this issue; for a detailed overview see the review of Saevarsson (2013). Few examples are listed in this paragraph. Coslett, Bowers, Fitzpatrick, Haws, and Heilman (1990) used a task which disentangles the hemispace where the line was presented from the one where it was bisected; other publications conducted manual and verbal tasks (e.g. Reuter-Lorenz & Posner, 1990). The verbal task requires to observe the experimenter moving a pen and to say when it is in the middle. In the manual task, patients must bisect by themselves plus two different starting points of the pen. Further, in pulley device tasks, the middle of a vertical line must be marked with a pointer controlled by a pulley and movement must be performed opposite to the pointer in the congruent condition (Bisiach et al., 1990). Patients bisected too far to the right in the congruent condition, while the incongruent condition reduced the rightward error. Stone and colleagues (1991) deployed a line cancellation task called Albert’s task which is explained later in the methods chapter. Moreover, some papers used a line bisection with cueing letters and judgment which end is nearer to the bisection mark (e.g. Harvey et al., 1995a; Milner, Harvey, Roberts, & Forster, 1993). Tegnér & Levander, 1991 used a line cancellation test in combination with a 90° angle mirror view. 10 out of 18 patients only cancelled stimuli on their visual right, which equals their motoric left and a perceptual bias (PB). Four out of these 18 patients showed a response bias (RB) as they only cancelled in their visual left/motoric right. Nico (1996) used a combination of the task from Tegnér and Levander (1991), with a line cancellation task and an overhead projector but the task was not sensitive for PMN and none of the 22 patients showed this deficit. Further, Mattingley, J.L. Bradshaw, Nettleton, and J. A. Bradshaw (1994) used the so-called grayscales
1.4.1 Line bisection

task, in which brightness gradients must be judged regarding which segment is darker. It showed that healthy participants choose the dark side left.
Healthy participants normally bisect the line to the left around 1.6% (Bradshaw, Nettleton, Nathan, & Wilson, 1985; Scarisbrick, Tweedey, & Kuslansky, 1987). Patients with left neglect after RHD show a bigger bias to the right (Pasquier, Bergego, & Deloche, 1989). Here, a displacement of the bisection mark towards the right is interpreted as a symptom of neglect, but it is not dissociable whether the line is bisected too far to the right because of premotor factor and/or perceptual factors (Bisiach et al., 1990). As seen in different studies, the length of the line affects the accuracy: patients make less error with shorter lines than with longer ones (Butter, Mark, & Heilman, 1988). Altogether, previous findings imply that patients with neglect will show a deviated bisection to the right (Azouvi et al., 2002).

1.4.2 Landmark task

In 1992, Milner, Brechmann and Pagliarini first used the LM, in which the patients point to the shorter segment of pre-bisected horizontal lines in a forced-choice setting. They found that the patients predominantly pointed to the left because they overestimated the length of the left segment. Unfortunately, the original task could not separate between perceptual (input-related) neglect and premotor (output-related) neglect, as it is not clear if the patient chooses the left side because he has visual or/and premotor neglect deficits (Toraldo, McIntosh, Dijkerman, & Milner, 2004). In contrast, the adapted Milner landmark task (Harvey et al., 1995a; Harvey et al., 1995b; Milner et al., 1993) is a good bedside tool that allows a differentiation between the perceptual and the premotor components (Milner et al., 1992; Milner & Goodale, 1995; Milner, 1987). The participant is requested to choose which end of the line is nearer to the bisection mark and point to it. They found, that seven of eight patients showed a PB (or VN), one of eight showed a RB (or PMN), and in general that the left side is perceived as shorter than identical segments on the right. Compared to the LB it demands fewer eye movement and motor aspects (Fink, Marshall, Weiss, & Zilles, 2001). Importantly, Bisiach, Ricci, Lualdi, and Colombo (1998a) introduced a new variant of Milner’s landmark task in which the patient must choose the longer segment, too. The new set consists of one verbal response version (LANDMARK-V)
where patients have to name the color of the shorter or longer segment of one red and one black segment. In the manual version (LANDMARK-M), patients are asked to point with their ipsilesional hand to the shorter or longer part of nine black, pre-bisected lines. Patients with PB underestimate the length of the left and patients with RB favor the ipsilesional (right) segment across all judgments. There were both positive correlations between PBs and the size of the error in the verbal task, and between RBs and the size of the error in the manual task. This version of the landmark task is very sensitive to premotor neglect, spatially incompatible movements are avoided and perceptual aspects controlled. Although, the ‘problem’ with this task is, that the patient only points to the longer part of the line, instead of also bisecting the line manually. In 2000, Capitani, Neppi-Mòdona, and Bisiach used shorter forms of the LANDMARK-V and LANDMARK-M. Further, they used a new scoring system: PB is the sum of all left- shorter naming divided by two, while RB is the sum of all right-longer naming divided by two. Vossel and colleagues (2010) also used a shorter version of the LANDMARK-M with only seven pre-bisected lines and normative data of Capitani and colleagues (2000) as a baseline. The stimuli were identical and controlled for perceptual aspects. The measure for perceptual bias was calculated “[...] on the basis of the relative frequency of left shorter and right longer responses (PB= [% left shorter responses+ % right longer responses]/2) [...]” (Vossel et al., 2012, p. 3950). Response bias was defined as “[...] the relative frequency of right longer and right shorter responses (RB= [% right longer responses+ % right shorter responses]/2) [...]” (Vossel et al., 2010, p.3950). They found that nine of the 22 patients with neglect displayed a strong PB, ten a strong RB and six showed both biases on the manual version of the landmark task. To summarize, patients with VN should perceive a centrally bisected line bisected too far on the left and point to the shorter segment, because they ignore the left side of the line (e.g. Vossel et al., 2012, p. 3950). Patients with PMN should persistently point to the right. It is to consider, that many versions of the landmark task and the line bisection (e.g. reversed view due to mirror or video; pulley device) can cause problems for the data analysis, even in healthy patients due to incompatible conditions. An improved version (LMM) with respect to previous versions of it is applied in the current study (see section 2.2.4.2 for description).
1.5 Neuroanatomy of neglect: Previous studies

The question about the neuroanatomical basis of unilateral neglect is still a controversial issue (e.g. Danckert & Ferber, 2006; Saevvarsson et al., 2014; Saevvarsson, 2013). Heilman and Valenstein (1972) postulate, that “(...) Unilateral neglect has been described following lateral frontal lesions in monkeys (Bianchi, 1895; Kennard & Ectors, 1938; Welch & Stuteville, 1958) and man (Bianchi, 1895; Kennard & Ectors, 1938; Welch & Stuteville, 1958).”. Brain injury mostly occur due to infarcts in supply areas of the middle cerebral artery, posterior infarcts (e.g. (Heilman et al., 2012, p. 317), traumatic brain injuries, or tumors (Vallar, 1993). Further, it was found, that neurons in the inferior parietal lobe (IPL) respond to visual stimuli, and even more when the stimuli also needed a movement (Freeman, 2001, p. 402; Vallar, 1993). This may be due to a connection of the limbic system and the frontal lobe in the inferior parietal lobe, as both, the limbic system, and the frontal lobe are important for attention and directing attention (Heilman, Watson, et al., 1993). The view of clear structural damage is questioned from different sites, as over the last decades many authors debated about whether neglect occurs due to unique functional disruptions and disconnected networks (e.g. Karnath & Rorden, 2012). In many cases, lesions are located in the right parietal and temporal part of the occipital and frontal cortex and in subcortical structures (e.g. Buxbaum et al., 2004; Vallar & Perani, 1986). Because of its widespread lesion variability, persisting neglect is considered to be caused by many different lesions and also lesions in terms of a damaged neural network for attention, orientation and awareness mainly in the right hemisphere (e.g. Corbetta & Shulman, 2011; Karnath & Rorden, 2012; Karnath, 1988; Mesulam, 1981, 1994; Ptak & Schnider, 2011; Vuilleumier, 2013). It is assumed that this network is composed of fiber tracks, which connect the dorsal and ventral prefrontal and premotor cortex (Bartolomeo et al., 2007). These findings led to one commonly accepted view, that three major right cortical areas are damaged in left spatial neglect. These areas are the IPL (e.g. Heilman, Watson, et al., 1993; Himmelbach & Karnath, 2003; Mort et al., 2003; Verdon et al., 2010), the TPJ (e.g. Chechlacz et al., 2010; Commiteri et al., 2007; Golay, Schnider, & Ptak, 2008; Karnath & Rorden, 2012; Mort, 2003; Rengachary et al., 2011), and the perisylvian network for spatial orientation. This network consists of: the STC (e.g. Himmelbach


1.5 Neuroanatomy of neglect: Previous studies

Neuroanatomy of neglect: Previous studies

Karnath, Berger, Küker, & Rorden, 2004; Karnath & Rorden, 2012), the underlying insula and ventrolateral prefrontal cortex (e.g. Committeri et al., 2007; Husain & Kennard, 1996; Karnath & Rorden, 2012; Mort et al., 2003). Corbetta and Shulman (2011) suggested, that neglect emerges from an impaired right-hemispheric ventral parieto-frontal attention network, which consists of the right IPL, the superior temporal gyrus (STG) (see also Karnath, Ferber, & Himmelbach, 2001; Mort et al., 2003), the IFG, and the insula. According to Verdon, Schwartz, Lovblad, Hauert, and Vuilleumier (2010), the right IPL is the visuo-spatial component, the right dorsolateral prefrontal cortex is the visuo-motor component and the deep temporal lobe areas the object-centered component. He and colleagues (2007) found, that the ventral network is responsible for core non-spatial reorienting, whereas the bilateral dorsal frontoparietal network is accountable for contralateral perception; further, lesions here cause core spatial bias in attention and eye movements. Other areas affected in neglect are the (inferior) frontal lobe (IFL; e.g. Ghacibeh, Shenker, Winter, Triggs, & Heilman, 2007; Husain & Kennard, 1996; Karnath & Thier, 2006; Pedersen et al., 1997; Vallar & Perani, 1986), and the basal ganglia (e.g. Karnath, Himmelbach, & Rorden, 2002; Vossel et al., 2010). Importantly, Himmelbach and Karnath (2003) and Rosset and colleagues (Rosset, Malhotra, Muir, Reeves, Duncan, Birschel, et al., 2009; Rosset, Malhotra, Muir, Reeves, Duncan, Livingstone, et al., 2009) do not share the opinion of many other reports (e.g. Saevarsson et al., 2014). These authors claim that areas concerning directional reaching deficits (e.g. basal ganglia, frontal lobe, IPL, and STC) are not associated with neglect categorical and may explain isolated reaching deficits to the left. More recently, Ptak and Schnider (2011) suggested that neglect occurs after lesions of the frontal eye field and the posterior intraparietal sulcus.

Right subcortical areas affected are the basal ganglia, especially the putamen and caudate nucleus (Damasio, Damasio, & Chui, 1980; Karnath et al., 2003), as well as the thalamic pulvinar (Damasio, et al., 1980; Karnath et al., 2003). Further, injuries to the gray matter of the STG (Husain et al., 2000) and lesions in the white matter in the temporal lobe lead to persistent neglect (Doricchi, Thiebaut de Schotten, Tomaiuolo, & Bartolomeo, 2008; Rosset, Malhotra, Muir, Reeves, Duncan, Birschel, et al., 2009; Samuelsson et al., 1997).

Previous findings suggest, that mainly frontal lesions lead to MN, more anterior lesions to PMN and predominantly parietal and temporal lesions to VN (e.g. Bisiach
1.5 Neuroanatomy of neglect: Previous studies

According to a literature study of Saévarsson (2013, p. 296) with over 367 PMN patients, most of them showed parietal lesions (49%), followed by frontal (43%), subcortical (42%), and temporal lesions (36%) and lastly occipital lesions (8%). The conclusion is that PMN mostly emerges after unspecified frontal and parietal damage. Vossel and colleagues (2010) stated, that VN often occurs after lesions in the frontal, parietal and occipital areas. Lesions especially in the putamen and the caudate nucleus, in contrast, cause PMN. Other publications suggest, that motor deficits are caused by lesions in the frontal and basal ganglia (Karnath et al., 2002; Rafal & Posner, 1987), as well as the posterior parietal lobe and the IPL (Bisiach et al., 1990). Most of the mentioned important neuroanatomical regions can be seen in Figure 6.

![Figure 6. Lateral surface of the left hemisphere: Here are important structures listed as, for instance, the IPL in the upper right, the STG in the lower middle, and the IFG in the middle left (image taken from: “Wikimedia Commons,” 2012).](image)

1.6 Therapy of neglect

Over the last few decades, different intervention and therapy methods have been used with the objective of improvement of neglect symptoms. This section explains briefly few of many examples of possible intervention methods. Interventions for patients with neglect attempt to strengthen the attention to the contralesional space. The most important method in this work is the prism adaptation (PA), which will be explained in section 2.3 (e.g. Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Luauté et al., 2006; Redding & Wallace, 2006; Rossetti et al., 1998; Serino, Barbiani,
Rinaldesi, & Làdavas, 2009). Other interventions are for example the neck muscle vibration (e.g. Karnath, Christ, & Hartje, 1993), visual scanning training (e.g. Luauté, Halligan, Rode, Rossetti, & Boisson, 2006) or vestibular stimulation (e.g. Cappa, Sterzi, Vallar, & Bisiach, 1987). Further, space remapping training with an elongated stick shall “(...) produce a virtual extension of body space that resulted in a remapping of far space as near space (Farnè & Làdavas, 2000).” (In Luauté, Halligan, Rode, Rossetti, & Boisson, 2006, p. 963), and also of the neglected hemispace. Limb activation, in contrast, uses the left arm as cue (e.g. I. H. Robertson, North, & Geggie, 1992; I. H. Robertson & North, 1992) when its moved, which also can reduce neglect symptoms. Another possibility is to use repetitive trans-cranial magnetic stimulation, which is based on Kinsbourne´s thoughts (1987) about two antagonistic hemispheres which control attention. Following this, reducing the hyperactivity of the left hemisphere after right lesions with the aid of rTMS reduces left neglect (e.g. Brighina et al., 2003; Oliveri et al., 2001). Patients in the acute neglect stage can try the forced use intervention, in which they are forced to look to the left due to opaque lenses on the right halves of the glasses (Arai Arai, Ohi, Sasaki, Nobuto, & Tanaka, 1997). For instance, Robertson and North (1994) let patients move their contralesional hand into the contralesional space in order to direct attention contralesional and reduce the severity of neglect. Rubens (1985), for example, used Caloric stimulation for patients with visual neglect, when they got cold water (30°C or less) in their left ear and warm water in their right ear. Due to that, patients experience a left lateral gaze movement and spatial neglect ceased (e.g. Cappa et al., 1987). Galvanic vestibular stimulation is a common method for neglect treatment and includes two electrodes, which stimulate the vestibular nerves in a way, that the brain perceives this as a head movement (Zubko, Wilkinson, Langston, & Sakel, 2013, p. 3), and that the temporo-parietal and frontal regions damaged in neglect are ‘activated’. Due to that, this stimulation might lead to improvement of neglect symptoms (e.g. Kerkhoff & Schenk, 2012, p. 1075, Zubko, Wilkinson, Langston, & Sakel, 2013). When optokinetic stimulation is used, patients need to follow contralesional-moving stimuli with their eyes, which shall improve the attention for the contralesional space and the recovery of visual neglect (e.g. Kerkhoff, Keller, Ritter, & Marquardt, 2006; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990). Newer approaches in rehabilitation research were mix and match of treatments, although this is only based on subjective instincts as no evident results are available yet (Kerkhoff & Schenk, 2012).
1.7 Main hypotheses

Neglect patients usually bisect lines too far on the right and it is not possible to determine if this is caused by an underestimation of the left side (PB) or by the failure to direct actions toward the left side of space (RB), or by a combination of both on a LB (e.g. Loetscher, Nicholls, Brodtmann, Thomas, & Brugger, 2012). As previous studies show, that the motor and the perceptual/ or attentional modality are closely linked (Heilman et al., 2012), PMN+ seem to profit more than other patients from prism adaptation therapy (e.g. Saevarsson & Kristjánsson, 2013). This thesis aims to differentiate between PMN+ and PMN- symptoms. According to earlier studies and the action-intention-hypothesis (Heilman et al., 2012), patients have been found to be aware of stimuli in the contralesional space but fail to perform in this hemispace due to the disability to act there, an ipsilesional action-intentional bias, or a rightward motor-intentional bias (Heilman et al., 1983). Summarized, this work aims to find differences between PMN- and PMN+ in patients' behavior following intervention and in its neuroanatomy.

1.7.1 PMN+ show stronger improvement in motor than perception related tasks

Contrary to PMN-, it is assumed that PMN+ will show better performance in “more” motor related tasks: landmark task manual (LMM), pointing task, LB. The scores in the “more” perceptual related tasks will be lower: Albert’s task, number cancellation, letter cancellation, star cancellation, cross copying, clock drawing). Due to the prism adaptation and also to effects on the eye movements (e.g. (Angeli, Benassi, & Lådavas, 2004; Dijkerman et al., 2003; Ferber, Danckert, Joanisse, Goltz, & Goodale, 2003), the motor behavior improves and neglect symptoms are reduced (e.g. (Angeli, Benassi, & Lådavas, 2004; Dijkerman et al., 2003; Ferber et al., 2003). Further, the prisms activate the dorsal stream, which is usually not damaged in neglect (Danckert & Ferber, 2006). As this stream is responsible for visually guided motor behaviors of eyes and limbs (e.g. Saevarsson & Kristjánsson, 2013; C. L Striemer & Danckert, 2010) and visual attention (e.g. Corbetta & Shulman, 2002; Milner & Goodale, 1995), motor related task performance is more likely improved than performance in visual
related tasks. It is also debatable whether they alter their performance in visual related tasks at all (e.g. Dijkerman et al., 2003; Ferber et al., 2003). Also the (pre)-motor modality of neglect will profit more of this intervention (e.g. Dijkerman et al., 2003; Ferber et al., 2003).

### 1.7.2 PMN+ will indicate stronger improvement in the LMM task

The second hypothesis is based on the assumption, that even if there are two directional systems affected (visual and motor), PMN+ will profit more than PMN- from the prism therapy and due to that they will show stronger improvement in the LMM (e.g. Saevarsson & Kristjánsson, 2013; C. L. Striemer & Danckert, 2010; C. L. Striemer & Danckert, 2010). PMN- will underestimate the length of the left segment in the oral condition and both groups will bisect the line too far on the right in the manual condition. Moreover is expected to be better in the manual condition than PMN+ in the first session, because PMN leads to preferred rightward movements and poor execution of movements towards the contralesional side (e.g. Saevarsson & Kristjánsson, 2013; C. L. Striemer & Danckert, 2013). For instance, Striemer and Danckert (2010) used a LB (as motor related task) and a landmark task (as perceptual related task). Both tasks measure PBs, but the LB is expected to profit more of the prisms. According to this, the performance of PMN+ in contrast to PMN- in the LMM should improve across sessions and after the prism adaptation.

### 1.7.3 PMN+ shows different neuroanatomical lesions than PMN-

Further, it is assumed that PMN+ patients show different brain injury than PMN-, because exact location of brain injury cannot be predicted based on previous findings. As already discussed in chapter 1.5, the exact neuroanatomy of neglect an its sub forms is a major controversial issue. Some authors consider the following areas to be accountable for directional reaching deficits: the basal ganglia, the frontal lobe, the posterior parietal cortex, the STC, the IPC, and the IPL (e.g. Ghacibeh et al., 2007; Husain & Kennard, 1996; Karnath et al., 2004; Karnath, Ferber, & Himmelbach, 2001; Karnath et al., 2002; Mort et al., 2003; Rossit, Malhotra, Muir, Reeves, Duncan,
Birschel, et al., 2009; Rossit, Malhotra, Muir, Reeves, Duncan, Livingstone, et al., 2009; Saevarsson, 2013; Vossel et al., 2010). Mostly frontal, superior temporal and parietal brain injuries are believed to cause neglect. As seen in chapter 1.5.1 there are different lesion associated with perceptual and premotor neglect. Motor deficits are caused mainly by lesions to the frontal area and basal ganglia (Bisiach et al., 1990), the posterior parietal lobe and the IPL (Bisiach et al., 1990). Frontal lesions are not necessarily related to (pre-) motor neglect, but highlighted in some studies (e.g. Husain et al., 2000). These findings might have showed up because of the incompatible conditions in the tasks that were used (see Saevarsson, 2013 for overview). Therefore, the right (dorsolateral) frontal cortex is very sensitive to such difficult tasks (e.g. Fink et al., 1999). Various anterior lesions lead to premotor neglect and right subcortical affected regions are especially the putamen, the caudate nucleus (Damasio et al., 1980; Karnath et al., 2003; Vossel et al. 2010), and the thalamic pulvinar (Damasio et al., 1980; Karnath et al., 2003). Perceptual or visual neglect mostly occurs after parietal and temporal lesions (Karnath et al., 2002; Rafal & Posner, 1987). Interestingly, Saevarsson (2013) found, that out of over 367 PMN patients, nearly half of them showed parietal lesions, followed by frontal (43%), subcortical (42%), and temporal lesions (36%) and lastly occipital lesions (8%). These overlaps could be explained by the fact that the perceptual and the motor modality are closely linked and that VN and PMN are likely present seldom independent from each other (Saevarsson, 2013).

2. Methods

2.1 Participants

To analyze the hypotheses and the effect of PMN, eighteen stroke patients suffering from chronic unilateral neglect participated voluntarily in this study. These patients were recruited from the Clinic Bogenhausen in Munich and the Schön Clinic Munich Schwabing. They were screened for eligibility by neuropsychologists before being asked to participate in the study. Different tests were used for this approach, such s: the static perimetry (e.g. Bisiach et al., 1990; Bisiach, Ricci, & Mòdona, 1998; Umiltà,
1995), the *table task* (e.g. Gauggel & Kerkhoff, 1997; Kerkhoff, Münßinger, & Marquardt, 1993), the *Visual Object And Space Perception Battery* (*VOSP*, Warrington & James, 1991), the *Birmingham Object Recognition Battery* (*BORB*, M. J. Riddoch & Humphreys, 1993), and the *Behavioral Inattention Test* (*BIT*, Halligan et al., 1991). The benefit for participating was the possibility of diagnose of a maybe undetected *PMN*, appropriate intervention, and information about their individual test results. Participating had no risks or implications for the patients and all data were anonymized. The patients helped to improve and optimize the diagnostic and therapy of *PMN*. To partake, they gave their informed consent for the study, which was formally approved (license no. 5838/13) by the Medical Ethic Committee of the Technical University in Munich. Patients were selected according to the following a priori inclusion criteria:

- Chronic neglect (affliction existed at least four weeks before participation),
- Right hemispheric or right subcortical brain injury
- Stable condition

In this context, a close look at the hospital records, eating pattern and their sleep rhythm of the patients was carried out. Moreover, patients were not invited to participate when they met an a priori exclusion criterion:

- Unilateral left-brain injury
- Difficulties in understanding task instructions
- Left-handedness
- Major visual field deficits
- Age under 18
- Acute brain injury (less than four weeks since brain injury)
- Flawless performance on standard testing (> 95%)

Most of the patients showed mild visual field deficits (hemianopia). Five patients were excluded a priori after meeting and testing them once, because they met some of the exclusion criteria: patient KG. suffered from left unilateral lesions and exhibited a right neglect, just as patient HR. Both, patient SE. and patient LC. were cancelled due
to left-handedness. Patient BX. showed nearly no neglect symptoms and was therefore excluded. In addition, patient GH., patient BG., and patient SJ. participated only in the first session because organizing, health and motivational issues but were included in the lesion mapping analyses. Patient NK. participated only in three sessions due to his unplanned release from the clinic, and therefore was only included in the lesion mapping analyses. Based on the results of the LM in the first session, the patients were categorized in two groups of having PMN+ (0) or not PMN- (1). The second group might suffer mainly from VN. If the score for the verbal condition is smaller than the score for the manual one, the patient is categorized into PMN- (1). If, on the contrary, the score for the landmark verbal is higher than for the manual version, the patient is categorized as PMN+ (0).

In summary, 13 patients of 18 were included in the lesion mapping part-five female and eight male patients with a mean age of 64 (64.46±10.51) years. Minimal age was 43 and maximum 79. Seven patients were classified into PMN+ and six into PMN- (see Table 3). The groups did not differ significantly.

<table>
<thead>
<tr>
<th>Age</th>
<th>Sample (N=13)</th>
<th>PMN+ (N=7)</th>
<th>PMN- (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>64.46</td>
<td>68.57</td>
<td>59.66</td>
</tr>
<tr>
<td>SD</td>
<td>10.51</td>
<td>7.23</td>
<td>12.29</td>
</tr>
<tr>
<td>Minimum</td>
<td>43</td>
<td>58</td>
<td>43</td>
</tr>
<tr>
<td>Maximum</td>
<td>79</td>
<td>79</td>
<td>74</td>
</tr>
</tbody>
</table>

*Table 3*

Distribution of age in the neuroanatomical sample (N=13)

Nine of 18 patients were included in the behavioral analysis-five female and four male with a mean age of 66 (65.89±11.25 years). Five patients were categorized in PMN+ and four in PMN- (see Table 4). Further, there is no significant difference concerning the age in the two groups (p= 0.195).
Table 4

Distribution of age in the behavioral sample (N=9)

Based on the medical reports and the brain scan information, Table 5 shows an overview of the patients name, age, etiology and lesion location (only lesions in the right hemisphere), the weeks since onset, the presence or absence of hemianopia, and the classification of the patient in neglect groups.
Table 5

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Etiology/ lesion location</th>
<th>Weeks since onset</th>
<th>Hemianopia</th>
<th>Neglect group</th>
</tr>
</thead>
<tbody>
<tr>
<td>WR.</td>
<td>58</td>
<td>Subarachnoid hemorrhage/ frontal basal ganglia, and ventricle crack</td>
<td>29</td>
<td>Yes</td>
<td>PMN+ (0)</td>
</tr>
<tr>
<td>SD.</td>
<td>59</td>
<td>Hemorrhagic stroke/ frontal, occipital, temporal, putamen, and insula</td>
<td>26</td>
<td>Yes</td>
<td>PMN- (1)</td>
</tr>
<tr>
<td>PM.</td>
<td>43</td>
<td>Ischemic stroke/ temporal, paraventricular, and caudate nucleus</td>
<td>20</td>
<td>No</td>
<td>PMN- (1)</td>
</tr>
<tr>
<td>NK.</td>
<td>55</td>
<td>Ischemic stroke/ parieto-occipital, temporal, and thalamus</td>
<td>10</td>
<td>Yes</td>
<td>PMN- (1)</td>
</tr>
<tr>
<td>HM.</td>
<td>79</td>
<td>Hemorrhagic stroke/ frontal, temporal, parietal, putamen, and insula</td>
<td>5</td>
<td>No</td>
<td>PMN+ (0)</td>
</tr>
<tr>
<td>PR.</td>
<td>63</td>
<td>Hemorrhagic stroke/ occipital, temporal, and IPL</td>
<td>16</td>
<td>Yes</td>
<td>PMN+ (0)</td>
</tr>
<tr>
<td>GH.</td>
<td>73</td>
<td>Hemorrhagic stroke/ occipital and parietal</td>
<td>7</td>
<td>Yes</td>
<td>PMN+ (0)</td>
</tr>
<tr>
<td>BG.</td>
<td>64</td>
<td>Hemorrhagic stroke/ fronto-temporal, temporo-basal, and basal ganglia</td>
<td>10</td>
<td>Yes</td>
<td>PMN+ (0)</td>
</tr>
<tr>
<td>SA.</td>
<td>70</td>
<td>Ischemic stroke/ occipital, anterior thalamus</td>
<td>15</td>
<td>Yes</td>
<td>PMN+ (0)</td>
</tr>
<tr>
<td>KC.</td>
<td>74</td>
<td>Ischemic stroke/ basal ganglia</td>
<td>10</td>
<td>No</td>
<td>PMN- (1)</td>
</tr>
<tr>
<td>EG.</td>
<td>74</td>
<td>Hemorrhagic stroke/ temporo-parietal</td>
<td>22</td>
<td>Yes</td>
<td>PMN- (1)</td>
</tr>
<tr>
<td>SJ.</td>
<td>53</td>
<td>Ischemic stroke/ frontal, occipital, temporal, parietal, putamen, and insula</td>
<td>5</td>
<td>Yes</td>
<td>PMN- (1)</td>
</tr>
<tr>
<td>HEM.</td>
<td>73</td>
<td>Hemorrhagic stroke/ basal ganglia</td>
<td>6</td>
<td>No</td>
<td>PMN+ (0)</td>
</tr>
</tbody>
</table>

Overview of the participants: The table shows information about the name abbreviation, the age, the etiology and lesion location, the weeks since onset, the presence or absence of hemianopia and the classification of the patient in the neglect groups.
2.2 Assessment procedure

2.2.1 General assessment and research design

Before testing, the patients that suited the study and were willing to participate, signed the informed consent, and allowed the anonymous usage of their data as well as for the video recording of parts of the session. Then a general patient assessment was performed where socio-demographic information (e.g. age, handedness, lesion data, education, social status, job etc.) was retrieved. Based on medical reports from the hospital and the current impression, the patients are explored a priori with regard to the participation criteria (see chapter 2.1), before they are invited to participate in the study. To determine any motor deficits or anosognosia, it was checked if the patient can move both arms when uncomfortable stimuli are presented or if he/she is strongly motivated to move the arm. In addition, abnormal hand use was determined. Further, to check for motor neglect, the patient needed to close the fists as many times as possible in one minute (see Coulthard, Rudd, & Husain, 2008). Further, abnormal eye movement was observed in general by asking patients to follow a finger in their hemispace. The first session day is considered as the baseline measurement. The assessment is divided in two categories - the experimental assessment with standard tests and the experimental assessment with reaching tasks. The intervention follows afterwards. Moreover, the standard neglect tasks in a randomized order to prevent possible confounding influences of learning. Afterwards, they execute a reaction task, a coin flipping reaching task, and an open-loop box pointing task. This section is followed by an appropriate intervention with prisms (see section 2.3.2). The open loop task takes place pre- and post-adaptation with the prisms. In session two, the intervention was applied first, followed by the experimental assessment. At the third and fourth session, only experimental assessments were conducted. Each experimental session lasted one to two hours.
During performance of the standard tests, the experimenter is always seated on the ipsilesional side (right) of the patient and tasks are performed with the ipsilesional hand. Parameters for the tests are accuracy and reaction time. All paper pencil tasks were presented on a DINA4 paper (210 x 297 mm) and performance time was measured with a timer. A mixture of different tasks to reveal neglect is used in this work, because the presence of neglect is dependent on the tasks, which are used (Schubert & Spatt, 2001). Standard neglect tasks were used: Albert’s task, letter cancellation, number cancellation, star cancellation, Greek cross copy drawing, clock drawing, and the LB (for explanation see Halligan et al., 1991; Saevarsson, 2009). All pictures of the different tasks that are shown following (section 2.2.3.1 to 2.2.4.2) are directly from patients who participated in the study. Lower scores in timed standard neglect tasks mean worse performance, stronger neglect severity, response slowing and mostly a start of the search on the right (e.g. Schubert & Spatt, 2001). In cancellation tasks, two or more omissions (on the left) are considered as pathological neglect (Vanier et al., 1990), as healthy participants missed none or only one item. The scores for the cancellation tasks are calculated with following formula: (number of marked items/total number of items) x 100. Further, other rating systems will be explained in the particular test descriptions. Beside the task specific instruction, patients were instructed with the following general order: “Please only use your right hand for the following tasks. Lay your left hand on your chest. Please perform every task as accurate and quick as possible. Please always drop the pen, when you’re finished.” (Bitte benutzen Sie für die folgenden Aufgaben nur Ihre rechte Hand. Legen Sie Ihre linke Hand auf Ihren Schoß. Bitte führen Sie alle Aufgaben so genau, und so schnell wie möglich aus. Bitte legen Sie immer den Stift ab, wenn Sie fertig sind).

2.2.2.1 Albert’s task

This task is also known as the line cancellation task. The patient is confronted with 40 short, skewed aligned lines (each 2.5cm) on the paper, which have to be crossed out once (see Figure 7). Following task specific instruction was given: “Please cross out
each line once.” (Bitte streichen Sie jeden Strich einmal durch).

Figure 7. Albert’s task: Neglect affected patients clearly misses lines on the left.

### 2.2.2.2 Number cancellation

In this task, the patients are provided with various numbers on a paper. On that paper the number 8 is aligned 40 times between other, distracting numbers and the patient must cross out all eights. Figure 8 illustrates the number cancellation task. The instruction is: “Please cross out all the 8’s as quickly and as accurately as possible.” (Bitte streichen Sie alle 8er so schnell und genau wie möglich durch).

Figure 8. Number cancellation: The neglect patient misses the numbers aligned on the left.
2.2.2.3 Letter cancellation

Similar to the number cancellation, the patient is asked to cancel 60 A´s on a paper with different distracting letters (see Figure 9): “Please cross out all A’s as quickly and as accurately as possible.” *(Bitte streichen Sie alle A’s so schnell und genau wie möglich durch).*

*Figure 9. Letter cancellation: The neglect patient misses the letters on the left side.*

2.2.2.4 Star cancellation

For the conduction of the star cancellation, patients were seated in front of a centrally arranged paper in front of them with 131 verbal and nonverbal stimuli randomly scattered. As seen in Figure 10, there are 56 small stars (targets) between 75 distractors (52 big stars, 13 letters, 10 short words). The instructions are: “Please cross out all the small stars as quickly and as accurately as possible.” *(Bitte streichen Sie alle kleinen Sterne so schnell und genau wie möglich durch).*
2.2.2.5 Greek cross copying drawing

One common probe for visuo-spatial impairment is the Greek cross copy drawing (e.g. Ovsiew, 1997). The patients must copy the figure of a Greek cross without putting the pen down (to aggravate the task). The score given by the experimenter and is subjectively rated on the basis of different criteria: size distortion, completion, and equality to the original (Lezak et al., 2004). Scores from 0 over 12.5, 25, 37.5, 50, 62.5, 75 to 100% are possible. Figure 11 shows the distorted cross copy drawing of a patient. The instruction is: “Please copy the Greek cross without raising the pen.” (*Bitte zeichnen Sie das Kreuz ab, ohne den Stift abzusetzen*).
2.2.2.6 Clock drawing

The task is to draw a basic clock with all handles and numbers. The clock drawing can give information about visuo-spatial and praxis abilities, and could reveal attentional and executive dysfunctions (Halligan et al., 1991). An example of the clock drawing is shown in Figure 12. The score is calculated based on different criteria: correct position of the numbers and handles, different length of the handles, all numbers within the circle, completion of the circle, any distortions, etc. Then the experimenter gives his rating according predefined scoring criteria, which can be 0; 12.5; 25; 37.5; 50; 62.5; 75; or 100%. This task uses different times to draw, but the basic instruction is the same: “Please draw a clock with all handles and numbers that shows ten to eight (7:50) or twenty to ten (9:40).” (Bitte zeichnen Sie eine Uhr mit allen Zeigern und Zahlen, die zehn vor Acht (7:50) oder zwanzig vor Zehn (9:40) anzeigt).
2.2.2 Experimental assessment: standard tests

2.2.2.7 Line bisection

In the LB, a DIN A4 paper with three horizontal, cascade-aligned lines is placed in front of the patient. The task is to bisect the line in the middle with a pen. The length of the lines is 204 mm and the middle has to be marked. The score is the deviation in mm from the center. The parameter is always the deviation of the patients’ bisection from the actual midpoint of the line. “(...) deviations from center were calculated as a percentage of total line length (leftward deviations coded as negative).” (Adunsky, Fleissig, Levenkrohn, Arad, & Noy, 2002; Suhr, Grace, Allen, Nadler, & McKenna, 1998). Figure 13 shows a sample of the Line bisection task. The instruction reads as follows: “Please mark the middle of the line.” (Bitte markieren Sie die Mitte der Linie)
2.2.3 Experimental assessment: landmark task

In this work, a new and modified version of the landmark task (LM) is applied, which is somewhat similar to the tasks of Striemer and Danckert (2010). They used a landmark verbal task, in which the patient has to decide verbally which end of the line is closer to the bisection, and a LB for the manual part (see also in Milner et al., 1993 for a similar approach). For the LB, ten 236mm long lines and for the landmark task 16 lines with 200mm length were used. Conversely, the improved version LM in this work contains nine black pre-bisected horizontal lines (180mm long) for each of the two conditions, to address motor and perceptual components. The great advantage of the LM is that the conditions are perceptually equivalent unlike previous versions such as by Striemer and Danckert (2010). Due to that, it is possible to differentiate between PB and RB without possible interferences like the influence of cognitive load, color, and length. The lines are in both, the manual and the verbal condition, pre-bisected at the same distance from the right end of the line (the right end of the line represents the zero point). In addition, the paper shows letters at the upper right corner for practical reasons, but these are covered by the experimenters’ fingertip to avoid influence. Oriented to Vossel and colleagues (2010) the nine lines are pre-bisected at different points- in the center, or at 5, 15, 30, and 60 mm difference to the left and right from the middle. According to this the length of the left segment varies from: 30
2.2.3 Experimental assessment: landmark task

(D), 60 (I), 75 (E), 85 (H), 90 (F, center), 95 (C), 105 (A), 120 (G) to 150 mm (B). This was used as parameters in the current study. Capitani and colleagues (2000) used a similar approach, but the length of the left segment only varies from 60 to 120 mm. Neglect was considered to be present if mean bisections deviated from center by 5% or more (Striemer & Danckert, 2013, p. 437).

2.2.3.1 Landmark task verbal

The patient is provided with a paper with pre-bisected lines and must decide and answer verbally, whether the line is bisected in the middle (‘yes’) or not (‘no’). Figure 14 shows the modified verbal version of the landmark task (LMV). The parameter is the deviation of the pre-bisection from actual center, when the patients’ answer was ‘yes’. Percentages are calculated with the following formula for the lines, which the patient decided to be bisected in the middle: \[1 - \text{(deviation in cm/middle of the line)}\] x 100. If the line is actually bisected in the middle and the patient answers ‘yes’, the score reaches 100%. If the answer is ‘no’ for each line the reached score is 0%. The instruction is: “Please only answer orally without using your hands; place your hands on your lap. Does the bisection mark divide the line exactly in the middle?” (Bitte antworten Sie nur mündlich, ohne Ihre Hände zu benutzen; legen Sie Ihre Hände auf Ihren Schoß. Teilt der Trennstrich die Linie genau in der Mitte?).

Figure 14. Landmark task verbal: The neglect patient is instructed to answer, if the pre-bisected line is bisected in the middle or not; in this picture the line is bisected at 105 mm.
2.2.3.2 Landmark task manual

In the LMM, the patient has to bisect a pre-bisected line in the middle with a pen. The parameter is the deviation of the patients’ bisection from the actual middle of the line in millimeters, and for the analysis in percentage. The percentages are also calculated as in the LMV ([1-(deviation in cm/middle of the line)] x 100), but with the difference that all percentages of the nine lines are summed up and then divided by nine to get an average score. Figure 15 illustrates the LMM. The instruction is: “Please only use your right hand to answer, without speaking. Please ignore the small line that pre-bisects the bigger line. Please mark the middle of the big line. If the bisection mark is already in the middle, please trace it, if not please draw a new bisection mark at the right place.” (Bitte antworten Sie nur mit Ihrer rechten Hand benutzen, ohne dabei zu sprechen. Bitte ignorieren Sie die kleine Linie, welche die Größere schon trennt. Bitte markieren Sie die Mitte der größeren Linie. Wenn der Trennstrich bereits in der Mitte ist, fahren Sie Ihn einfach nach, wenn nicht, zeichnen Sie bitte an der richtigen Stelle einen neuen Trennstrich ein).

Figure 15. Landmark task manual: The neglect patient is requested to bisect a pre-bisected line at the subjective midpoint; in this picture, the line is pre-bisected at 150mm.
2.2.4 Experimental assessment: reaching tasks

2.2.4.1 Reaction task

With the aid of the reaction task, the reaction time and proportion of right versus left reaching movements are recorded. The used devices are an adaptation box with chin support and napkins (open-loop box; see Figure 16), in front of the patient, and response buttons are located on the patients’ left- and right side. Further, headphones, a laptop with tone cues, and a video camera on a tripod for recording the movements and location marks for the buttons (defined reaching distance of the patient) are used. To familiarize the patient with the sounds and to explore auditory extinction, the tones are played once before the trials. In trial one and two hand movements are covered and the patient hears 180 tone cues each trial. A third trial is optional and is done with “fit“ patients. The hand movements are covered until the latest stage of the movement to avoid visual feedback. The instructions are: “Through the headphones you will hear a tone now. You will hear this tone sometimes only on the right, sometimes only on the left and sometimes in both ears. If the sound is coming from the left, press the left button. If you hear the sound only on the right, press the right button. When you hear the sound in both ears, you should decide randomly each time which button you press. Please use only your right hand to press the buttons. Please perform the task as quickly and as accurately as possible.” (Durch die Kopfhörer werden Sie gleich einen Ton hören. Dieser Ton wird manchmal nur auf dem rechten, manchmal nur auf dem linken und manchmal auf beiden Ohren zu hören sein. Wenn Sie den Ton nur links hören, drücken Sie bitte den linken Knopf. Wenn Sie den Ton nur rechts hören, drücken Sie bitte den rechten Knopf. Wenn Sie den Ton mit beiden Ohren hören, dürfen Sie jedes Mal zufällig entscheiden, welchen Knopf Sie drücken. Bitte benutzen Sie nur Ihre rechte Hand zum Drücken der Knöpfe. Bitte führen Sie die Aufgabe so schnell und so genau wie möglich aus).
2.2.4 Experimental assessment: reaching tasks

2.2.4.2 Coin flipping task

The patient must flip each coin in front of him once. The parameter is accuracy (forgotten vs. flipped coins). The used devices are the adaptation box without chin support (see Figure 17), 25 mixed black and white coins on each side, a timer, a sleeping mask, and a video camera on a tripod. On the first trial the patient has full visibility of all 50 game pieces and of the hand movements. On the second trial the patient is blindfolded by a sleeping mask and the exact same task has to be accomplished again. The instructions are: „From the signal you have upto five minutes to turn as many game pieces as possible. Please perform the task as diligently and fast as possible. Please let me know when you are finished.“ (Ab dem Signal haben Sie bis zu fünf Minuten Zeit, umso viele Spielsteine wie möglich umzudrehen. Bitte führen Sie die Aufgabe so sorgfältig und schnell wie möglich aus. Bitte geben Sie Bescheid, wenn Sie fertig sind).
2.2.4 Experimental assessment: reaching tasks

![Image](image1.png)

*Figure 17. Coin flipping task: On the second trial, the coins in front of the participant must be flipped once while wearing the sleeping mask.*

### 2.2.4.3 Open-loop-box pointing task

The pointing task is also part of the prism adaptation. The patient must point straight forward and the parameter is the inaccuracy of this pointing straight forward (not to the contralesional side per se). Used devices are prism glasses, the adaptation box with chin support and napkins, a sleeping mask and a video camera on a tripod. On the first trial the patients are blindfolded, the chin is placed on the support, and they are asked to perform ten pointing movements straight forward with their right index finger and then return their hand to their body (see *Figure 18*). The experimenter records the direction and degrees and analyzes the video data afterwards (e.g. Hauer & Quirbach, 2007; Saevarsson, 2009). The instructions are the following: “Please perform the task as quick and as accurate as possible. Please point from your body midline straightforward.” (*Bitte führen Sie die Aufgabe so schnell und so genau wie möglich aus. Bitte zeigen Sie von Ihrer Körpermitte geradeaus nach vorne*).

The body midline is the imaginary line from the nose to the navel and the patient has to repeat this 15 times. On the second trial, the patient wears the prism glasses (ten degrees right shift lenses) and lays his chin on the support. The targets (one blue and
one red dot on the table; see Figure 19) are located left- and right-handed and the patient has to perform cued and random 60 pointing movements to it. In consequence of the adaptation, the patient mostly points too far to the right side, which gradually decreases during the task until the sight is corrected. On the last trial the patient is blindfolded again with the sleeping mask and has to point 15 times straight forward again where the patient mostly points more to the left after the adaptation. The instruction here is: “Now, I will put you on the prism glasses. Please point to the announced targets.” (Nun werde ich Ihnen eine Prisemenbrille aufsetzen. Bitte zeigen Sie jeweils auf die angesagten Ziele).

2.3 Interventions

The intervention method used in this study was the prism adaptation combined with the open-loop pointing task. As seen in the past, more than 90% of the studies about PA report it as a very successful intervention method (e.g. Fortis, Chen, Goedert, & Barrett, 2011; Frassinetti et al., 2002; Luauté et al., 2006; Serino, Barbiani, Rinaldesi,
& Lådavas, 2009) which shows positive effects on neglect symptoms, too (e.g. Newport & Schenk, 2012; Saevarsson, 2009). This effect is ensured by the prism glasses which deviate the view 10 to 15 angular degrees to the right and bring an enduring shift and improvement of their straight forward direction to the left (e.g. Rossetti et al., 1998). Different publications, which used PA (e.g. Heilman & Valenstein, 2012; Rossi, Kheyfets, & Reding, 1990) found an improvement of neglect symptoms after four weeks of treatment and improved test performance in clinical and experimental tasks (e.g. Pisella, Rode, Farne, Tilikete, & Rossetti, 2006; Rossetti et al., 1998). The dual pathway model of vision can explain the effect of PA; the dorsal stream serves the visuo-motor control and the ventral stream the conscious perception (Milner & Goodale, 1995). As the prisms activate the dorsal stream, which is most active during prism adaptation (e.g. Milner & Goodale, 1995) it is more likely that performance in motor related tasks than perceptual tasks is getting better (e.g. Striemer & Danckert, 2010). PA might improve even higher order visual cognition, which is strengthened by the fact that healthy patients wearing leftward prisms also show neglect like symptoms, too (e.g. Colent, Pisella, Bernieri, Rode, & Rossetti, 2000; Girardi, McIntosh, Michel, Vallar, & Rossetti, 2004; Michel, Rossetti, Rode, & Tilikete, 2003; Michel, 2006). All in all, prisms have been shown to be a good intervention method and improve many areas besides neglect, like postural imbalance (e.g. McIntosh, Rossetti, & Milner, 2002; Rode, Rossetti, & Boisson, 2001; Shiraishi, Yamakawa, Itou, Muraki, & Asada, 2008; Tilikete et al., 2001). Studies, which doubt the profit of PA only proofed this in patients with visual field losses (e.g. Rousseaux, Bernati, Saj, & Kozlowski, 2006), which is the reason for different results. The open-loop box pointing task (section 2.2.6.3) is used together with the prisms in this task to show the proprioceptive shift (e.g. Redding & Wallace, 1993; Uhlarik & Canon, 1971; Wilkinson, 1971).
2.3 Interventions

Figure 19. Prism adaptation: On the left picture, the patient points to the announced targets while wearing the relocating prism glasses. The picture on the right shows the shift of the view due to the prisms (image taken from “Krinner”, 2007)

2.4 Statistics

The descriptive and the interference statistics was performed with the computer program IBM SPSS Statistics version 22 (Statistical Package for the Social Sciences; SPSS Science, Chicago, USA). The normal distribution of the sample has been verified with the help of the Kolmogorov-Smirnov-Test. A determinant of \( p \leq .05 \) means a significant deviation of the distribution of the data from the normal distribution. The significance level was chosen as follows: significant result when the error probability is at most 5\% (\( p \leq .05 \)) and highly significant when it exceed 1\% (\( p \leq .01 \)) (see Bortz, 1999). First, the mean age of both groups (\( PMN^+, PMN^- \)) and the gender distribution were determined. In order to confirm, that the mean ages of the two groups did not differ significantly, a t-test for independent samples was conducted. In addition, the Levene-Test was used for assessing the equality of variances for one variable in two groups. After that, for each standard test a mixed repeated measures analysis of variance (ANOVA) with sessions (four levels: session 1, session 2, session 3, session 4) and each test (level: e.g. Albert’s, Letter Cancellation) according to the grouping factor was done. Further, a mixed repeated measures ANOVA with sessions (four levels: session 1, 2, 3, and 4) and tests (‘motor related tasks’: \( LB, LMM, \) Pointing) according to the grouping factor. Further, another mixed
repeated measures ANOVA with four sessions and six tests (‘perceptual related tasks’: Albert’s, letter Cancellation, star Cancellation, number Cancellation, clock drawing, Greek cross copy drawing) and the grouping factor was conducted. All tests were Bonferroni-corrected. According to the result, it was presented with percentage (%), \(M, SD, SE\), and \(p\).

### 2.5 Voxel-based lesion-symptom mapping

To investigate systematically the lesion localization of \(PMN^+\) and the relationship between brain injury and behavior, a voxel-based lesion-symptom mapping analysis (VLSM) was conducted (e.g. Bates et al., 2003; Chatterjee, 2005; Karnath et al., 2004, 2001, 2003; Rorden & Karnath, 2004). Available brain scans provided by the clinics were MRI’s (Magnetic Resonance Imaging), which included the T1, T2, the fluid attenuated inversion recovery (FLAIR), and the and diffusion images. For five patients only low quality cCTs (cranial computed tomography) were available, so the lesions were drawn directly with the MRICron software version 6/2013 (available online: http://www.mccauslandcenter.sc.edu/micro/mricron/) on an MRICron template (ch2.bet.nii.gz) (for a similar approach see Suchan & Karnath, 2011). In a second step, the original DICOM images (Digital Imaging and Communications in Medicine) were converted into NIfTI files (Neuroimaging Informatics Technology Initiative; nii.gz) for the later coregistration with SPM8 (Statistical Parametric Mapping software 8; Available online: www.fil.ion.ucl.ac.uk/spm). The lesions were drawn directly on the original FLAIR. For all the patients with MRI’s, the brain scan and the lesion volume were reoriented, co-registered, and then normalized to a standard brain using SPM8 combined with the clinical toolbox (available online: http://www.mccauslandcenter.sc.edu/CRNL/clinical-toolbox), which provides a standard older adult brain template. These tools run under Matlab (http://www.mathworks.com). The lesions (n=13) were used as a voxel of interest (VOI) for further analysis in MRICron. Next, the overlap of the normalized lesion voxels for each patient group was determined with the aid of the NPM software (Non-Parametric Mapping, included in the MRICron software package). The presence (0) or absence (1) of premotor neglect symptoms was included as a predictor in the binary behavior analysis. Second, a continuous behavioral measures analysis was performed
with VOIs weighted by the patients’ scores in the first session of the LMM. In order to
find the affected regions the maps of PMN+ and PMN- were overlaid on the .aal
template (automated anatomical labeling) in Mricron. The Brunner-Munzel test for
continuous behavioral data and binary images was used to find voxels associated with
PMN+ and PMN- (e.g. Karnath et al., 2004, 2001, 2003; Kümmerer et al., 2013; Mort
et al., 2003; Chris Rorden, Karnath, & Bonilha, 2007; Verdon et al., 2010). Due to the
small sample size this test was conducted with a threshold of 1.000 permutations
(Liebermeister false discovery rate (L+FDR). All results reported were significant at
p \leq .05 uncorrected at the single voxel level (minimizing for false positives) and
survived correction cutoffs at p \leq .05 for multiple comparisons (Bates et al., 2003;
Committeri et al., 2007).

3. Results

3.1 General results of the standard tests

In all of the measured effects in the conducted mixed repeated-measures ANOVA the
Mauchly’s test indicated, that the assumption of sphericity was violated, the
greenhouse-Geisser corrected degree of freedom was therefore used. Correction of
the degrees of freedom revealed no significant differences between the two
comparison groups.

3.1.1 Slightly better performance of PMN+ in the Albert’s task

The calculations do not show significant difference between groups in the Albert’s
task (p= .614) – no improvement is confirmed in this test. However, interpreting
numerically Figure 20, PMN+ shows a minor improvement trend compared to PMN-.
PMN+ also achieves the best results overall in the third session (M= 83.00, SD= 23.61) and performs better than PMN- (M= 63.75, SD= 39.86). Regarding the
difference between sessions for both groups, the strongest trend (p= .660) is between
the third session (M= 73.37, SE= 10.60) and the fourth session (M= 63.31, SE= 12.01).
3.1 General results of the standard tests

3.1.2 Minor improvement of PMN+ in the number cancellation

The performance of the two research groups did not differ significantly \((p = .743)\) in the number cancellation task. However, interpreting the Figure 21, PMN+ patients improve numerically more between sessions compared to the other group. Further, there is a strong trend \((p = .330)\) for both groups for improvement between the first \((M = 53.00, SE = 9.12)\) and the third session \((M = 65.46, SE = 10.23)\). PMN- performs slightly better than PMN+ in session 3 \((M = 66.15, SD = 34.18)\) following two times prism adaptation sessions.
3.1 General results of the standard tests

3.1.3 Trend for improvement in the letter cancellation

The two groups show no significant difference ($p = .753$) in the letter cancellation between sessions. Compared to the other standard tests, the strongest trend ($p = .114$) for both groups concerning the session difference is seen in the letter cancellation between session 1 ($M = 34.81, SE = 9.21$) and session 3 ($M = 50.80, SE = 8.28$). Figure 22 demonstrates that $PMN+$ shows the best performance in the third session ($M = 51.00, SD = 23.40$).

![Figure 22. Results Letter cancellation: Mean Performance (%) of the two groups across four sessions](image)

3.1.4 High improvement difference between sessions in the star cancellation

There is no significant group difference in the star cancellation task ($p = .662$), but according to the Figure 23, the performance of $PMN-$ improves between sessions and achieves the best results in the fourth session ($M = 66.05, SD = 29.04$). Further, a strong trend ($p = .279$) was revealed between session 1 ($M = 46.73, SE = 8.99$) and session 3 ($M = 62.44, SE = 9.57$).
3.1 General results of the standard tests

3.1.5 Strong trend for a group difference in the Greek cross copying task

No significant difference between the two groups on the Greek cross copy task was revealed. Compared to the other standard tests but the highest trend regarding the group difference is found ($p= .403$). Further, numerically according to Figure 24, PMN- is better in every session than PMN+ and shows the best results in the fourth session ($\bar{M}= 61.13$, $SD= 16.16$). Moreover, there is a trend in improvement between session 2 ($\bar{M}= 37.06$, $SE= 8.38$) and session 4 ($\bar{M}= 52.96$, $SE= 8.27$) with $p= .556$.
3.1.6 PMN+ gets slightly worse across sessions in the clock drawing

No significant difference between the groups ($p= 0.826$) was found for the clock drawing test (Figure 25). Further, $PMN-$ achieves the highest score in the second session ($M= 59.57$, $SD= 36.99$). Differences between sessions are not significant ($p= \text{n.s}$). $PMN+$ seems to get worse numerically from session 1 ($M= 53.20$, $SD= 36.95$) to session 4 ($M= 45.94$, $SD= 33.57$) across the sessions.

![Figure 25. Results Clock drawing: Mean Performance (%) of the two groups across four sessions](image)

3.1.7 PMN- shows better performance in the line bisection

The two groups do not differ significantly ($p = .683$) for the line bisection task. As Figure 26 explains, $PMN-$ shows numerically better performance in every session and the best score in session 2 ($M= 69.20$, $SD= 35.10$). The strongest trend of improvement in this task is between session 3 ($M= 56.24$, $SE= 10.51$) and session 4 ($M= 63.67$, $SE= 9.49$) with $p= .411$. 
3.1 General results of the standard tests

3.2 General results of the reaching tasks

3.2.1 PMN- shows better results in the reaction task

The groups do not show significant differences across sessions ($p = .466$) on the reaction task. *Figure 27* shows that *PMN*- performs better than *PMN+* in the first three sessions, but the performance of both groups gets numerically worse following each session. The best performance is by *PMN-* in the first session ($M = 90.83$, $SD = 3.81$).
3.2 General results of the reaching tasks

3.2.2 Nearly equal performance in the coin-flipping task

The two groups are not significantly different from each other ($p= .762$) on the coin-flipping task (see Figure 28); both groups show nearly the same performance. The best numerical score is reached of $PMN-$ in the fourth session ($M= 57.50$, $SD= 20.68$).

![Figure 28. Results Coinflipping task: Mean Performance (%) of the two groups across four sessions](image)

3.2.3 Similar performance in the open-loop box task

There is no significant difference between the groups ($p= .668$). Further, according to Figure 29, they performed quite similar in the pointing task, even if $PMN+$ shows slightly better results. Numerically, $PMN-$ shows the best performance in session 2 after the first prism adaptation ($M= 96.10$, $SD= 10.81$).
3.2 General results of the reaching tasks

3.3 Results: hypotheses

3.3.1 Marginally significant improvement in the motor related tasks

Concerning the perceptual related tasks (explained in section 1.7.1), there is no significant difference between groups ($p = .929$). Interpreting the plot (Figure 30), $PMN-$ shows improved performance across sessions in nearly every test, except the Albert’s task. In the Albert’s task $PMN+$ achieved the best score overall ($M = 83.00$, $SD = 23.61$). No difference was expected for the perceptual tasks. The biggest improvement trend across all test is between session 1 ($M = 49.58$, $SE = 7.71$) and session 3 ($M = 58.87$, $SE = 7.09$) of the perceptual tasks with $p = .139$. Figure 31 shows both group performances in motor related tasks (explained in section 1.7.1), where $PMN+$ should show higher improvement, but the difference is not significant ($p = .953$). However, there is a marginally strong trend between session 1 ($M = 72.81$, $SE = 5.04$) and session 2 ($M = 77.98$, $SE = 5.23$) with $p = .052$. $PMN-$ achieves the best score in session 2 of the open-loop box pointing task ($M = 96.10$, $SD = 10.81$), which is followed by the performance of $PMN+$ in the same task ($M = 95.70$, $SE = 5.57$). No significant interaction is found ($p = ns.$).
Figure 30. Results Motor related tasks: Mean Performance (%) across four sessions in the perceptual related tasks (Albert’s, letter-, number-, star cancellation, clock drawing, Greek cross copy drawing)
3.3 Results: hypotheses

Figure 31. Results Perceptual related tasks: Mean Performance (%) across four sessions in the motor related tasks (LMM, LB, open-loop box pointing task)
3.3.2 PMM+ does not indicate more improvement in the LMM

There is no difference between the two research groups ($p = .887$) and PMN+ does not show higher improvement compared to PMN-. Overall, there is a trend of improvement between sessions: between session 1 ($M = 70.83, SE = 9.47$) and session 4 ($M = 80.24, SE = 12.01$) with $p = .783$. Interestingly, PMN+ reached the highest score (see Figure 32) in the fourth session ($M = 90.58, SD = 31.71$).

![Figure 32. Results LMM: Mean Performance (%) of the two groups across four sessions](image)

3.3.3 Lesions in the putamen are an indicator for PMN+

In order to find the terms of affected brain regions specific to PMN+ (see section 2.1 for an operational definition of the two experimental groups) the lesion maps were overlaid on the .aal template in MRIcron. The voxels were filtered according to the false discovery rate $L+FDR$-value with a significance level of $p \leq .05$. According to the VLSM analysis, there are significant differences of the lesions in the two groups. Permutations were kept on 1000 and the non-parametric Brunner-Munzel rank was used to determine significant lesion areas in the continuous analysis.
The multislice image of the significant lesion voxels of \( PMN^+ \) and the maximal lesion overlap is presented in Figure 33. Here, mainly the putamen is affected (MNI: 23x20x-3).

*Figure 33. Multislice of the PMN+ lesions: The significant lesion areas are shown in red and mainly affect the putamen*
The main lesion areas of PMN- are shown in Figure 34 and are presented following in descending order: angular gyrus, STG (temporal), middle and inferior temporal gyrus (temporal), hippocampus (temporal), middle temporal pole (temporal), superior temporal pole (temporal), and precentral areas (MNI: 53x-11x-7).

Figure 34. Multislice of the PMN- lesions: The significant lesion areas are shown in blue and mainly temporal.
Figure 35 shows the lesion overlap for both groups in the same picture (MNI: 58x-11x-4).

Figure 35. Multislice of the overlap analysis of PMN+ and PMN-. The significant lesions for PMN+ (red) and PMN- (blue) are shown on the same template.
The continuous analysis shows (Figure 36), that the following regions are commonly associated with lower scores (PMN+) in the LMM:

- superior frontal gyrus (frontal)
- middle orbital frontal gyrus (frontal)
- middle frontal gyrus (frontal)
- inferior orbital frontal gyrus (frontal)
- precentral areas (precentral)
- supplementary motor area
- insula
- caudate nucleus (MNI: 28x32x-10).

*Figure 36. Multislice for PMN+ of the continuous analysis*
4. Discussion

Findings and hypotheses

The major aim of this thesis was to study PMN in light of various behavioral, therapeutic and neuroanatomical aspects. In this chapter, the results are discussed in terms of the hypotheses as well as their implications. Furthermore, limitations to the study will be explained; proposals will be made to improve the diagnosis of premotor neglect as well as suggestions for further research are provided. Overall, the main results of the behavioral analyses were not significant. However, many interesting trends were detected. As the strongest trend for the standard tests was found in the letter cancellation, it might be clinical valuable to assess therapeutic effects. Further, the strongest trend for group differences between the groups was revealed in the Greek cross copy drawing, in which PMN- performs better. Interestingly, there were no differences between sessions and nearly no difference between groups in the Clock drawing task. This could be explained by the fact, that the Clock drawing might address other factors, like the working memory, construction skills and higher cognitive functions, more than spatial neglect symptoms. Most of the standard tests are part of a test battery for visual neglect from the BIT, why the test should be more sensitive to PMN-. Keeping this in mind, it could be an explanation for the better performance of PMN- in two of these tasks (e.g. star cancellation, Greek cross copy drawing). The reaction task revealed the second highest group trend compared to all other tests. Overall, only small trends could be found and the results should be interpreted with caution.

Hypothesis 1: PMN+ show higher improvement in motor than perception related tasks

Hypothesis 1 is not confirmed, as no significant group difference between PMN+ and PMN- was revealed, on both the perceptual and the motor related tasks. PMN- seems to perform numerically better in all standard tasks, unlike the Albert’s task that revealed the opposite finding. This could lead to the conclusion, that the Albert’s task may be more sensitive for motor impairments in neglect, which is in line with
previous findings of Na and colleagues (Na, Adair, & Williamson, 1998), but rejected by other authors (e.g. Nico, 1996). Interestingly, the only marginally significant improvement difference was found between session 1 and session 2 in the motor related tasks. This might be explained by the transient effect of the PA in the first session. Further, there was a strong trend in the session difference regarding the perception-related tasks.

_Hypothesis 2: PMN+ will indicate higher improvement in the LMM task_

The second hypothesis is not verified, which might be associated with the disadvantages of this modified task. The pre-bisection of the line might distract the patients even if they are instructed to ignore it. Further, as only the first session of the LMM was used to classify the patients into PMN+ and PMN-, the results could indicate that this classification regarding the difference between LMM and LMV was not clear. However, PMN+ achieved the highest score in the fourth session ($M=90.58$, $SD=31.71$), which might indicate therapeutic benefits of the prism adaptation.

_Hypothesis 3: PMN+ show different neuroanatomical lesions than PMN-_

Hypothesis 3 is verified as the two groups differed significantly ($p \leq .05$). Even if it was expected that they could show similar lesions, as PMN+ is believed to also show VN symptoms. It is to consider, if PMN+ might emerge a different form of VN as PMN-. The analysis of binary images and groups showed that PMN+ was mainly affected by lesions in the putamen, which is in line with previous publications on PMN lesions (e.g. Damasio et al., 1980; Karnath et al., 2003; Saevarsson, 2013; Vossel et al., 2010).

Further, common neglect regions for PMN- for the most part were temporal and confirm previous findings (e.g. Bisiach et al., 1990; Bisiach, Ricci, & Mòdona, 1998; Karnath, Ferber, & Himmelbach, 2001; Mort et al., 2003; Umiltà, 1995). The VLSM for continuous analysis indicated that mainly frontal lesions, lesions in the supplementary motor area, the insula and the caudate nucleus are appear with PMN+. These findings are also confirmed by previous studies (e.g. Damasio, Damasio, & Chui, 1980; Karnath et al., 2003; Saevarsson, 2013).
4. Discussion: Limitations of the study

Limitations of the study

As the study consists of a cognitive challenging assessment that endures for one to two hours, it was sometimes necessary to motivate the patients verbally to persevere. Further, it is not straightforward to differentiate between premotor and non-premotor neglect patients as the motor and perceptual modalities are closely associated. One major problem of the study is the small sample size, which affects behavioral as well as neuroanatomical analyses. However, the data collection is finished and this thesis is part of a bigger study. A bigger sample than used in the current study is recommended for a VLSM, because of the wide spread variability of brain injury and/or low statistical power (e.g. Timmann et al., 2009). It is well known, that at least 20 patients are necessary to get reasonable statistical power and that VLSM is always confronted with the problem of individual brain organizations (e.g. Fellows et al., 2005; Timmann et al., 2009). However, even with 13 patients, the neuroanatomical findings in this study accord well with previous findings for PMN and VN. There might be also a general limitation in VLSM studies on chronic neglect patients, as there already has been spontaneous recovery and functionally reorganization of the damaged areas. This recovery causes shifts of the shape, location and quantity of the lesions (Karnath & Rorden, 2012, p. 1013). Keeping the problems with a small sample size in mind, different clinics were requested for possible patients.

Further, as many neglect patients suffer from disease comorbidity, they meet some of the exclusion criteria or do not ‘fit’ for the study purpose due to different reasons. The inclusion criteria in the current study were therefore defined broadly. For instance, most of the patients showed mild hemianopia; they were included when it was very mild but this could have influenced the results.

Another well-known issue is the test sensitivity to different types of neglect. In Hypothesis 1, the tests were categorized into more perception and motor related tasks. It can be argued against, which tests are used for the two categories. Na and colleagues (1998) stated, that the Albert’s task is more sensitive to motor impairments and the LB more sensitive to perceptual biases. However, in this study, the tasks are used vice versa and other studies showed that the Albert’s task is not sensitive to PMN (e.g. Nico, 1996). It is debatable which test of those two is more effective to reveal motor impairments. For further studies, it is also to review, to change or exclude the coin-flipping task, which was not as effective as expected to differentiate
between \(PMN^+\) and \(PMN^-\). This task might be more working memory based than motor or spatial related.

**Future research**

For future research the relationship between memory and spatial imagery should be examined further (e.g. Kerkhoff, 2001) as neglect patients might have problems with tasks that address their working memory (e.g. the coin-flipping task). Further, very difficult tasks and those with incompatible conditions (e.g. Bisiach et al., 1995; Tegnér & Levander, 1991) lead to motivational problems and giving up of the patient (e.g. Husain et al., 2000). This could falsely lead to a diagnosis of \(PMN\), when patients give up after starting on the right side of the page. Several other topics, as the relationship between neglect and extinction, might be very interesting for future research. Extinction is claimed to be a milder form of neglect according to the classification system ICD-10 and it needs further investigation how it interacts with neglect and whether it is a subtype of neglect or a distinct disorder. One general issue of neglect research is the differentiation of the different modalities. It is not clear whether it is possible to clearly dissociate the modalities and if there are ‘pure’ forms.

Speaking from previous studies, there have been many attempts to divide, for instance, the motor and the perceptual type of neglect with different tests. I assume that there is neither ‘pure’ \(PMN\) nor ‘pure’ \(VN\), but both of them can be presented stronger than the other one. As \(VN\) is accompanying nearly every form of neglect, it is considered that \(PMN^+\) show mainly or dominant premotor symptoms but also \(VN\) symptoms. Conversely, \(PMN^-\) show mainly \(VN\) symptoms.

Regarding an appropriate intervention method for neglect, it is not straightforward to chose the most effective one for the patient. As there are many different types of neglect treatment suggested, it is a difficult decision, which intervention or which combination of interventions should be conducted. Saevarsson and colleagues (2011) found, that “(...) combining different interventions leads to increased general improvement compared with other non-combined designs, even when the number of treatment sessions is not constant.” (Saevarsson et al., 2011, p. 95). Studies that are more recent tried besides the ‘mechanical’ approaches like, for instance, the prism adaptation in this work, the medicinal way. However, the effects of drugs are
controversial. Dopamine, for instance, was able to improve neglect symptoms in some studies (e.g. Fleet, Valenstein, Watson, & Heilman, 1987; Parton, Coulthard, & Husain, 2005), but not in others and even made the symptoms worse (e.g. Grujic et al., 1998). The prism adaptation is a partially effective method for rehabilitation of neglect and showed positive effects on the patients in this work. This topic has been discussed in the chapter about prism adaptation already. But it also does not reduce all symptoms in neglect, which has been shown in different studies (Barrett, Goedert, & Basso, 2012; Fortis, Goedert, & Barrett, 2011).
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Neglected premotor neglect

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Unilateral neglect, or neglect for short, is commonly described as the failure to respond and attend to stimuli presented on the contralesional side. It cannot be explained by primary motor and sensory impairment (Heilman et al., 1987), and is usually caused by a stroke. Although neglect patients often recover spontaneously within several weeks, they demonstrate poorer amelioration and require longer hospitalizations following a stroke compared to stroke patients without the affliction (e.g., Busbaum et al., 2006; Gillen et al., 2005). Many different subtypes of neglect have been specified to date (e.g., Saevasson et al., 2011). One of these, premotor neglect (PMN), also known as intentional motor neglect, directional action neglect, etc.; see Saevasson, 2013a) denotes an intentional, voluntary, and directional (e.g., eye, hand, and head) motor bias from the ipsilesional side to an object in the contralesional side of space (Watson et al., 1978; Halligan and Marshall, 1989; Bischof et al., 1990; Coovadale et al., 1990; Heilman et al., 2008; Saevasson, 2013a). For instance, patients may fail to reach an apple on their left side with their right hand (a directional akinesia; Heilman et al., 1987) although they may be visually aware of the object. The foundation of PMN diagnosis is based on various studies that indicate performance improvement or decline when patients perform tasks that require directional movements under different visual conditions (see Saevasson, 2013a for discussion). PMN is often seen alongside other neglect forms (in approximately 45% of cases), although exact incidence has not been specified (Saevasson, 2013a). Unfortunately, many neglect reviews and empirical studies ignore PMN altogether (e.g., Saevasson et al., 2008; Karnath, 2014), or report it merely as an unimportant accompaniment and not specific to neglect (e.g., Himmelbach and Karnath, 2003; Rossi et al., 2009a; Striemen and Dackert, 2013). For example, Himmelbach et al. (2007, p. 1980) claim that PMN is not a “consequence of spatial neglect but rather indicate[s] a phenomenon occurring in some of these patients as well as in other stroke patients (without neglect), i.e., a phenomenon occurring with (so far not further identified) brain damage.” In line with this view, the number of studies on PMN has decreased considerably since the 1990s (Saevasson, 2013a). Conversely, many authors argue for the importance of PMN (e.g., Mattingley and Driver, 1997; Konczak and Karnath, 1998; Voue et al., 2010; Saevasson, 2013b) although non-neglect-based terms such as directional hypokinesia are often used. For instance, the most commonly applied neglect definition of Heilman et al. (1987) refers to PMN when describing the affliction. Controversially, several mainstream literature does not reject this description despite the fact that some authors seem to prefer “spatial” or “hemispatial” neglect as a synonym, although representational neglect is non-spatial in nature. The nature of PMN is poorly understood and may hold the key to advanced neglect assessment and rehabilitation (Punt and Riddoch, 2006; Saevasson, 2013a), thus we argue for the existence and importance of PMN with regard to various clinical, neuroanatomical, and methodological issues.

Previous studies questioning the importance of PMN suffer from significant methodological limitations. This is partially due to difficulties in differentiating between similar PMN and visual neglect symptoms (see Saevasson, 2013a for discussion). Performance on standard and PMN tests can be interpreted as indicating visual neglect (i.e., failure to notice items on the left side; e.g., Ladas et al., 1999) and PMN (see Mattingley and Driver, 1997; Saevasson, 2013a). Rossi et al. (2009a,b) revealed that stroke patients with and without neglect showed similar impaired reaches to the left side. They concluded that the directional reaching deficits were non-neglect-specific (see also Himmelbach and Karnath, 2003; see Kim et al., 2013 for similar findings and methods but different interpretation of PMN). Noticeably, they report only the group results with high standard errors on their reaching tasks. It is therefore uncertain how the patients performed individually. In other words, it is not clear what percentage of the groups demonstrated reaching deficits to the contralesional side. It is important in this context that the line does not always indicate PMN symptoms; therefore, it is uncertain whether a group of patients is representative of PMN. In other words, by diluting the group with patients who do not suffer from PMN, it is not likely to reveal any difference in PMN testing between two groups of right-brain damaged patients that do and do not have neglect (Korden et al., 2007). This would be evident in a group of neglect patients in which none or only few suffered from PMN. Similarly, Himmelbach and Karnath (2003) criticize various studies (e.g., Hamisi et al., 2000).
that compare reaching deficits in right-hemisphere damaged neglect patients to healthy subjects. To test this point empirically, it would be questionable, for instance, to evaluate a group of patients with neglect in order to explore motor neglect since only a proportion of patients with neglect suffer from motor neglect (Saevareid et al., 2013a). Or in Brewer’s (1994, p. 119) words: “It is a mistake, in my view, to try to unify the wide variety of phenomena classified as manifestations of "neglect" by appeal to a single diagnostic or explanatory model of the neglect deficit.” Moreover, Rossit et al. (2009a,b) used mainly the Behavioral Inattention Test (BIT; Wilson et al., 1987) to diagnose neglect in right-hemisphere injured patients. It is debatable whether to divide participants into neglect and non-neglect subgroups when using the BIT as it does not provide an adequate assessment unless used alongside additional diagnostic resources that are not sensitive to personal and extrapersonal neglect; in addition, the BIT cannot distinguish between the motor and perceptive components of neglect (Plautzer et al., 2009). No cut-off scores are given for the BIT and no clear evidence exists for its validity (Carr, 1993).

Additionally, therapists sometimes complain that patients perform well on the BIT although their neglect appears clearly in more stressful circumstances in daily life (e.g., Håkanson and Saevareid, 2008). Neuroanatomical evidence against the existence of PMN is infirm and contradictory. Rossit et al. (2009a,b) highlight nodes in the fronto-parietal cortex, and fronto lobe as being responsible for directional reaching deficits in stroke patients, and claims that these areas are not associated with neglect per se, citing the neuroanatomical findings of Karnath et al. (2001, 2006) and Umeda et al. (2003). Furthermore, Rossit et al. indicate that damage in the inferior parietal cortex involved in reaching and awareness deficits to the left side was also responsible for directional reaching deficits without neglect. Similarly, Himmelbach and Karnath (2003) hypothesized that the posterior parietal and superior temporal cortex are responsible for directional reaching, and the inferior parietal lobe and superior temporal cortex produce spatial neglect in right-hemisphere injured patients may be quite common (see Saevareid and Kristjánsson, 2013 on no neglect improvement following prism adaptation). Indeed, the literature indicates isolated cases of the affection where only one modality, such as motor or conceptual, is affected (e.g., Laplane and Degos, 1983; Oltrogge et al., 2001). Therefore, Himmelbach and Rossit et al. tested right-hemisphere injured patients that may have suffered from an isolated form of PMN and other forms of non-diagnosed neglect. Furthermore, several authors claim that different neuroanatomical mechanisms may explain isolated forms of neglect within the syndrome (e.g., Chechlacz et al., 2012). Coulthard et al. (2006, 2007) argue against the idea that impairments found only in neglect are the sole indication of what the syndrome is. Instead, they assert that neglect is a combination of a group of mental deficits such as impaired spatial memory and directional motor deficits. They explain that PMN can consist of less efficient contralesional reaches and target location on one side, but not to both directions. However, whether and how PMN belongs to the neglect syndrome should be a crucial issue. PMN may be better indicators of poor clinical outcomes than sensory ones (Parsons and Goodhead, 2006). PMN feedback are believed to be predictors of successful prism adaptation therapy for neglect (Saevareid et al., 2009; Steenem and Dijkerman, 2013). For instance, Goedert et al. (2014) found bigger improvement in neglect testing following two weeks of prism adaptation therapy by PMN patients compared to patients suffering from visual neglect without PMN. Similarly, practicing limb movements (Robertson et al., 1992; Pattitri et al., 2013) and increasing contralesional eye movements with prism adaptation intervention improves neglect (Serino et al., 2006). It is also proposed that unspecified fronto and parietal areas play a crucial role in PMN, even if its exact neuroanatomical mechanism is largely not understood. Saevareid (2013a) reviews 43 studies that apply various assessment...
approaches and concludes that frontal and parietal structures are most commonly injured in PMN. For instance, Voulou et al. (2010) measured a visual and response bias in neglect with the "hurdled" manual landmark task. They found that a visual bias in neglect is caused by frontal, parietal, and occipital injury, while caudate nucleus and putamen were associated with PMN. Mattingly et al. (1998) used a left-right response button task to explore these same components. They show that brain lesions in the inferior parietal lobe—not frontal cortex—explain PMN symptoms and suggest that the inferior parietal lobe operates as a sensorimotor interface. In addition, ignorance of PMN aspects of neglect assessment and the methodological limitations of BIT with respect to neuropsychological underpinnings call for our current understanding of neglect into question (Flament and Driver, 1997, Swann, 2013a for a discussion and suggestions of PMN assessment) in every study on perceptual neglect that requires directional movement because of difficulties in differentiating between the clinical effects of these two subgroups of PMN and visual neglect. One can claim that the criteria of neglect (2004) and others and it is imperfect that and the centrifugal directional action components of neglect should have a consistent and definite assessment focus (Swann, 2013a).

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