Neglect-Dyslexie:

Ursachen, Assessment und Therapie

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Abstract

Lesen ist eine bedeutende kulturelle Fähigkeit, die ein Mensch über viele Jahre trainieren muss, um sie zu beherrschen. Wir sind umgeben von Informationen in geschriebener Form und lesen Busfahrpläne, Kontoauszüge, Straßennamen oder die Menüauswahl in der Kantine zumeist ganz nebenbei und unbewusst. Darüber hinaus ist die Fähigkeit zu lesen mehr als nur eine Möglichkeit, Informationen aufzunehmen. Viele Menschen lesen zum Vergnügen, zur Entspannung oder einfach nur zum Zeitvertreib, ohne Mühe und oft stundenlang. Wie sehr das Lesen den Alltag prägt, wird vor allem dann deutlich, wenn diese Fähigkeit gestört ist. Menschen, die die Lesefähigkeit nicht erworben oder durch eine Hirnschädigung wieder verloren haben, sind im Alltag mit einer Vielzahl von Hindernissen konfrontiert: Ihnen sind viele Informationen nicht, oder nur eingeschränkt, zugänglich. Zusätzlich schmälern Lesestörungen die Chancen auf eine berufliche Rehabilitation, da Lesen in nahezu jedem Arbeitsbereich eine Rolle spielt (Publikation I: Reinhart, Höfer, & Kerkhoff, 2013a).

Angesichts der Leichtigkeit und Geschwindigkeit, mit der die meisten Menschen geschriebene Sprache verarbeiten, ist es erstaunlich, dass es sich beim Lesen um eine komplexe Fähigkeit handelt, an der eine Reihe von visuell-perzeptiven und kognitiven Prozessen beteiligt sind. Die Störung eines oder mehrerer dieser Verarbeitungsprozesse kann sich gravierend auf die Lesefähigkeit auswirken: Während ein geübter Leser zwischen 150 und 250 Wörter pro Minute lesen und verstehen kann, sinkt die Lesegeschwindigkeit bei einigen Lesestörungen auf wenige Wörter pro Minute (Publikation II: Reinhart, Höfer, & Kerkhoff, 2013b; Zihl, 2010). Dadurch wird das Lesen sehr anstrengend und das ehemalige Vergnügen zur Qual.

Gegenstand dieser Dissertation ist die Neglect-Dyslexie (ND), eine neurologisch bedingte, erworbene Lesestörung, die infolge einer rechts- oder (seltener) linkshemisphärischen Hirnläsion auftritt. Diese Lesestörung ist durch das Auslassen oder Substituieren von Buchstaben oder Wortteilen auf der kontraläsionalen (d.h. in der zur geschädigten Hirnhälfte gegenüberliegenden) Wortseite charakterisiert. Die ND wurde bisher vor allem in Einzelfallstudien untersucht (Vallar, Burani, & Arduino, 2010), welche zu einigen Erkenntnissen über die Mechanismen der Störung führten. Auf deren Grundlage entwickelten Caramazza & Hillis (1990) in Anlehnungen an Marrs Modell der visuellen

Objekterkennung (Marr & Nishihara, 1978; Marr, Ullman, & Poggio, 2010) ein gut evaluiertes Modell (Haywood & Coltheart, 2000; Vallar et al., 2010) über die frühen Stufen der visuellen Worterkennung. Gemäß diesem Modell kann der Leseprozess auf drei unterschiedlichen Verarbeitungsstufen gestört sein, was zu unterscheidbaren charakteristischen Lesefehlern führt. Da bisher nur wenige Gruppenstudien mit überwiegend kleinen Stichproben zur ND durchgeführt wurden (eine Übersichtsarbeit von Vallar et al., 2010, berichtet nur elf Gruppenstudien) sind noch viele Fragen ungeklärt. Diese umfassen etwa die Inzidenz, die Assoziation zu anderen Komponenten des Neglectsyndroms, modulierende Faktoren (z.B. lexikalische Worteffekte) sowie wirksame Behandlungsverfahren der Störung.

Diese Fragen sind auch deshalb bisher unbeantwortet, da in vielen Studien unterschiedliches Lesematerial und verschiedenste Paradigmen (vor allem die Präsentation einzelner Wort vs. Texte) verwendet wurden. Ein standardisierter und psychometrisch evaluierter Test zur spezifischen Erfassung einer ND ist bislang nicht verfügbar. Ein valides und sensitives Testverfahren wäre für die klinische Anwendung höchst wünschenswert, weil insbesondere Patienten mit ND die Lesestörungen nicht spontan beklagen, sondern diese oft erst bei gezielter Befragung angeben (Kerkhoff, Schaub, & Zihl, 1990). Man kann also davon ausgehen, dass die ND in der klinischen Praxis häufig übersehen wird. Da ohne genaue Diagnostik eine entsprechende Behandlung kaum möglich ist, überrascht es auch nicht, dass bislang noch keine spezifischen Therapiemethoden zur Behandlung der ND existieren. Aktuell werden diverse Stimulationsverfahren und lerntheoretisch begründete Therapieansätze in der Rehabilitation des (visuell-) räumlichen Neglects erfolgreich eingesetzt (Kerkhoff & Schenk, 2012). Ob diese Verfahren allerdings auch zur Reduktion von ND-Fehlern führen, ist bisher nicht ausreichend belegt.

Wie bereits zu Beginn erwähnt, wurde die ND in der Vergangenheit vor allem in Einzelfallstudien und fast ausschließlich mit Einzelwort-Paradigmen untersucht. Die Studien dieser Dissertation wurden im Gegensatz dazu mit Patientengruppen und Lesetexten durchgeführt, um einerseits die Erkenntnisse über die Störungsmechanismen zu erweitern und andererseits die Störung mit alltagsnäherem Stimulusmaterial als bei Einzelwortpräsentation zu untersuchen. Im Detail beschäftigen sich die Publikationen dieser Dissertation mit den folgenden Fragestellungen:

Ist die ND eine Folge des kontraläsionalen räumlichen (egozentrischen) Neglects oder manifestiert sich die Störung in einem stimulus- bzw. wortbezogenen Referenzrahmen (Abschnitt 3.1.1)?

Wird die ND durch einen homonymen Gesichtsfeldausfall verstärkt (Abschnitt 3.1.2)?

Ist der Wortlängeneffekt ein häufiges Phänomen bei ND-Patienten und würde er sich damit für die Entwicklung eines spezifischen ND-Tests eignen (Abschnitt 3.1.3)?

Eignen sich sogenannte Bottom-Up-Stimulationsverfahren, wie die Kopfrotation und die optokinetische Stimulation, zur Therapie der ND (Abschnitt 3.1.4)?

Die publizierten Originalarbeiten befinden sich als Anhang am Ende dieser Dissertation.

Inhaltsverzeichnis

Liste der Originalarbeiten

Die Arbeiten I und II geben eine Einführung über die Klinik, Anamnese und Therapie visueller Lesestörungen nach Hirnläsionen. Publikation III untersucht den Zusammenhang zwischen visuell-räumlichem Neglect und ND. In Studie IV wird die Frage analysiert, ob der in Einzelfällen berichtete Wortlängeneffekt (längere Wörter provozieren mehr ND-Fehler als kürzere) bei ND-Patienten häufig ist und damit zur Konstruktion von sensitiverem Testmaterial genutzt werden kann. Die Studien V und VI untersuchen, ob sich die in der Rehabilitation des visuell-räumlichen Neglects eingesetzten Verfahren Kopfrotation (V) und optokinetische Stimulation (VI) zur transienten Modulation (V) und längerfristigen Therapie (VI) der ND eignen.

Reinhart, S., Höfer, B., & Kerkhoff, G. (2013a). Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Klinik und Anamnese. *Sprache Stimme Gehör*, *37*(1), 46-53. IF[1] = 0,104.

Reinhart, S., Höfer, B., & Kerkhoff, G. (2013b). Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Therapie. *Sprache Stimme Gehör*, *37*(2), 105-111. IF = 0,104.

Reinhart, S., Wagner, P., Schulz, A., Keller, I., & Kerkhoff, G. (2013). Line bisection error predicts the presence and severity of neglect dyslexia in paragraph reading. *Neuropsychologia*, *51*(1), 1-7. IF = 4,372.

Reinhart, S., Schaadt, A. K., Adams, M., Leonhardt, E., & Kerkhoff, G. (2013). The frequency and significance of the word length effect in neglect dyslexia. *Neuropsychologi*a, 51(7), 1273-1278. IF = 4,372.

Reinhart, S., Keller, I., & Kerkhoff, G. (2010). Effects of head rotation on space- and word-based reading errors in spatial neglect. *Neuropsychologia*, *48*(13), 3706-3714. IF = 4,372.

Kerkhoff, G., **Reinhart, S.**, Ziegler, W., Artinger, F., Marquardt, C., Keller, I. (2013). Smooth pursuit eye movement training promotes recovery from auditory and visual neglect. *Neurorehabilitation and Neural Repair*, *27*(9), 789-798. IF = 4.877.

[1] Impaktfaktoren (IF) nach Thompson Reuters für das Jahr 2012 (Sprache Stimme Gehör) bzw. 5-Jahres-Faktoren (Neuropsychologia und Neurorehabilitation and Neural Repair)

Abbildungsverzeichnis

Abkürzungen

ND: Neglect-Dyslexie
OKS: Optokinetische Stimulation
VET: Visuelles Explorationstraining

1 Das Neglect-Syndrom

Beim Neglect-Syndrom (synonym werden auch die Begriffe unilateraler Neglect oder Hemineglect verwendet) handelt es sich um eine multimodale Störung, bei der die Patienten nicht oder nur stark verzögert auf kontraläsionale sensorische Reize reagieren (Heilman, Watson, & Valenstein, 2012). Die Symptome können sich in verschiedenen sensorischen Modalitäten und Funktionen äußern: Patienten mit personalem Neglect vernachlässigen beispielsweise die kontraläsionale Körperseite bei der Gesichtspflege. Patienten mit akustischem Neglect reagieren verzögert auf Geräusche oder Ansprache von der kontraläsionalen Raumseite oder lokalisieren solche Reize falsch. Patienten mit motorischem Neglect benutzen ihre kontraläsionalen Gliedmaßen seltener, obwohl sie funktional dazu in der Lage wären (Kerkhoff, 2001). Das Neglect-Syndrom ist mit einer weltweiten Inzidenzrate von 3-5 Millionen neuen Patienten pro Jahr eine der häufigsten Störungen nach einem Schlaganfall (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1997).

In den vergangenen Jahrzehnten wurden unter dem Begriff Neglect viele unterschiedliche Formen kontraläsionaler Vernachlässigung beschrieben, die allein, oft aber im Zusammenhang mit anderen Symptomen des Neglects auftreten können. Heute bezeichnet daher der Begriff Neglect nicht mehr eine einheitliche Störung, sondern ein heterogenes Syndrom mit multiplen Komponenten (Halligan, Fink, Marshall, & Vallar, 2003). All diesen Formen des Neglects ist gemeinsam, dass sie häufiger bzw. persistenter nach unilateralen rechts- als nach linkshemisphärischen Läsionen des Gehirns auftreten[2] und nicht durch elementare Funktionsstörungen auf früheren Verarbeitungsebenen (z.B. Hemiparese, Hemianopsie) erklärbar sind (Heilman et al., 2012).

Mit einer spontanen Remission der Symptomatik ist zumindest beim visuell-räumlichem Neglect bei etwa zwei drittel der Patienten im Laufe weniger Monate zu rechnen (Fink & Heide, 2004). Trotzdem ist eine frühzeitige Behandlung wichtig, da die Störung beim restlichen Drittel der Betroffenen chronifiziert (Karnath, Rennig, Johannsen, & Rorden, 2011; Rengachary, He, Shulman, & Corbetta, 2011). Darüber hinaus erschwert der Neglect das Ergebnis anderer (z.B. physiotherapeutischer) Rehabilitationsmaßnahmen (Paolucci, Antonucci, Grasso, & Pizzamiglio, 2001; Stone, Patel, Greenwood, & Halligan, 1992).

[2] Für eine bessere Lesbarkeit bezieht sich der gesamte Text, wenn nicht anders beschrieben, auf linksseitigen Neglect nach einer rechtsseitigen Hirnläsion.

Umgekehrt kann die erfolgreiche Therapie des Neglects die Wirksamkeit solcher funktionalen Therapiemaßnahmen positiv beeinflussen (Kalra, Perez, Gupta, & Wittink, 1997; Mizuno et al., 2011).

1.1 Visuell-räumlicher und objektzentrierter Neglect

Der Neglect wurde wissenschaftlich am häufigsten in der visuellen Modalität untersucht. Patienten mit visuell-räumlichem Neglect vernachlässigen linksseitige Objekte, indem sie diese nicht berichten, nicht darauf reagieren und sich ihnen nicht zuwenden (Heilman et al., 2012). Im Alltag äußert sich die Störung beispielsweise darin, dass die Patienten nach rechtsseitigen Hirnläsionen häufig linksseitig an Möbeln oder am Türrahmen anstoßen beziehungsweise Dinge nicht finden, wenn sich diese links von der eigenen Körpermittellinie befinden (man spricht daher auch von egozentrischem Neglect). Diagnostisch fallen Patienten mit visuell-räumlichem Neglect durch linksseitige Auslassungen in verschiedenen Durchstreichtests oder durch erhöhte Reaktionszeiten auf linksseitige Reize bei visuellen Suchaufgaben auf. Darüber hinaus ist bei vielen Patienten eine pathologische rechtsseitige Abweichung bei der Halbierung einer horizontalen Linie beobachtbar (Azouvi et al., 2002; Schenkenberg, Bradford, & Ajax, 1980).

Manche Patienten mit rechtshemisphärischen Läsionen vernachlässigen zusätzlich oder ausschließlich die linke Seite von einzelnen Objekten und zwar unabhängig davon, auf welcher Raumseite sich das Objekt befindet (auch objektzentrierter oder allozentrischer Neglect genannt. Abbildung 1). Diese Form des Neglects wird häufig mit dem Abzeichnen von Vorlagen oder mit dem Zeichnen aus dem Gedächtnis (z.B. eine Uhr, ein Gesicht) diagnostisch erfasst. Die Zeichnungen sind dabei auf der kontraläsionalen Seite unvollständig oder verzerrt (Kerkhoff, 2001). Auch wenn viele Neglectpatienten mit objektzentriertem Neglect ebenfalls in Durchstreichaufgaben linksseitige Auslassungen zeigen, sind beide Formen des Neglects dissoziierbar (Hillis et al., 2005; Gainotti & Ciaraffa, 2013; Grimsen, Hildebrandt, & Fahle, 2008; Landis, 2000). Es gibt Evidenz dafür, dass diese Dissoziation auch auf neuroanatomischer Ebene vorliegt (Chechlacz et al., 2010; Chechlacz, Rotshtein, & Humphreys, 2012; Grimsen et al., 2008; Hillis et al., 2005; Ota, Fujii, Suzuki, Fukatsu, & Yamadori, 2001). So führen unilaterale Läsionen des okzipitoparietal verlaufenden dorsalen Pfades der visuellen Verarbeitung (Ungerleider & Haxby, 1994) zu egozentrischem Neglect und Läsionen des ventralen, okzipitotemporalen Pfades zu objektzentriertem visuellem

Neglect (Grimsen et al., 2008). Dass in der klinischen Praxis beide Neglectformen häufig zusammen auftreten und daher immer wieder als zwei Seiten der gleichen Medaille angesehen wurden (Driver & Pouget, 2000; Karnath & Niemeier, 2002) liegt möglicherweise daran, dass nach ausgedehnten Mediainfarkten beide Verarbeitungsrouten verletzt und damit gleichzeitig gestört sein können.

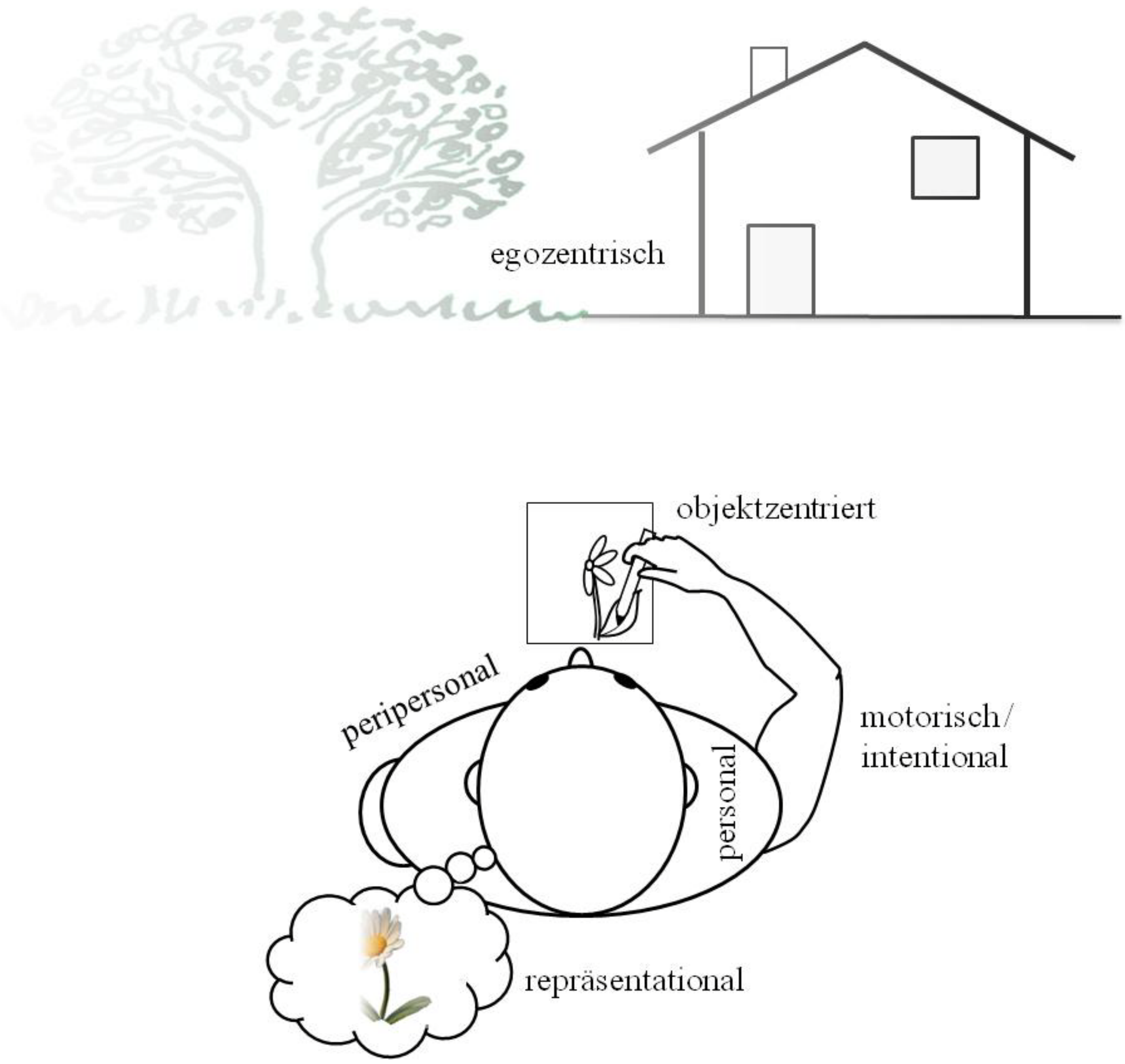

Abbildung 1. Schematische Darstellung von unterschiedlichen Symptomen des Neglect-Syndroms nach rechtshemisphärischen Gehirnläsionen, das sich in unterschiedlichen Repräsentationssystemen und Modalitäten manifestieren kann.

1.1.1 Therapie und Erklärungsmodell des visuell-räumlichen Neglects

Zur Therapie des visuell-räumlichen Neglects wurden unterschiedliche Bottom-Up- oder Top-Down-Verfahren entwickelt (Luauté, Halligan, Rode, Rossetti, & Boisson, 2006; Robertson & Murre, 1999). Bei Top-Down-Verfahren lernt der Patient, seine Aufmerksamkeit bewusst verstärkt auf die vernachlässigte Seite zu richten und dort über einen längeren Zeitraum aufrecht zu erhalten. Dies kann beispielsweise durch visuelles Explorationstraining (VET; Kerkhoff, 1998) oder nicht-räumliches Training der Alertness bzw. der Daueraufmerksamkeit erreicht werden (Robertson, Tegner, Tham, Lo, & Nimmo-Smith, 1995). Allerdings ist die Anwendung von Top-Down-Verfahren bei manchen Patienten vor allem in der akuten Phase nach dem Schlaganfall schwierig, da sie eine aktive Mitarbeit und eine gewisse Krankheitseinsicht voraussetzen. Letztere ist bei der Mehrzahl der Neglect-Patienten zumindest initial stark reduziert (Pedersen et al., 1997; Stone, Halligan, & Greenwood, 1993). Darüber hinaus stellt die längerfristige willentliche Aufmerksamkeitsausrichtung nach links für Patienten mit rechtshemisphärischen Läsionen infolge häufig assoziierter nichträumlicher Aufmerksamkeitsdefizite eine sehr anspruchsvolle Aufgabe dar (Husain & Rorden, 2003; Sturm et al., 2006), sodass die Konzentrationsleistung schon bei geringfügiger Mehrbelastung oder Ablenkung einbrechen kann (Bonato, Priftis, Marenzi, Umilta, & Zorzi, 2010).

Bottom-Up-Verfahren funktionieren dagegen auch ohne die aktive Mitwirkung der Patienten. Sie beruhen auf der Annahme, dass der visuell-räumliche Neglect durch eine gestörte Repräsentation des eigenen Körpers im Raum hervorgerufen wird (Karnath, 1994a). Diese Raumrepräsentation wird aus den Informationen verschiedener sensorischer Modalitäten generiert (visuelle, auditive, taktile, propriozeptive und vestibuläre Information, Abbildung 2). Beim Neglect scheint die Verarbeitung des egozentrischen räumlichen Bezugssystems aufgrund von Läsionen der daran beteiligten Areale fehlerhaft zu sein, was zu einer pathologischen Abweichung der subjektiven Geradeausrichtung zur ipsiläsionalen Seite (d.h. nach rechts bei einer rechtsseitigen Läsion) führt. Diese Abweichung lässt sich durch zusätzliche oder modifizierte Informationen mittels Stimulation einer spezifischen sensorischen Modalität modulieren, was therapeutisch genutzt werden kann.

Chokron, Dupierrix, Tabert, & Bartolomeo (2007) stellen diese Theorie allerdings in Frage, da in diversen Studien kein Zusammenhang zwischen der Ausprägung des visuell-räumlichen Neglects und der subjektiven Geradeausrichtung gefunden werden konnte. Sie favorisieren stattdessen eine attentionale Theorie. Hiernach beruht die Wirksamkeit der Bottom-Up-Stimulation auf einer Reorientierung der pathologisch rechtsgerichteten räumlichen Aufmerksamkeit in eine symmetrischere Richtung (Gainotti, 1996).

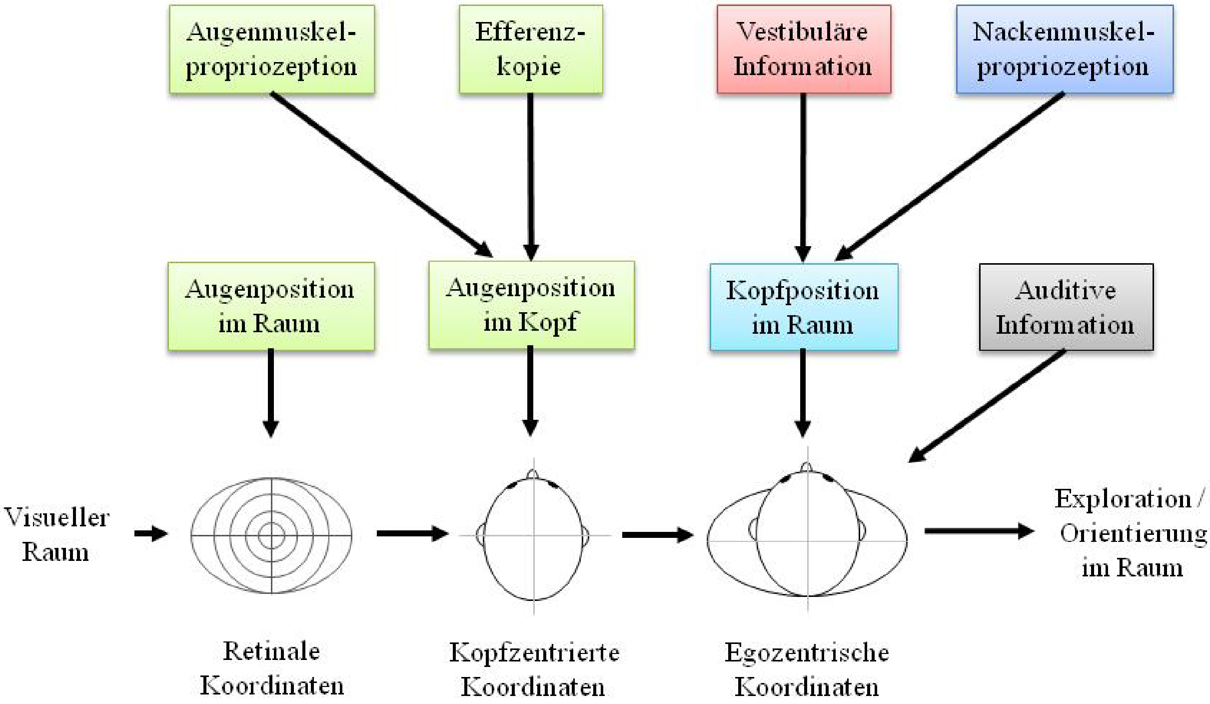

Abbildung 2. Transformation der multimodalen sensorischen Informationen in ein egozentrisches Referenzsystem. Erst eine stabile dreidimensionale Repräsentation des Raumes ermöglicht die Orientierung im Raum und die symmetrische Exploration der sich im Raum befindenden Objekte. Modifiziert nach Karnath (1994b).

Auch wenn es über die zugrundeliegenden Mechanismen des Hemineglects noch keinen Konsens gibt, ist die transiente und dauerhafte Wirkung verschiedener sensorischer Stimulationsverfahren wie beispielsweise die kalorisch-vestibuläre Stimulation (Karnath, 1994b), die galvanisch-vestibuläre Stimulation (Utz, Keller, Kardinal, & Kerkhoff, 2011), die transkutane Nacken-Muskelvibration (Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002), die Kopfrotation (Publikation V: Reinhart, Keller, & Kerkhoff, 2010) oder die optokinetische Stimulation (OKS; Reinhart, Schindler, & Kerkhoff, 2011) hinreichend belegt (siehe Übersicht in Kerkhoff, 2003; Kerkhoff & Schenk, 2012). Allerdings werden nicht alle diese Verfahren in der Praxis für die Rehabilitation eingesetzt, da sie teilweise unangenehme Nebenwirkungen haben (z.B. Schwindel und Erbrechen bei kalorisch-vestibulärer Stimulation; Rode, Tiliket, Charlopain, & Boisson, 1998) oder nur mit detaillierten

Fachkenntnissen (z.B. anatomische Kenntnisse bei der Nackenmuskelvibration) sinnvoll angewendet werden können. Diesbezüglich unproblematische und in der Neurorehabilitation bereits etablierte Verfahren sind das VET, die OKS und die Kopf- bzw. Rumpfrotation.

1.1.2 Visuelles Explorationstraining

Beim VET werden die Patienten instruiert, ein Display oder Blatt Papier systematisch von links oben nach rechts unten nach bestimmten Zielreizen abzusuchen. Die Patienten bekommen dabei vom Therapeuten Feedback über ihre Explorationsstrategie und sollen dadurch lernen, ihren Blick und ihre Aufmerksamkeit willentlich auf die vernachlässigte Seite zu richten (Kerkhoff & Schenk, 2012; Luauté et al., 2006). Das VET wird an vielen Kliniken in der Neglecttherapie standardmäßig eingesetzt (Kerkhoff & Schenk, 2012; Lincoln & Bowen, 2006), obwohl die Effektivität der Methode bisher kaum untersucht ist (Kerkhoff & Schenk, 2012). Darüber hinaus hat VET den Nachteil, dass die Wirksamkeit auf die visuelle Modalität beschränkt zu sein scheint (Kerkhoff, 1998) und das Training außerdem relativ aufwändig ist, da mindestens 40 Sitzungen (à 50 Minuten) nötig sind, um stabile Effekte zu erzielen (Kerkhoff & Schenk, 2012).

1.1.3 Optokinetische Stimulation mit Augenfolgebewegungen

Bei der Therapie mit OKS verfolgen die Patienten mit den Augen ein Reizmuster, das sich (im Falle eines linksseitigen Neglects) auf einem Bildschirm oder einer Leinwand kohärent von rechts nach links bewegt. Die Augenbewegungen bewirken gemäß der zwei hauptsächlich vertretenen Theorien entweder eine Rekalibrierung der pathologischen ipsiläsionalen Abweichung der subjektiven Geradeausrichtung (Vallar, Antonucci, Guariglia, & Pizzamiglio, 1993; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995) oder eine Verbesserung der räumlichen Aufmerksamkeitszuwendung zur kontraläsionalen Seite (Chokron et al., 2007; Doricchi, Siegler, Iaria, & Berthoz, 2002; Gainotti, 1996; Mattingley, Bradshaw, & Bradshaw, 1994). Diese Methode erwies sich in mehreren Studien als wirksam im Sinne einer transienten und auch dauerhaften Reduktion verschiedener Neglect-Symptome, wie des ipsiläsionalen Linienhalbierungsfehlers (Mattingley et al., 1994;

Kerkhoff, Keller, Ritter, & Marquardt, 2006; Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990), linksseitigen Auslassungen bei Durchstreichaufgaben (Kerkhoff et al., 2006) und der pathologischen Verzerrung der Größen- und Distanzschätzung (Kerkhoff, 2000). Auch körperbezogene Neglectsymptome, wie das Defizit, die Position der Arme (Vallar et al., 1993) oder die Position des Körpers im Raum (Karnath, 1996) akkurat einzuschätzen, konnten durch OKS positiv moduliert werden.

1.1.4 Kopf oder Oberkörper-Rotation

Bei dieser Bottom-Up-Stimulationsmethode wird der Kopf oder der Oberkörper des Patienten passiv um ca. 20° in die kontraläsionale Richtung rotiert. Die zusätzliche bzw. veränderte Information für das Generieren der Repräsentation des egozentrischen Koordinatensystems (z.B. der subjektiven Geradeausrichtung) wird dabei durch die Propriozeption der Nackenmuskulatur (veränderte Länge der Nackenmuskeln) bzw. durch die veränderte Stellung der Augen im Kopf erzeugt (Karnath, 1994a; Abbildungen 2 und 3). Auch mit dieser vergleichsweise einfachen Manipulation konnten in verschiedenen Studien egozentrische Neglectsymptome vorübergehend signifikant gemildert werden (Chokron et al., 2007; Karnath, Schenkel, & Fischer, 1991; Kerkhoff, 2001). Schindler & Kerkhoff (1997) fanden zudem sowohl für die Kopf- als auch für die Oberkörperrotation eine bedeutsame Reduktion von ND-Fehlern beim Lesen von einzelnen, tachistoskopisch dargebotenen Wörtern. Da die Wörter allerdings zentral dargeboten wurden und sich damit der egozentrische und der objektzentrierte (wortzentrierte) Referenzrahmen nicht unterscheiden (Siehe Abschnitt 2.2), lässt sich durch diese Studie keine Aussage darüber treffen, ob die Verfahren nur einen oder beide Referenzrahmen modulieren.

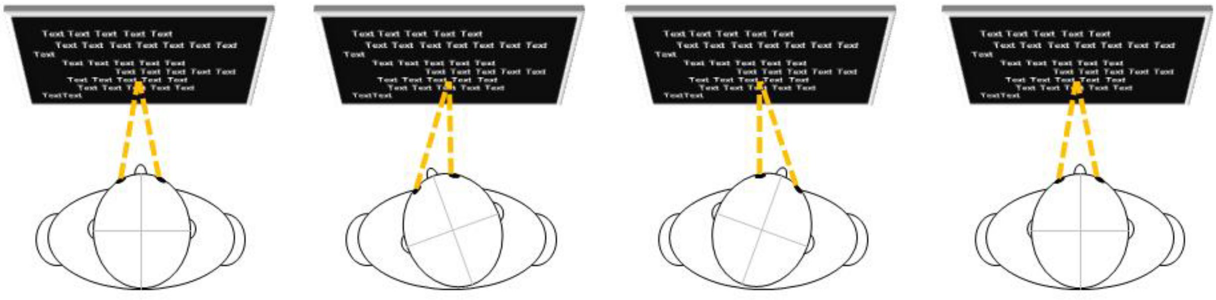

Abbildung 3. Schematische Darstellung der Kopfrotation beim Lesen eines Textes (modifiziert nach Studie V: Reinhart et al., 2010). Die Kopfrotation moduliert die Stellung der Augen im Kopf, welche durch die propriozeptiven Sensoren der Augenmuskulatur registriert und weitergeleitet wird. Diese Information wird zum Generieren der Raumrepräsentation genutzt und moduliert verschiedene Neglectsymtome wie zum Beispiel die Leseleistung.

2 Periphere Lesestörungen nach Schlaganfall

Lesestörungen werden von Schlaganfallpatienten relativ häufig beklagt, allerdings meistens erst dann, wenn sie gezielt danach befragt werden. Für etwa die Hälfte der Patienten mit visuellen Defiziten stellt die Lesestörung das bedeutendste visuelle Problem dar (Kerkhoff et al., 1990). Lesestörungen können je nach Art der Lesefehler in zentrale und periphere Störungen klassifiziert werden (Coslett, 2012). Bei zentralen Lesestörungen (phonologische, Oberflächen- und Tiefendyslexie) sind höhere linguistische Prozesse, wie der semantische Abruf der Wortbedeutung, fehlerhaft. Periphere Störungen (Hemianope Dyslexie, ND und Reine Alexie) manifestieren sich dagegen ausschließlich auf frühen, visuellen Verarbeitungsstufen, also noch bevor die visuelle Information mit einer Bedeutung assoziiert wird (Coslett, 2012).

2.1 Hemianope Dyslexie

Bei homonymen Gesichtsfeldausfällen sind die Leseprobleme eine Folge der fehlenden visuellen Information aus dem Bereich des Skotoms. Vor allem Einschränkungen fovealer und parafovealer Gesichtsfeldbereiche sind problematisch, da zum flüssigen Lesen ein intakter zentraler, asymmetrischer Gesichtsfeldbereich von ca. 3° auf der linken und 5° auf der rechten Seite der Fovea nötig ist (Schuett, 2009). Die Asymmetrie dieses auch als „perzeptuelles Lesefenster“ bezeichneten Bereiches führt in Kulturkreisen mit einer Leserichtung von links nach rechts dazu, dass rechtseitige homonyme Gesichtsfelddefekte das Lesen deutlich mehr beeinträchtigen als linksseitige. Dies liegt darin begründet, dass der größere Teil des Lesefensters im blinden Bereich liegt und bei einer Leserichtung von links nach rechts keine visuelle Information zur Programmierung exakter Lesesakkaden nach rechts zur Verfügung steht. Die Lesestörung bei Patienten mit homonymen Hemianopsien äußert sich daher vor allem in kleinen, unorganisierten Lesesakkaden, längeren Fixationszeiten und folglich in einer deutlich reduzierten Lesegeschwindigkeit (Schuett, 2009). Zusätzlich ist das Auffinden des Zeilenanfangs (bei linksseitigen Ausfällen) oder des Zeilenendes (bei rechtsseitigen Ausfällen) erschwert. Lesefehler sind relativ selten und äußern sich entsprechend der Seite des Gesichtsfeldausfalls im Auslassen von Buchstaben am Wortanfang oder Wortende (Schuett, Heywood, Kentridge, & Zihl, 2008). Ob eine Hemianopsie durch die fehlende kontraläsionale visuelle Information bei gleichzeitiger mangelnder okulomotorischer Kompensation eine ND verstärkt, kann auf Grundlage der wenigen Studien nur vermutet werden (Lee et al., 2009). In einer neueren Studie (Weinzierl, Kerkhoff, van Eimeren, Keller, & Stenneken, 2012) konnte kein Zusammenhang zwischen der Ausdehnung bzw. dem Vorhandensein eines Gesichtsfelddefektes und der Ausprägung einer ND festgestellt werden. Dieser Aspekt wird in Abschnitt 3.1.2 vor dem Hintergrund der Ergebnisse der Publikation Nr. IV dieser Dissertation (Reinhart, Schaadt, Adams, Leonhardt, & Kerkhoff, 2013) detaillierter analysiert und diskutiert.

2.2 Neglect-Dyslexie

Das Lesen kann bei Neglectpatienten in unterschiedlicher Weise gestört sein. Neben dem Auslassen von ganzen Wörtern auf der kontraläsionalen Textseite kommt es nach rechtshemisphärischen Läsionen zu Fehlern auf der linken Wortseite. Diese Fehler auf Wortebene (ND-Fehler im engeren Sinne) äußern sich durch Auslassen oder Substitution von initialen Buchstaben oder Wortteilen. Solche initialen Fehler sind – im Vergleich zu gesunden Personen spezifisch für Neglectpatienten (Weinzierl et al., 2012). Auch Additionen von Buchstaben vor den Wortanfang sind möglich, aber selten (Vallar et al., 2010).

Gegenstand der wissenschaftlichen Fragestellungen zur ND war in der Vergangenheit vor allem die Repräsentationsebene, auf der sich die Symptomatik manifestiert. Hierzu wurde von Caramazza & Hillis (1990) ein vielbeachtetes Modell publiziert, welches durch die unterschiedlichen charakteristischen Lesefehler von ND-Patienten in verschiedenen Leseaufgaben weitgehend bestätigt werden konnte (Haywood & Coltheart, 2000). Das Modell lehnt sich an das Modell der visuellen Analyse von Objekten (Marr et al., 2010) an und geht von einem Verarbeitungsprozess aus, bei dem die visuelle Information sukzessive zu einer kohärenten Objekt- bzw. Wortrepräsentation integriert wird (Abbildung 4). Dieser Prozess lässt sich in drei Stufen unterteilen, bei denen der örtliche Bezug der teilintegrierten visuellen Informationen durch unterscheidbare Referenzsysteme charakterisiert ist: der (1) retinozentrierte (beobachterzentriert bzw. egozentrisch), (2) der stimuluszentrierte (allozentrisch) und (3) der wortzentrierte (objektzentrierte) Referenzrahmen (Abbildung 4). Welche Stufe der visuellen Wortverarbeitung gestört ist, lässt sich gemäß des Modells von Caramazza & Hillis (1990) anhand spezifischer Lesefehler der Patienten ableiten. Beim ersten Teilprozess werden zunächst die visuellen Eigenschaften eines Wortes (z.B. die Linien der einzelnen Buchstaben, Kurven, Winkel) analysiert. Diese Informationen, inklusive ihr Ort, sind im Gehirn retinal, flüchtig und abhängig von der aktuellen Blickrichtung des Beobachters repräsentiert (Caramazza & Hillis, 1990). Bei visuell-räumlichem (egozentrischem) Neglect manifestiert sich die Störung bereits auf dieser Ebene, was bedeutet, dass die gesamte aktuelle visuelle Information der kontraläsionalen Seite des Gesichtsfeldes vernachlässigt wird. Patienten mit einer Störung auf dieser Stufe vernachlässigen daher beim Textlesen linksseitige Wörter und lesen bevorzugt die rechte Textseite (Reinhart et al., 2010, 2011). Bei Einzelwortparadigmen treten ND-Fehler häufiger auf, wenn das Wort auf der linken Seite des Fixationskreuzes steht (Caramazza & Hillis, 1990; Hillis, Rapp, Benzing, & Caramazza, 1998). Geht man davon aus, dass auf dieser Ebene die einzelnen visuellen Eigenschaften der Buchstaben bzw. des Wortes noch nicht zu kohärenten Stimuli gruppiert sind und das Ausmaß der Vernachlässigung von rechts nach links zunimmt, sollte die Fehleranzahl bei zentral präsentierten Worten mit dem Abstand zwischen den Buchstaben wachsen (z.B. HAUS vs. H A U S). Dieser Effekt wurde ebenfalls in Einzelfallstudien beobachtet und als Evidenz für die Existenz eines retinozentrierten Neglects gewertet (Hillis & Caramazza, 1995b; Hillis et al., 1998).

Auf der nächsten Verarbeitungsstufe werden die analysierten visuellen Eigenschaften der Buchstaben gruppiert und ihre Position relativ zueinander kodiert, unabhängig von ihrer retinalen Position. Der Stimulus selbst bildet also das Bezugssystem der gruppierten visuellen

Worteigenschaften und nicht mehr die absolute Position seines Abbildes auf der Retina. Dementsprechend vernachlässigen ND-Patienten mit Störungen der zweiten Verarbeitungsstufe die linke Wortseite *unabhängig* davon, auf welcher (egozentrischen) Seite des Gesichtsfeldes das Wort abgebildet ist. Auch dieses Fehlermuster konnte in Einzelfällen (Young, Newcombe, & Ellis, 1991; Kinsbourne & Warrington, 1962; Ellis, Flude, & Young, 1987; Hillis & Caramazza, 1995a) sowie in Gruppenstudien beobachtet werden (Ptak, Di Pietro, & Schnider, 2012). Bei vertikal abgebildeten Wörtern gelingt das Lesen dagegen ohne ND-Fehler (Ellis et al., 1987; Hillis & Caramazza, 1995a).

Auf der letzten visuellen Verarbeitungsstufe werden aus den gruppierten Buchstabenelementen Buchstabenentitäten analysiert, deren Position durch die abstrakte Wortform determiniert ist. Diese Repräsentation ist unabhängig von der retinalen Position, der Orientierung oder der Schriftart des Wortes, aber immer noch „rein“ visuell und ohne eine Assoziation zur Wortbedeutung (Caramazza & Hillis, 1990). Wörter sind im Vergleich zu den meisten Objekten insofern besonders, da sie (in westlichen Kulturen) eine kanonische links-rechts Orientierung aufweisen. Das bedeutet, dass der Wortanfang auch dann als die linke Wortseite wahrgenommen wird, wenn das Wort um 180° rotiert ist und sich damit die *linke Wortseite* auf der *rechten egozentrischen Seite* befindet. Entsprechend treten ND-Fehler am Wortanfang bei einer Störung der dritten Ebene selbst dann auf, wenn die Wörter vertikal oder um 180° gedreht präsentiert werden (Hillis & Caramazza, 1995b; Miceli & Capasso, 2001). Die Verarbeitung und Repräsentation der abstrakten Wortform wird vermutlich vom sogenannten visuellen Wortformareal im linken Gyrus fusiformis geleistet, welches selektiv auf Buchstabenfolgen reagiert, nicht dagegen auf visuell ähnliche Linienzeichnungen (Cohen et al., 2003; Dehaene & Cohen, 2011; McCandliss, Cohen, & Dehaene, 2003).

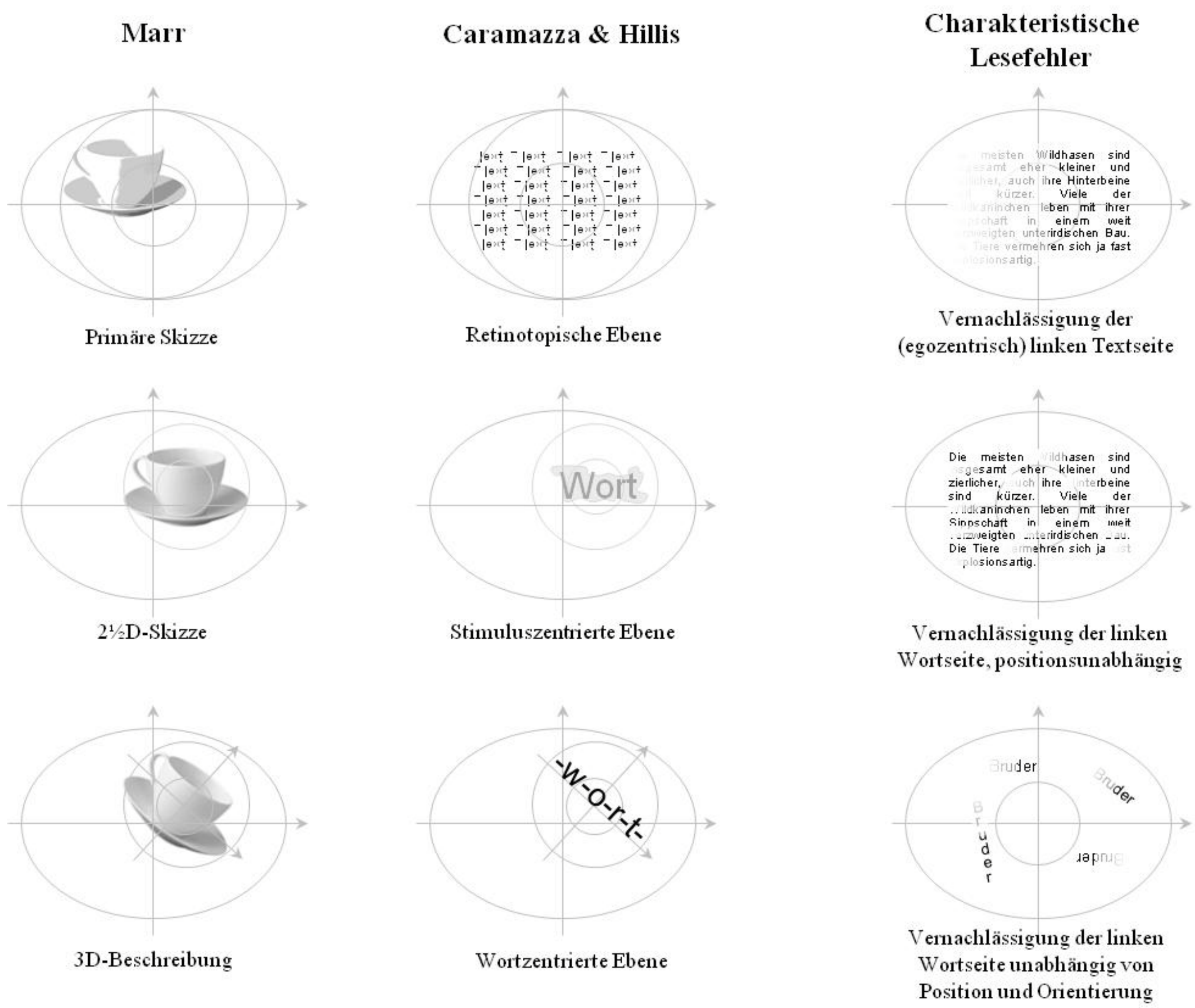

Abbildung 4. Vergleich des Modells der visuellen Analyse von Objekten von Marr et al. (2010) mit dem Modell der Repräsentationsebenen der visuellen Worterkennung von Caramazza & Hillis (1990). Auf der ersten Verarbeitungsstufe werden die visuellen Eigenschaften (Flächen, Linien, Winkel etc.) eines Objekts bzw. Wortes analysiert und sind egozentrisch repräsentiert. Beim egozentrischen Neglect werden visuelle Informationen der egozentrisch kontraläsionalen Seite vernachlässigt und dementsprechend Objekte und Worte auf dieser Seite übersehen. Auf der nächsten Verarbeitungsstufe werden die analysierten visuellen Eigenschaften gruppiert und ihre Positionen relativ zueinander (stimuluszentriert) repräsentiert. Manifestiert sich der Neglect auf dieser Stufe wird die kontraläsionale Seite des Stimulus unabhängig von seiner egozentrischen Position vernachlässigt. Nach der dritten und letzten Stufe der visuellen Worterkennung ist das Wort vollständig vom Hintergrund gelöst und kann mental rotiert werden. Wörter sind auf dieser Ebene als abstrakte Graphemfolgen repräsentiert. Diese Wortrepräsentation (visuelle Wortform) beinhaltet bereits die für westliche Kulturen übliche kanonische links-rechts-Orientierung und ist unabhängig von visuellen Eigenschaften wie z.B. der Schriftart oder der Rotationsrichtung. Auf dieser Ebene gibt es beispielsweise keinen Unterschied in der Repräsentation der Wörter BRUDER, bruDeR, **bruder** oder Bruder. Manifestiert sich der Neglect auf dieser Repräsentationsebene, wird ebenfalls die kontraläsionale Seite des Wortes vernachlässigt. Dies geschieht – im Unterschied zum stimuluszentrierten Neglect – auch dann, wenn das Wort vertikal oder um 180° rotiert präsentiert wird.

2.2.1 Neglect-Dyslexie und objektzentrierter Neglect

Bei ihrem Modell der visuellen Wortverarbeitung gehen Caramazza & Hillis (1990) davon aus, dass ND und objektzentrierter Neglect die gleichen Ursachen haben, da die Bezugssysteme für die Repräsentation von Wörtern und Objekten für beide allozentrisch und somit identisch seien. Dementsprechend sollten Patienten mit ND auch die kontraläsionale Seite eines Objektes vernachlässigen. Subbiah & Caramazza (2000) untersuchten diese Frage, indem sie einer Patientin (M.R.) mit ND Chimären-Bilder (zusammengesetzt aus zwei Hälften von unterschiedlichen Tierzeichnungen) präsentierten. Hypothesenkonform identifizierte die Patientin nur die rechte Seite der Bilder und erkannte nicht, dass es sich um real nicht existierende Objekte handelte. Allerdings gibt es auch Evidenz dafür, dass beide Störungen unabhängig voneinander auftreten und damit unterschiedlich sein können. So berichteten beispielsweise Young, de Haan, Newcombe, & Hay (1990) über einen Patienten (K.L.) mit einem selektiven Neglect für die linke Seite von Gesichtern, jedoch ohne Zeichen einer linksseitigen ND. Da die Fragestellung bisher nur an sehr wenigen Einzelfällen untersucht wurde, ist die mögliche Assoziation der ND mit oder die Dissoziation von einem objektzentrierten Neglect noch ungeklärt und wird in Abschnitt 3.1.1 (Publikationen Nr. III, IV und V: Reinhart & Wagner et al., 2013; Reinhart & Schaadt et al., 2013; Reinhart et al., 2010) diskutiert.

2.2.2 Zusammenhang zwischen visuell-räumlichem Neglect und ND

Ebenfalls selten untersucht ist der Zusammenhang zwischen ND im engeren Sinne und kontraläsionalem visuellem Neglect, wie er sich beispielsweise in der Vernachlässigung linksseitiger Reize bei Durchstreichaufgaben zeigt. Die wenigen beschriebenen Einzelfälle und Gruppenstudien deuten auf eine Dissoziation der Störungen hin (Behrmann, Black, McKeeff, & Barton, 2002; Cantoni & Piccirilli, 1997; Costello & Warrington, 1987; Haywood & Coltheart, 2001; Lee et al., 2009; Patterson & Wilson, 1990). Allerdings weist Riddoch (1990) darauf hin, dass diese Befunde möglicherweise artifizieller Natur sind, da Lesen eine anspruchsvolle Aufgabe darstellt und diejenigen Patienten mit ND ohne Auffälligkeiten in den gängigen Durchstreichtests in schwierigeren Aufgaben eventuell doch die linke Seite vernachlässigen würden. Ob ND und visuell-räumlicher Neglect zwei Seiten der gleichen Medaille sind, wird im Kontext der Publikationen III, IV und V dieser

Dissertation (Reinhart et al., 2010; Reinhart & Schaadt et al., 2013; Reinhart & Wagner et al., 2013) in Abschnitt 3.1.1 detailliert diskutiert.

2.2.3 Inzidenz und Assessment

Da die ND vor allem in Einzelfallstudien untersucht wurde, ist eine genauere Abschätzung der Inzidenz der Störung nur eingeschränkt möglich. In den wenigen Studien mit größeren Stichproben werden Häufigkeiten von 20% (Lee et al., 2009; McGlinchey-Berroth et al., 1996) bis 50% (Bisiach, Meregalli, & Berti, 1990; Ptak et al., 2012) berichtet. Ein Grund für diese hohe Varianz liegt möglicherweise in der unterschiedlichen Anzahl der verwendeten Wörter (z.B. 12 vs. 40 Wörter in den Studien von McGlinchey-Berroth et al., 1996 und Ptak et al., 2012) oder in unterschiedlichen Eigenschaften der verwendeten Wort-Stimuli (zusammengesetzte Wörter, bei denen das Lesen des rechten Wortteiles ein sinnvolles Wort ergibt in der Studie von Ptak et al., 2012, vs. Wörter, die nur bezüglich ihrer Häufigkeit kontrolliert wurden in der Studie von Lee et al., 2009). Standardisierte Tests zur Erfassung der ND mit einer ausreichenden Zahl von sensitivem Wortmaterial würden wahrscheinlich eine präzisere Einschätzung der Inzidenz ermöglichen, wurden bisher aber nicht entwickelt.

2.2.4 Effekte lexikalischer Worteigenschaften

Ein großer Teil der wissenschaftlichen Veröffentlichungen zur ND beschäftigt sich mit der Modulation der Fehlerhäufigkeit durch unterschiedliche Worteigenschaften. So ist beispielsweise die Wahrscheinlichkeit für ND-Fehler bei lesbaren Nichtwörtern höher als bei regulären Wörtern (Sieroff, 1991; Caramazza & Hillis, 1990; Di Pellegrino, Ladavas, & Galletti, 2001). In Einzelfallstudien konnte durch die Manipulation weiterer lexikalischer Eigenschaften, wie der grammatikalischen Wortklasse (Nomen werden öfter korrekt gelesen als Adjektive oder Verben), der Gegenständlichkeit eines Wortes (konkrete Wörter vs. abstrakte), der Wortfrequenz (hochfrequente Wörter vs. seltene) und der Wortlänge, die Fehlerwahrscheinlichkeit moduliert werden (Vallar et al., 2010). Gruppenstudien berichten niedrigere Fehlerraten für Wörter im Vergleich zu lesbaren Nichtwörtern und für hochfrequente vs. niedrigfrequente Wörter (Arduino, Burani, & Vallar, 2002; Stenneken, van Eimeren, Keller, Jacobs, & Kerkhoff, 2008).

Die Beurteilung, welcher dieser Effekte für eine Population von ND-Patienten relevant ist, ist auf Grundlage der Einzelfallbeschreibungen schwierig. Sie wäre allerdings insofern bedeutsam, da Antworten auf diese Fragen neben einem besseren theoretischen Verständnis der Störung auch die Entwicklung spezifischer Tests für die ND ermöglichen würden. Darüber hinaus könnten dadurch gezielt Wörter mit einer hohen Fehlerwahrscheinlichkeit selektiert und für eine Therapie mit massivem Lesetraining genutzt werden, wie es bereits experimentell bei der Reinen Alexie eingesetzt wurde (Ablinger & Domahs, 2009; Woodhead et al., 2013; Zihl, 2010).

2.2.5 Wortlängeneffekt

Einige Einzelfallberichte beschrieben einen positiven Zusammenhang zwischen der Wortlänge und der Fehlerfrequenz (Behrmann, Moscovitch, Black, & Mozer, 1990; Di Pellegrino et al., 2001; Ellis et al., 1987; Nichelli, Venneri, Pentore, & Cubelli, 1993; Riddoch, Humphreys, Cleton, & Fery, 1990; Subbiah & Caramazza, 2000; Tegner & Levander, 1993; Vallar, Guariglia, Nico, & Tabossi, 1996), wobei andere Einzelfallstudien diesen nicht bestätigten (Behrmann et al., 1990; Cantoni & Piccirilli, 1997; Costello & Warrington, 1987; Hillis & Caramazza, 1991; Miceli & Capasso, 2001). In der einzigen Gruppenstudie mit einer kleinen Stichprobe von N=7 (Takeda & Sugishita, 1995) war nur bei zwei der Patienten eine (nicht signifikante) Tendenz eines Wortlängeneffektes beobachtbar. Schwartz, Ojemann, & Dodrill (1997) fanden dagegen in einer größeren Stichprobe von Epilepsiepatienten nach einer präoperativen rechtshemisphärischen Injektion von Amobarbital eine hohe Korrelation von r = 0,65 zwischen der Position des Neglect-Punktes (die Buchstabenposition, ab der das Wort korrekt gelesen wird; Ellis et al., 1987) und der Wortlänge. Ob und wie häufig dieser Effekt auch bei ND-Patienten mit strukturellen Hirnläsionen infolge von Hirninfarkten oder -blutungen auftritt und inwiefern er für die Entwicklung eines ND-Tests relevant sein könnte, wird im Zusammenhang mit den Ergebnissen der Studie IV dieser Dissertation (Reinhart & Schaadt et al., 2013) in Abschnitt 3.1.3 diskutiert.

3 Fragestellungen und Diskussion der Ergebnisse

In der vorliegenden Dissertation wurden die folgenden Fragestellungen untersucht:

Ist die ND eine Folge des kontraläsionalen räumlichen (egozentrischen) Neglects oder manifestiert sich die Störung in einem stimulus- bzw. wortbezogenen Referenzrahmen?

Wird die ND durch einen homonymen Gesichtsfeldausfall verstärkt?

Ist der Wortlängeneffekt ein häufiges Phänomen bei ND-Patienten und würde er sich damit für die Entwicklung eines spezifischen ND-Tests eignen?

Eignen sich sogenannte Bottom-Up-Stimulationsverfahren, wie die Kopfrotation und die optokinetische Stimulation, zur Therapie der ND?

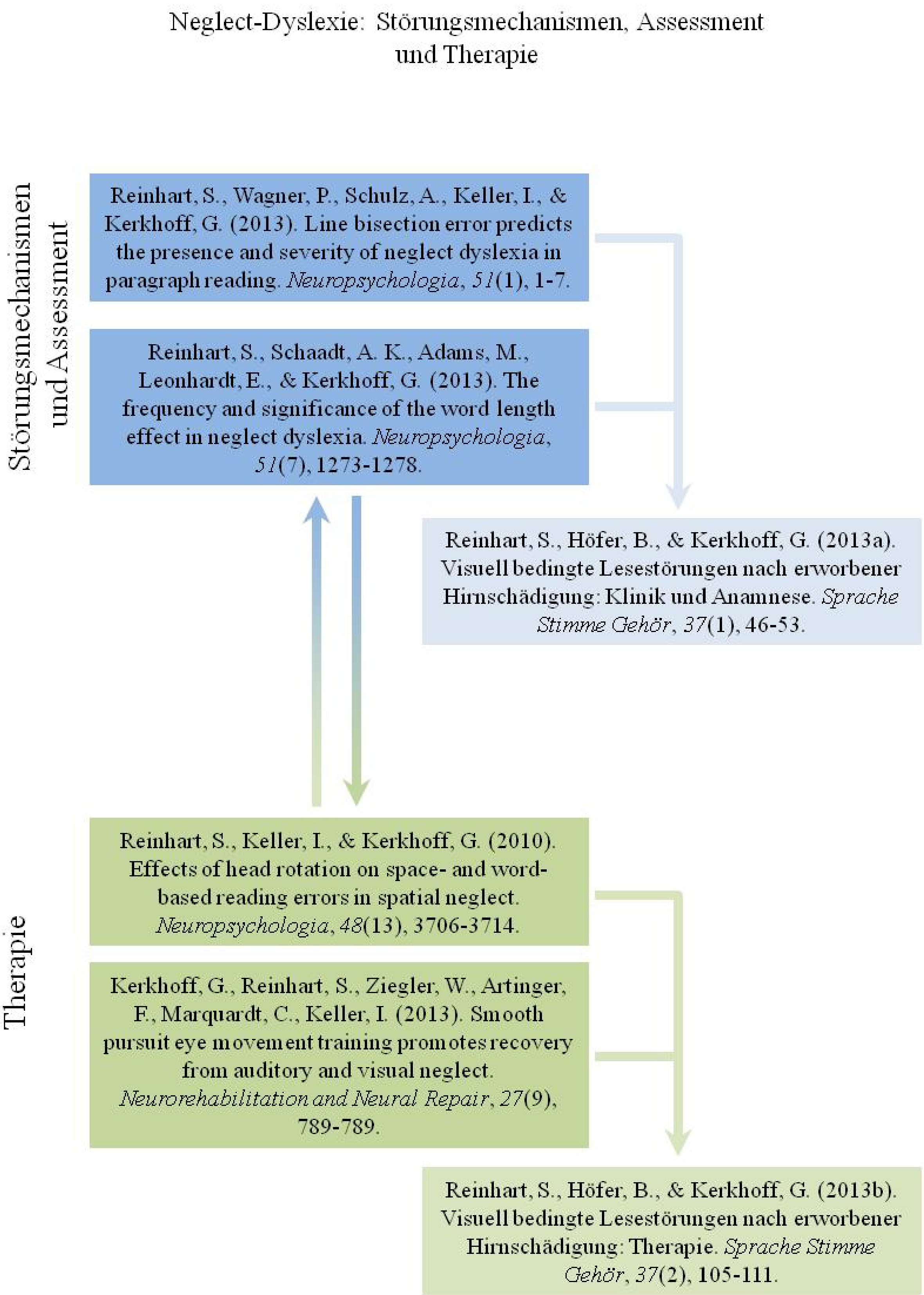

Abbildung 5. Grafische Darstellung der dissertationsrelevanten Studien

3.1 Diskussion der Ergebnisse

3.1.1 Fragestellung 1: Ist die ND eine Folge des kontraläsionalen räumlichen (egozentrischen) Neglects oder manifestiert sich die Störung in einem stimulus- bzw. wortbezogenen Referenzrahmen?

Publikationen:

III Reinhart, S., Wagner, P., Schulz, A., Keller, I., & Kerkhoff, G. (2013). Line bisection error predicts the presence and severity of neglect dyslexia in paragraph reading. *Neuropsychologia*, *51*(1), 1-7.

IV Reinhart, S., Schaadt, A. K., Adams, M., Leonhardt, E., & Kerkhoff, G. (2013). The frequency and significance of the word length effect in neglect dyslexia. *Neuropsychologi*a, 51(7), 1273-1278.

V Reinhart, S., Keller, I., & Kerkhoff, G. (2010). Effects of head rotation on space- and word-based reading errors in spatial neglect. *Neuropsychologia*, *48*(13), 3706-3714.

Wie in Abschnitt 2.2.2 erläutert, gab es bisher nur wenige und kontroverse Befunde aus Einzelfallstudien zur Frage, inwieweit ND mit visuell-räumlichem Neglect oder objektzentriertem Neglect korreliert. Die Ergebnisse unserer Studien mit größeren Stichproben von ND-Patienten lassen darauf schließen, dass es sich bei visuell-räumlichem Neglect und ND zwar um häufig miteinander assoziierte, aber unterschiedliche Störungen handelt, die auch unabhängig voneinander auftreten können. Wir fanden in den Studien III und IV (Reinhart & Wagner et al., 2013; Reinhart & Schaadt et al., 2013) keinen signifikanten Zusammenhang zwischen dem linksseitigen Bias der räumlichen Vernachlässigung in visuellen Ausstreichaufgaben (CoC; Rorden & Karnath, 2010) und der Ausprägung der ND (Fehlerfrequenz und Ausdehnung der vernachlässigten Buchstabenfolge). Drei der Patienten aus Studie III zeigten linksseitige Auslassungen im Star Cancellation Test (Halligan, Marshall, & Wade, 1989; Wilson, Cockburn, & Halligan, 1987), aber keine ND-Fehler beim Lesen. Vice versa gab es in Studie IV zwei Patienten mit unauffälligem CoC, aber mit ND-typischen Lesefehlern. Weitere Evidenz für eine Dissoziation von ND und visuell-räumlichem Neglect liefert Studie V (Reinhart et al., 2010) bei der die Anzahl der vernachlässigten linksseitigen Wörter beim Textlesen (als Indikator für einen visuell-räumlichen Neglect) durch Kopfrotation nach links abnahm, während die Häufigkeit der ND-Fehler durch diese Manipulation unverändert blieb. Diese Ergebnisse sind vergleichbar mit denen der Studie von Reinhart et al. (2011), bei der der Einsatz optokinetischer Stimulation ebenfalls nur die Frequenz linksseitiger Wortauslassungen, nicht aber die Anzahl der wortbezogenen ND-Fehler modulierte.

Im Gegensatz dazu fanden wir in den Studien III & IV (Reinhart & Wagner et al., 2013; Reinhart & Schaadt et al., 2013) eine positive Korrelation zwischen der rechtsseitigen Abweichung von der subjektiven Mitte bei der Linienhalbierung (Linienhalbierungsfehler) und der Häufigkeit von ND-Fehlern (r = 0.61 bzw. r = 0.48) sowie mit der relativen Länge der vernachlässigten Buchstabenfolge am Wortanfang (in Relation zur Wortlänge; r = 0.73 bzw. r = 0.43). Eine plausible Erklärung hierfür ist, dass sich beide Stimuli (eine horizontale Linie und ein Wort) auf einer frühen visuellen Verarbeitungsstufe stark ähneln: Bei beiden handelt es sich um längliche Objekte mit einer kanonischen links-rechts-Orientierung. Young et al. (1990) fanden bei ihrer Patientin M.R. zwar keinen Zusammenhang zwischen ND und objektzentriertem Neglect, benutzten allerdings Abbildungen von Gesichtern als Stimuli, die sich in ihren Stimuluseigenschaften (eher rund, weder eindeutiger Anfang noch Ende) im Gegensatz zu Linien stark von Wörtern (länglich, eindeutige links-rechts-Orientierung) unterscheiden. Patient K.L. Subbiah & Caramazza (2000) zeigte dagegen ND-typische Lesefehler und gleichzeitig eine Vernachlässigung der linken Seite länglicher, horizontal ausgerichteter Stimuli. Möglicherweise besteht also ein Zusammenhang zwischen ND und objektzentriertem Neglect, vorausgesetzt, die Stimuli sind bezüglich Form und Ausrichtung ähnlich.

3.1.2 Fragestellung 2: Wird die ND durch einen homonymen Gesichtsfeldausfall verstärkt?

Publikation:

IV Reinhart, S., Schaadt, A. K., Adams, M., Leonhardt, E., & Kerkhoff, G. (2013). The frequency and significance of the word length effect in neglect dyslexia. *Neuropsychologia*, *51*(7), 1273-1278.

Auch wenn der Hemianopen Dyslexie und der ND verschiedene Störungsmechanismen zugrunde liegen (Schuett et al., 2008), gibt es doch Gemeinsamkeiten in der Symptomatik. Sowohl die ND als auch die Hemianope Dyslexie sind durch Lesefehler auf der kontraläsionalen Wortseite charakterisiert (auch wenn diese Fehler bei der Hemianopen Dyslexie seltener sind; Schuett et al., 2008). Bei der Hemianopen Dyslexie sind die Fehler durch die fehlende visuelle Information des linken Gesichtsfeldes bedingt: Da Lesesakkaden in der Regel in der Wortmitte landen (Rayner, 1979; Di Pellegrino et al., 2001; Dunn-Rankin, 1978; Joseph, Liversedge, Blythe, White, & Rayner, 2009) befindet sich bei linksseitigen Gesichtsfeldausfällen mit geringem Restgesichtsfeld die linke Hälfte eines Wortes im Bereich des Skotom. Patienten mit Hemianopsie ohne Neglect kompensieren den Gesichtsfelddefekt in der Regel mit einer erhöhten Anzahl kleinamplitudiger Sakkaden sowie mit verlängerten Fixationszeiten, was zu einem starken Anstieg der Lesezeiten führt (Schuett, 2009). Da Neglectpatienten häufig zusätzlich unter nicht-räumlichen Aufmerksamkeitsstörungen leiden (Husain & Rorden, 2003; Sturm et al., 2006) und in der Regel ein geringes Störungsbewusstsein für die kontraläsionale Vernachlässigung zeigen (Pedersen et al., 1997; Stone et al., 1993), kann man das Ausbleiben einer adäquaten okulomotorischen Kompensation annehmen. Dies würde bei ND-Patienten mit einem zusätzlichen homonymen Gesichtsfeldausfall zu einer höheren ND-Fehlerrate führen.

Zur Untersuchung dieser Frage teilten wir die Stichprobe aus Studie IV (Reinhart & Schaadt et al. 2013) in Patienten mit einem residualen Gesichtsfeld auf der Skotomseite von ≤ 5° (N = 9) bzw. > 5° (N = 10). Entgegen der Hypothese gab es zwischen den Gruppen keine signifikanten Unterschiede in der prozentualen ND-Fehlerfrequenz, im durchschnittlichen prozentualen vernachlässigten Wortanteil oder im gemittelten Wortlängeneffekt. Man kann daraus im Einklang mit der Theorie von Caramazza & Hillis (1990) schließen, dass sich die ND auf höheren visuellen Prozessebenen manifestiert, auf denen der Wortstimulus bereits unabhängig von seiner retinalen Position analysiert wird.

3.1.3 Fragestellung 3: Ist der Wortlängeneffekt ein häufiges Phänomen bei ND-Patienten und würde er sich damit für die Entwicklung eines spezifischen ND-Tests eignen?

Publikation:

IV Reinhart, S., Schaadt, A. K., Adams, M., Leonhardt, E., & Kerkhoff, G. (2013). The frequency and significance of the word length effect in neglect dyslexia. *Neuropsychologia*, *51*(7), 1273-1278.

Etwa 50% aller Patienten mit einer erworbenen Hirnschädigung berichten von Problemen beim Lesen, sobald man sie gezielt danach fragt (Kerkhoff et al., 1990). Im Kontrast dazu liefern objektive Messungen mit standardisierten Texten (z.B. die „Saarbrücker Lesetexte"; Kerkhoff, Wimbauer, & Reinhart, 2012) vor allem bei Patienten in der chronischen Phase der Störung relativ unauffällige Ergebnisse, auch wenn dieselben Patienten Schwierigkeiten beim Lesen bzw. linksseitige Auslassungen von Buchstaben angeben (Publikation I: Reinhart et al., 2013a). Dieser Widerspruch liegt möglicherweise darin begründet, dass sich Patienten in einer Testsituation in der Regel stärker auf die Aufgabe (lautes Vorlesen) konzentrieren als beim beiläufigen Lesen im Alltag (vs. stilles Lesen). Um eine valide ND-Diagnose mittels Textleseaufgaben stellen zu können, ist daher das Testen unter Alltagsbedingungen bzw. das zeitaufwändige Lesen von längeren Passagen notwendig – beides ist in der klinischen Praxis schwer umsetzbar. Ökonomischere Verfahren, die mit weniger Aufwand eine für die valide Auswertung ausreichende ND-Fehleranzahl erzeugen, wären daher aus diagnostischer Sicht wünschenswert.

In den vergangenen Jahrzehnten wurden verschiedene Worteigenschaften identifiziert, welche die Fehlerhäufigkeit bei ND modulieren (vgl. Übersicht in Vallar et al., 2010). Allerdings handelt es sich bei nahezu allen hierzu durchgeführten Studien um (teilweise nicht replizierte) Einzelfälle. Es ist daher zurzeit noch unklar, welche dieser Worteffekte aus diagnostischer Sicht relevant sind bzw. welche Worteigenschaften die Fehlerfrequenzen bei vielen ND-Patienten spezifisch beeinflussen können. In diesem Zusammenhang untersuchten wir, ob der Wortlängeneffekt (siehe Abschnitt 2.2.5) bei ND-Patienten ein häufiges Phänomen darstellt (Studie IV: Reinhart & Schaadt et al., 2013). Wir fanden einen signifikanten Wortlängeneffekt bei 79% (15 von 19) der ND-Patienten und konnten zeigen, dass sowohl die Anzahl der vernachlässigten Buchstaben als auch die ND-Fehlerfrequenz bei längeren Wörtern höher sind. Da bei Texten kürzere Wörter häufiger vorkommen als längere, ist die Erfassung der ND mit einzeln präsentierten, längeren Wörtern vermutlich effizienter.

3.1.4 Fragestellung 4: Eignen sich sogenannte Bottom-Up-Stimulationsverfahren, wie die Kopfrotation und die optokinetische Stimulation, zur Therapie der ND?

Publikationen:

V Reinhart, S., Keller, I., & Kerkhoff, G. (2010). Effects of head rotation on space- and word-based reading errors in spatial neglect. *Neuropsychologia*, *48*(13), 3706-3714.

VI Kerkhoff, G., Reinhart, S., Ziegler, W., Artinger, F., Marquardt, C., Keller, I. (2013). Smooth pursuit eye movement training promotes recovery from auditory and visual neglect. *Neurorehabilitation and Neural Repair*, *27*(9), 789-798.

Lesen ist sowohl für die berufliche Reintegration als auch für die Lebensqualität der Betroffenen ein wichtiger Faktor, was die Therapie der Neglect-assoziierten Lesestörungen umso bedeutsamer macht. Leider wurde diesem Thema in Studien bisher nur wenig Beachtung geschenkt (Reinhart et al., 2010, 2011). Vor diesem Hintergrund untersuchten wir das Potenzial der Bottom-Up-Verfahren Kopfrotation (Studie V: Reinhart et al., 2010) und OKS, (Studie VI: Kerkhoff & Reinhart et al., 2013), die beide in verschiedenen Studien transient und auch dauerhaft wirksam verschiedene Neglectsymptome reduzieren konnten (Chokron et al., 2007; Karnath et al., 1991; Kerkhoff & Schenk, 2012). In einer Studie von Schindler & Kerkhoff (1997) verminderte die Kopfrotation nach links vorübergehend die ND-Fehlerfrequenz bei einzeln zentral präsentierten Wörtern um durchschnittlich ca. 50 %. Demgegenüber stehen die Ergebnisse einer eigenen Studie, bei der die Patienten Texte bei gleichzeitiger OKS lasen (Reinhart et al., 2011). Hier reduzierte die sensorische Stimulation nur die linksseitigen (egozentrischen) Wortauslassungen während die Anzahl der ND-Fehler davon unbeeinflusst blieb. Da die Kopfrotation und die OKS als sensorische Stimulationsverfahren ähnlich wirken (Karnath, 1994a; Kerkhoff & Schenk, 2012), sollten beide Verfahren auch zu vergleichbaren Ergebnissen beim Lesen von Texten führen. Tatsächlich bewirkte in Studie V (Reinhart et al. 2010) die Rotation des Kopfes um 20° nach links nur eine Reduktion linksseitiger Wortauslassungen, aber keine signifikante Modulation der ND-Fehler. Die Ergebnisse beider Verfahren (Reinhart et al., 2010, 2011) sprechen dafür, dass die unterschiedlichen Fehlerarten (Wortauslassungen auf Text- und Buchstabenauslassungen auf Wortebene) Störungen zweier unterschiedlicher Referenzrahmen (egozentrisch vs. objektzentriert) widerspiegeln (Siehe Abschnitt 2.2) und sowohl Kopfrotation als auch OKS nur den egozentrischen Referenzrahmen beeinflussen. Dass in der Studie von Schindler & Kerkhoff (1997) die Kopfrotation die ND-Fehlerfrequenz minderte, liegt möglicherweise daran, dass sich bei zentraler Präsentation der Wörter der egozentrische und der objektzentrierte Referenzrahmen überdecken bzw. vielleicht sogar identisch sind. Dadurch könnte die Modulation des egozentrischen Referenzrahmens auch eine Modulation des objektzentrierten Referenzrahmens bewirken. Ob die Stimulationsverfahren während des Lesens *einzelner*, zentral dargebotener Wörter die ND-Fehlerfrequenz allerdings dauerhaft reduzieren und ob dieser Effekt auf das Lesen von Texten transferiert werden kann, muss erst in weiteren Studien gezeigt werden.

Aufgrund der positiven Ergebnisse der transienten Reduktion der linksseitigen Wortauslassungen durch sensorische Stimulationsverfahren untersuchten wir in Studie VI (Kerkhoff & Reinhart et al., 2013), ob linksseitige Wortauslassungen durch die wiederholte Anwendung von OKS auch dauerhaft reduziert werden. Darüber hinaus verglichen wir die Wirksamkeit der OKS mit VET, welches häufig in der Neurorehabilitation des Neglect-Syndroms angewendet wird (Kerkhoff & Schenk, 2012; Lincoln & Bowen, 2006). Für die Untersuchung erhielten die Patienten zweier randomisierter Gruppen jeweils fünf Therapiesitzungen innerhalb einer Woche (50 Minuten pro Sitzung) OKS (N=24) oder VET (N=21). Innerhalb der OKS-Gruppe reduzierten sich die Wortauslassungen beim Textlesen um ca. 50%. Dieser Effekt blieb über einen Zeitraum von zwei Wochen hinweg bis zur Nachuntersuchung stabil. Im Gegensatz dazu konnte für das VET keine signifikante Beeinflussung der Auslassungen festgestellt werden. Die generelle Wirksamkeit von VET als Neglectbehandlung wurde in der Vergangenheit zwar bereits mehrfach belegt, allerdings ist für einen signifikanten Effekt eine hochfrequente Behandlung von mindestens 20-40 Sitzungen notwendig. Außerdem sind die Effekte auf den visuellen Neglect beschränkt und transferieren nicht auf andere Sinnesmodalitäten (Kerkhoff & Schenk, 2012). Da sich die Minderung der Wortauslassungen in Studie VI (Kerkhoff & Reinhart et al., 2013) bereits nach fünf Sitzungen OKS einstellte, kann man diese Methode gegenüber dem VET bei der Behandlung von neglectbedingten Lesestörungen als deutlich effizienter einschätzen.

4 Zusammenfassung und Ausblick

Die ND beeinträchtigt die Lesefähigkeit der Betroffenen teilweise erheblich, was mit einer Beeinträchtigung der Informationsaufnahme, erschwerter beruflicher Rehabilitation und letztendlich mit einer deutlichen Minderung der Lebensqualität einhergeht (Publikation I: Reinhart et al., 2013a). Obwohl die Inzidenzangaben über verschiedene Studien hinweg stark variieren (Bisiach et al., 1990; Lee et al., 2009; Ptak et al., 2012), kann man davon ausgehen, dass es sich um eine relativ häufige Störung handelt (20-50% der Neglectpatienten). Angesichts dieser Häufigkeit und der kulturellen und gesellschaftlichen Bedeutung des Lesens ist es erstaunlich, dass bisher weder ökonomische Tests noch etablierte Therapieverfahren zur Diagnostik bzw. Rehabilitation der ND existieren. Die Störung wurde in der Vergangenheit überwiegend mit (wenigen) Einzelfallstudien untersucht (Vallar et al., 2010), was generalisierte Aussagen über die Phänomenologie der Störung, die involvierten Störungsmechanismen sowie mögliche Zusammenhänge und Interaktionen mit anderen Störungen (z.B. Gesichtsfeldausfälle, visuell-räumlicher Neglect) einschränkt. Die im Rahmen dieser Dissertation durchgeführten Studien dienten daher dem Zweck, die Erkenntnisse über die Störung anhand größerer Stichproben von ND-Patienten zu untermauern und zu erweitern sowie wirksame therapeutische Interventionen zu finden.

Auch wenn sich die Symptomatiken – nicht jedoch der Schweregrad – der Hemianopen Dyslexie und der ND ähneln (beide charakterisieren Lesefehler auf der kontraläsionalen Wortseite), beruhen die Störungen auf verschiedenen Mechanismen (Schuett et al., 2008; Studie IV: Reinhart & Schaadt et al., 2013). Wir konnten zeigen, dass die Ausprägung der ND (Fehlerfrequenz, vernachlässigter Wortanteil und der Wortlängeneffekt) nicht durch eine zusätzliche Gesichtsfeldeinschränkung beeinflusst wird (Studie IV: Reinhart & Schaadt et al., 2013). Daraus kann man im Einklang mit der Theorie von Caramazza und Hillis (1990) schließen, dass sich die ND auf höheren visuellen Prozessebenen manifestiert, auf denen der Wortstimulus bereits unabhängig von seiner retinalen Position analysiert wird. Dagegen ist die Hemianope Dyslexie vermutlich eine Folge der fehlenden visuellen Information aus dem Bereich des Skotoms (Schuett et al., 2008). Das Defizit repräsentiert demnach eine Störung auf einer frühen visuellen Verabeitungsstufe.

Über diese Unabhängigkeit der ND von einer frühen, retinalen Repräsentation hinaus fanden wir eine Dissoziation zwischen ND und visuell-räumlichem Neglect (Studien III & IV: Reinhart & Wagner et al., 2013; Reinhart & Schaadt et al., 2013). In beiden Studien war die ND mit allozentrischem Neglect länglicher Objekte (Linienhalbierungsfehler) assoziiert, während kein Zusammenhang mit einem visuell-räumlichem Neglect bestand. Diese Dissoziation zwischen visuell-räumlichem Neglect und ND besteht auch auf neuroanatomischer Ebene: In einer Studie von Lee et al. (2009) waren vor allem rechtsseitige, okzipito-basal gelegene Hirnregionen (Gyrus lingualis, Gyrus fusiformis) kritische Läsionsareale für das Auftreten von ND. Diese sind Bestandteil der ventralen Route der Objektverarbeitung (Ungerleider & Haxby, 1994) und homologe Areale des visuellen Wortformareals des linken fusiformen Gyrus, welches vermutlich die Verarbeitung und Repräsentation der abstrakten Wortform leistet (Cohen et al., 2003; Dehaene & Cohen, 2011; McCandliss et al., 2003). Dagegen scheinen für visuell-räumlichen Neglect rechtsseitige Läsionen in inferior parietal und superior temporal gelegenen Arealen kritisch zu sein (Karnath & Rorden, 2011; Lee et al., 2009; Mort et al., 2003), welche die räumliche Aufmerksamkeitszuwendung bzw. Raumrepräsentation leisten. Die Dissoziation der Verarbeitungsprozesse (Verarbeitung einzelner Worte versus Generierung der Raumrepräsentation bzw. Aufmerksamkeitszuwendung) zeigte sich auch in der unterschiedlichen Modulierbarkeit der Prozesse durch Bottom-Up-Stimulationsverfahren. So bewirkte die Kopfrotation (Studie V: Reinhart et al., 2010) oder die optokinetische Stimulation (Studie VI: Kerkhoff & Reinhart et al., 2013; Reinhart et al., 2011) eine geringere Anzahl vollständiger Wortauslassungen während die Frequenzen wortbasierter ND-Fehler davon unbeeinflusst blieben.

Repetitiv angewandt sind Bottom-Up-Verfahren ein sehr wirksamer Ansatz für die Rehabilitation der mit egozentrischem Neglect assoziierten Lesestörung. Wir konnten zeigen, dass die OKS die (linksseitigen) Wortauslassungen auch über einen längeren Zeitraum hinweg reduziert und dabei dem klinisch häufig angewandten VET deutlich überlegen ist (Studie VI: Kerkhoff & Reinhart et al., 2013).

Ein geeignetes Verfahren zur Rehabilitation der wortbasierten ND-Lesefehler, die allerdings viel seltener als die raumbasierten Auslassungen sind (Reinhart et al., 2010, 2011), steht gegenwärtig noch nicht zur Verfügung. Bottom-Up-Verfahren können auch bei ND (zumindest transient) wirksam sein, wenn einzelne, zentral dargebotene Worte anstatt ganzer Texte präsentiert werden (Schindler & Kerkhoff, 1997). Ob ein entsprechendes repetitives Training die Wortfehler dauerhaft reduziert und ggf. eine verbesserte Leseleistung bei einzeln präsentierten Wörtern auf das Lesen von Texten transferiert, wurde bisher nicht untersucht und bedarf weiterer Studien. Möglicherweise kann die ND besser mit massivem Lesetraining behandelt werden, wie es beispielsweise experimentell bei Reiner Alexie (Ablinger &

Domahs, 2009; Woodhead et al., 2013; Zihl, 2010) oder bei Hemianoper Dyslexie (Aimola et al., 2013) eingesetzt wurde. In einer aktuellen Studie mit Patienten mit Hemianoper Dyslexie (Aimola et al., 2013) wurde durch massives, computerbasiertes Lesetraining, das von den Teilnehmern unter Supervision selbständig zuhause durchgeführt wurde, eine Steigerung der Leseleistung um durchschnittlich 18% erzielt. Das Training von nicht-räumlichen Aufmerksamkeitsfunktionen der Kontrollgruppe hatte dagegen keinen Einfluss auf die Leseleistung. Woodhead et al. (2013) fanden bei neun Patienten mit Reiner Alexie eine erhöhte Lesegeschwindigkeit sowie eine Reduktion der Lesefehler nach sechswöchigem (20 Minuten täglich) audio-visuellem Lesetraining. Allerdings fand sich dieser Effekt nur bei trainierten Wörtern; ein Transfer zu untrainierten Wörtern oder auf das Lesen von Texten fand nicht statt.

Berücksichtigt man diese Ergebnisse für die Entwicklung eines vergleichbaren Trainings für ND-Patienten, dann sollte dieses spezifisch sein und vor allem Wörter beinhalten, welche von ND-Patienten häufig fehlerhaft gelesen werden. Um diese kritischen Wörter gezielt aus der Fülle möglicher Wörter selektieren zu können, sind weitere Erkenntnisse über deren Eigenschaften notwendig. Wir konnten in einer der ersten mit ND-Patienten durchgeführten Gruppenstudie (Studie IV: Reinhart & Schaadt et al., 2013) die Wortlänge als eine wichtige modulierende Eigenschaft für die Frequenz der ND-Fehler identifizieren. Dieser Wortlängeneffekt war bei etwa drei Viertel aller Patienten beobachtbar.

Wie zu Beginn dieser Zusammenfassung beschrieben, variieren die Angaben der Inzidenzangaben zur ND erheblich. Die klinische Erfahrung zeigt, dass die objektive Erfassung der ND vor allem in der chronischen Phase der Störung mit den in der Praxis verwendeten Tests (z.B. NET von Fels, Wilson, & Geissner, 1997; Saarbrücker Lesetexte von Kerkhoff, Wimbauer, & Reinhart, 2012) schwierig ist: Viele Patienten beklagen zwar bei gezielter Nachfrage charakteristische ND-Fehler im Alltag, sind aber in Testsituationen beim Lesen kurzer Texte relativ unauffällig. Um eine ausreichende Fehleranzahl für eine valide diagnostische Auswertung zu erhalten, wäre das Lesen längerer Passagen erforderlich, was allerdings den Aufwand für die Testung erhöhen würde. Man kann daher davon ausgehen, dass die ND in der klinischen Praxis relativ häufig übersehen wird. Dies ist vielleicht auch eine Ursache dafür, dass sich bislang nur wenige Studien mit der Therapie der Störung befasst haben. Da bei Lesetexten kürzere Wörter häufiger vorkommen als längere, ist die Erfassung der ND mit einzeln präsentierten, längeren Wörtern diagnostisch vermutlich effizienter. Ob auch andere, in Einzelfällen beschriebene Worteffekte (Vallar et al., 2010) die Fehlerfrequenzen bei einer größeren Gruppe von ND-Patienten spezifisch erhöhen und sich damit für die Entwicklung neuer Diagnostik- und Therapieverfahren eignen, ist Gegenstand derzeit laufender Studien.

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6 Curriculum Vitae

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Academic Achievements:

06 / 1997	Diploma in social education at the University of Applied Sciences, Fulda
09 / 2010	Diploma in psychology at the Saarland University, Saarbrücken

Academic Career:

1993-1997	Student in social education (Diploma), University of Applied Sciences, Fulda
2006-2010	Student in psychology (Diploma), Saarland University, Saarbrücken
2007-2010	Research assistant (wissenschaftliche Hilfskraft) at the department of Cognitive Psychology and Methods at Saarland University
2008-2009	Research assistant at the department of Experimental Psychology at Saarland University
2009-2010	Research assistant at the department of Clinical Neuropsychology at Saarland University

Since 2010	Research fellow (wissenschaftlicher Mitarbeiter) at the department of Clinical Neuropsychology at Saarland University
Since 2010	Research Activities in Neuro-Visual Diagnostics and Rehabilitation, Visual-Spatial Vision, Reading Disorders, Neglect, Sensory, and Motor Disorders after Brain Damage

Ad-hoc Reviewer for the following journals:

- Neuropsychologia
- Frontiers in Human Neuroscience
- Frontiers in Cognition
- Journal of Clinical Ophthalmology
- Research in Developmental Disabilities
- ISRN Rehabilitation

7 Vollständige Publikationsliste

Artikels in press:

Kerkhoff, G., Bucher, L., Brasse, Leonhart, E., Holzgraefe, M. Völzke, V., Keller I., **Reinhart**, S. (in press). Smooth Pursuit Bedside Training reduces disability and unawareness during the activities of daily living in neglect. A randomized controlled trial. *Neurorehabilitation & Neural Repair*. IF = 4.877.

Schaadt, A.-K., MA, Schmidt, L., Kuhn, C., Summ, M., Adams, Garbacenkaite, R., Leonhardt, E., **Reinhart**, S., Kerkhoff, G. (in press). Perceptual re-learning of binocular fusion after hypoxic brain damage – four controlled single case treatment studies. *Neuropsychology*. IF = 4.148.

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******[3] **Reinhart**, S., Höfer, B., & Kerkhoff, G. (2013a). Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Klinik und Anamnese. *Sprache Stimme Gehör*, *37*(1), 46-53. IF (2012) = 0.104.

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[3] Dissertation-relevant publications are marked with asterisks.

** **Reinhart**, S., Schaadt, A. K., Adams, M., Leonhardt, E., & Kerkhoff, G. (2013). The frequency and significance of the word length effect in neglect dyslexia. *Neuropsychologia*, *51*(7), 1273-1278. IF = 4.372.

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2012:

Reinhart, S., Schmidt, L., Kuhn, C., Rosenthal, A., Schenk, T., Keller, I., Kerkhoff, G. (2012). Limb activation ameliorates body-related deficits in spatial neglect. *Frontiers in Human Neuroscience, 6,* 1-7. IF = 3.108.

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Kuhn, C., Rosenthal, A., Bublak, P., Grotemeyer, K.H., **Reinhart**, S., Kerkhoff, G. (2012). Does spatial cueing affect line bisection in chronic homonymous hemianopia? Submitted, *Neuropsychologia, 50*(7), 1656-1662. IF = 4.372.

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Kerkhoff, G., Keller, I., Artinger, F., Hildebrandt, H., **Reinhart**, S., Marquardt, C., & Ziegler, W. (2012). Recovery from auditory and visual neglect after optokinetic stimulation with pursuit eye movements – transient modulation and enduring treatment effect. *Neuropsychologia*, *50*(6), 1164-1177. IF = 4.372.

2011:

Reinhart, S., Schaadt, K., & Kerkhoff, G. (2011). Behandlung von Missempfindungen nach Schlaganfall mittels Spiegeltherapie: eine Fallstudie. *Neurologie & Rehabilitation, 17,* 251- 257.

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2010:

** **Reinhart**, S., Keller, I., & Kerkhoff, G. (2010). Effects of head rotation on space- and word-based reading errors in spatial neglect. *Neuropsychologia*, *48*, 3706-3714. IF = 4.372.

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9 Anhang: Originalarbeiten

Anhang A:

Reinhart, S., Höfer, B., & Kerkhoff, G. (2013a). Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Klinik und Anamnese. *Sprache Stimme Gehör, 37*(1), 46-53.

Anhang B:

Reinhart, S., Höfer, B., & Kerkhoff, G. (2013b). Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Therapie. *Sprache Stimme Gehör, 37*(2), 105-111.

Anhang C:

Reinhart, S., Wagner, P., Schulz, A., Keller, I., & Kerkhoff, G. (2013). Line bisection error predicts the presence and severity of neglect dyslexia in paragraph reading. *Neuropsychologia*, *51*(1), 1-7.

Anhang D:

Reinhart, S., Schaadt, A. K., Adams, M., Leonhardt, E., & Kerkhoff, G. (2013). The frequency and significance of the word length effect in neglect dyslexia. *Neuropsychologia*, *51*(7), 1273-1278.

Anhang E:

Reinhart, S., Keller, I., & Kerkhoff, G. (2010). Effects of head rotation on space- and word-based reading errors in spatial neglect. *Neuropsychologia, 48*(13), 3706-3714.

Anhang F:

Kerkhoff, G., **Reinhart, S.**, Ziegler, W., Artinger, F., Marquardt, C., Keller, I. (2013). Smooth pursuit eye movement training promotes recovery from auditory and visual neglect. *Neurorehabilitation and Neural Repair*, *27*(9), 789-798.

Anhang A[1]

Reinhart, S., Höfer, B., & Kerkhoff, G. (2013a). Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Klinik und Anamnese. *Sprache Stimme Gehör*, *37*(1), 46-53.

Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Klinik und Anamnese

Abstract

Lesen ist nicht nur relevant in Alltag und Beruf, sondern auch eine wichtige Voraussetzung für kognitive Leistungen wie etwa das kurz- und längerfristige Behalten und Weiterverarbeiten sprachlicher Informationen. Visuell bedingte Leseprobleme gehören zur Klasse der peripheren Lesestörungen und sind häufig nach Hirnschädigung beobachtbar. Im vorliegenden Beitrag geben wir zunächst einen Überblick über die wichtigsten Ursachen solcher Lesestörungen sowie ihre spezifische Anamnese. Die häufigsten Ursachen sind: homonyme Gesichtsfeldausfälle, visueller Neglect, beeinträchtigte elementare Sehleistungen (Sehschärfe, Kontrastsehen, Augenbewegungsstörungen), das Bálint-Holmes-Syndrom und die Reine Alexie oder Hemialexie. In einem späteren Beitrag werden bewährte und neue Therapieansätze sowie ausgewählte Ergebnisse aus eigenen Therapiestudien für Patienten mit visuellen Lesestörungen dargestellt.

[1] Aufgrund der Lizenzbedingungen des Verlages wird an dieser Stelle nur das Abstract des Artikels dargestellt.

Anhang B[2]

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Visuell bedingte Lesestörungen nach erworbener Hirnschädigung: Therapie

Abstract

Visuell bedingte Lesestörungen treten häufig aufgrund homonymer Gesichtsfeldausfälle, eines visuellen Neglects, beeinträchtigter elementarer Sehleistungen (Sehschärfe, Kontrastsehen, Augenbewegungsstörungen), beim Bálint-Holmes-Syndrom, der Reinen Alexie oder der Hemialexie auf. Für die Therapie der hemianopen Dyslexie haben sich die Fließtextmethode und Kurzzeitdarbietungen von Worten an der Grenze des blinden Gesichtsfeldes bewährt. Für die Neglectdyslexie zeigt die Methode der optokinetischen Therapie gute Effekte im Sinne einer Verminderung der Auslassungen von Worten im vernachlässigten Halbraum. Die taktil-kinästhetische Fazilitierung ist bei der Reinen Alexie und buchstabierendem Lesen wirksam. Schließlich zeigt die Methode der Einzelwortdarbietung an sequenziellen Positionen in der Zeile (Fenster-Textmethode) gute Effekte in der Lesetherapie von Patienten mit Reiner Alexie oder Bálint-Holmes-Syndrom.

[2] Aufgrund der Lizenzbedingungen des Verlages wird an dieser Stelle nur das Abstract des Artikels dargestellt.

Anhang C

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Line bisection error predicts the presence and severity of neglect dyslexia in paragraph reading

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ABSTRACT

Cancellation tasks and line bisection tasks are commonly used to diagnose spatial neglect after right hemisphere lesions. In such tasks, neglect patients often show leftsided omissions of targets in cancellation tests as well as a pathological rightward deviation in horizontal line bisection. However, double dissociations have also been reported and the relation between performance in both tasks is not clear. Another impairment frequently associated with the neglect syndrome are omissions or misread initial letters of single words, a phenomenon termed neglect dyslexia (ND). Omissions of whole words on the contralesional side of the page are generally considered as egocentric or space-based errors, whereas misreadings of the left part of a word in ND can be viewed as a type of stimulus-centered or word-based, perceptual error. As words, sentences and horizontal lines have a similar spatial layout in the sense that they all are horizontally aligned, long stimuli with a canonical left–right orientation (with a defined beginning on the left and an end on the right side), we hypothesized a significant association between the horizontal line bisection error (LBE) in neglect and the extent (number) of neglected or substituted letters within single words in ND (neglect dyslexia extension, NDE). To this purpose, we computed Center-of-Cancellation (CoC) scores in a cancellation task as well as Center-of-Reading (CoR) scores in an experimental paragraph reading test. We found that the CoR was a better indicator for egocentric word omissions than the CoC in a group of 17 patients with left visuospatial neglect. Furthermore, the LBE predicted the severity of ND, indicated by highly significant correlations between the LBE and the extent of the neglected letter string within single words (NDE; $r=0.73$, $p<0.001$) as well as between the LBE and the frequency of ND errors ($r=0.61$; $p=0.009$). In contrast, we found no significant correlation between the CoC and the severity of ND. These results indicate two different pathological mechanisms being responsible for contralesional spatial neglect and ND. In conclusion, the LBE is a more sensitive predictor of the presence *and* severity of the reading disorder in spatial neglect than conventional cancellation tasks.

1. Introduction

1.1. Different reference frames in neglect

Visual neglect has fascinated researchers during the last decades because of the multifaceted nature of the syndrome (see e.g. the recent special issue on neglect edited by Schenk and Karnath (2012)). Patients with visual neglect after unilateral right brain lesions do not report, respond, or orient to contralesional stimuli (Heilman, Watson, & Valenstein, 2012; Kerkhoff, 2001). Neglect patients typically show leftward omissions in cancellation or visual search tasks and a rightward deviation in horizontal line bisection (Schindler & Kerkhoff, 2004; Utz, Keller, Kardinal, & Kerkhoff, 2011). This ipsilesional line bisection error in neglect patients differs from the contralesional shift in chronic (Hesse, Lane, Aimola, & Schenk, 2012) or the slight ipsilesional shift in acute hemianopia (Machner, Sprenger, Hansen, Heide, & Helmchen, 2009). Several studies have shown that ego- and allocentric neglect phenomena are dissociable and rely on different neural structures (Halligan, Fink, Marshall, & Vallar, 2003). These results are consistent with the hypothesis that egocentric visual information processing is linked primarily to parieto-frontal brain areas in the dorsal stream whereas allocentric, object-centered visual processing is linked more closely to ventral stream areas (Grimsen, Hildebrandt, & Fahle, 2008; Hillis et al. 2005; Honda, Wise, Weeks, Deiber, & Hallett,

Abbreviations: COC, Center of Cancellation; CoR, Center of Reading; ND, Neglect Dyslexia; LBE, Line Bisection Error; NDE, Neglect Dyslexia Extension; CN, Contralesional spatial Neglect

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1998; Vallar, Burani, & Arduino, 2010; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010). Contralesional spatial neglect (CN) is commonly assessed with cancellation tasks like the bells test (Gauthier, Dehaut, & Joanette, 1989) or with a horizontal line bisection task (Doricchi et al., 2005; Schenkenberg, Bradford, & Ajax, 1980), as patients often show leftsided omissions of targets in cancellation tests and a pathological rightward deviation in line bisection. However, the relation between both tasks is not clear. For example, Azouvi et al. (2002) found that both tasks are correlated but load on different factors whereas Halligan, Marshall, and Wade (1989) found high factor-loads on the same factor. Binder, Marshall, Lazar, Benjamin, and Mohr (1992) reported a non-significant correlation of $r=0.39$ between the line bisection error and the performance in a cancellation test. They therefore concluded that both tasks indicate distinct syndromes of hemineglect, associated with lesions in discrete brain areas. Furthermore, several double dissociations have been reported between line bisection and cancellation tests (Binder et al., 1992; Ferber & Karnath, 2001; Ferro & Kertesz, 1984; Halligan & Marshall, 1992; Marshall & Halligan, 1995; McGlinchey-Berroth et al., 1996). Hence, it is questionable whether impairments in line bisection and in cancellation tests underly the same disturbed cortical processes or reflect distinct aspects of the neglect syndrome based on different affected spatial reference systems and brain areas. In the study of Binder et al. (1992) as well as in an investigation of Rorden, Fruhmann, and Karnath (2006) a pathological LBE was associated with lesions in posterior brain regions whereas patients with abnormal cancellation performance and no LBE were injured primarily in anterior brain areas.

Considering the reported anatomical and behavioral dissociations as well as the evidence that both tasks can be modulated specifically indicate that different reference frames are necessary to perform the tasks. For example, visual search performance in neglect patients depends on the size of the visual scene (Eglin, Robertson, Knight, & Brugger, 1994) and the rightward line bisection error (further termed LBE) increases as a function of line length (Bisiach, Bulgarelli, Sterzi, & Vallar, 1983; Halligan & Marshall, 1988; Marshall, 1998). However, Keller, Schindler, Kerkhoff, Rosen, and Golz (2005) found only the LBE increasing with the distance between the subject and the stimulus whereas the performance in a cancellation task remained unaffected by that manipulation. Interestingly, the LBE seems to be influenced by the subject's reading direction habit. Chokron and Imbert (1993) found in normal subjects that Israeli (who read from right to left) tend to bisect a line at the right of the objective center whereas French subjects placed their bisection mark at the left of the physical middle, a phenomenon well known as pseudo neglect (Jewell & McCourt, 2000). In line with this result, Speedie et al. (2002) found in an intercultural investigation that neglect patients of European languages tend to bisect a horizontal line with a rightward deviation whereas patients of Semitic languages showed a bisection error closer to the physical center of the line. In contrast, they found no such difference in the performance in a cancellation task between both groups.

Taken together, there is ample evidence that both tasks require distinct spatial reference frames, with an egocentric frame for searching spatially distributed targets and a stimulus- or even an object-centered reference frame for the bisection of a single perceptual object (the horizontal line) with a canonical left–right orientation.

1.2. Neglect dyslexia (ND)

Neglect dyslexia (further termed ND) reflects a peripheral reading disorder associated with the neglect syndrome. Left-sided neglect can impair reading in different ways. Patients typically omit initial whole words of a text line (text or space related omissions, Reinhart, Keller, & Kerkhoff, 2010). However, ND in the narrow sense defines word-related errors characterized by omissions or substitutions of initial letters of single words horizontally presented in central vision. These substitutions or omissions of letters mostly lead to reading errors that resemble or form alternative words but not neologisms (e.g., misreading "start" as "art" or "mouse" as "house", cf. Ellis, Flude, & Young, 1987; Kinsbourne & Warrington, 1962). Several single case studies found a clear word-length effect in ND for the frequency of errors (Tegner & Levander, 1993; Subbiah & Caramazza, 2000; Behrmann, Moscovitch, Black, & Mozer, 1990) as well as for the number of omitted or substituted letters which increases with the length of the word in single word reading (Behrmann et al., 1990; Ellis et al., 1987; Subbiah & Caramazza, 2000; Tegner & Levander, 1993). Most of the reported single cases made more substitution than omission errors (for a review see Vallar et al. (2010)) but investigations of groups with ND have shown a variation of these two error types in different patients (Cubelli & Beschin, 2005; Kinsbourne & Warrington, 1962; Lee et al., 2009; Savazzi, Frigo, & Minuto, 2004).

Based on the assumption that words represent a class of visual objects Caramazza and Hillis (1990) adapted Marr and Nishiharas' levels of processing model (Marr & Nishihara, 1978; Marr, Ullman, & Poggio, 2010) for the early stages of visual word recognition. According to their model, words are processed hierarchically at three representational levels from the (1) viewer-centered analysis of visual features of the word followed by a (2) stimulus-centered representation to an (3) abstract word-centered description of the letter string. Disturbances of these different processing levels should be associated with specific reading errors, with viewer-centered omissions of words (or analog omissions of targets in a cancellation task) reflecting impairments on the viewer-centered level and ND errors reflecting impaired stimulus- or word-centered levels.

Even though ND is mostly related to contralesional hemispatial neglect (Vallar et al., 2010; further termed CN) the association of both disturbances is unclear. Several double dissociations have been reported in group studies (Behrmann, Black, McKeeff, & Barton, 2002) and single case studies (Cantoni & Piccirilli, 1997; Costello & Warrington, 1987; Haywood & Coltheart, 2001; Patterson & Wilson, 1990; Patterson & Wilson, 1990). By contrast, Lee et al. (2009) found the severity of CN to be a significant predictor for the frequency of ND errors. In two recent investigations we found that a manipulation of the egocentric reference frame by head rotation (Reinhart, Keller, & Kerkhoff, 2010), or optokinetic stimulation (Reinhart, Schindler, & Kerkhoff, 2011) only reduced egocentric or viewer-centered word omissions whereas the stimulus- or word-based ND errors remained completely unaffected by these manipulations in the same text reading task. Taken together, there is some evidence that neglect assessed with reading tasks can independently occur in the viewer-centered (left-sided word omissions) and object-centered (left-sided letter omissions/substitutions) reference frames but there are also contrary results. These contrary results may be attributable to different assessments of CN that were used to investigate this issue. For example, Lee et al. (2009) assessed the severity of CN with a neglect test battery containing line bisection tasks. By contrast, Arduino, Burani, and Vallar (2002) found that ND was not significantly affected by the severity of CN assessed with a test battery *without* a line bisection task.

As the use of the results of a whole test battery (containing line bisection and cancellation tasks) blends different aspects of neglect (object-centered and spatial neglect), it should be more insightful to investigate the association between ND and other aspects of neglect using the results of the single tests. Using such a more sophisticated approach, Ptak, Di Pietro, and Schnider (2012) asked their 19ND patients to read 40 capital letter words pseudo-randomly scattered in five columns on a sheet of paper. They found that the frequency of ND errors was independent from the viewer-centered spatial position of the word whereas the frequency of entirely omitted words linearly increased from the right to the left side of the page. Furthermore, a regression analysis revealed only the ipsilesional line bisection to be a significant predictor of the frequency of ND errors whereas all other predictors (age, time since lesion, lesion volume, number of omissions in three cancellation tests and omissions in a reading test) remained non-significant.

Given the results of Ptak et al. (2012) and the above noted evidence that the line bisection error as well as the neglected part of the word increases with the length of the line or respectively the length of the word, we examined the relations between the severity of CN, object-centered neglect, and the severity of ND. More specifically, in the present study we investigated whether the line bisection error is also a predictor for the *extension of the neglected initial letter string* (termed Neglect Dyslexia Extension; NDE) as another measure of the severity of ND besides the frequency of ND errors. Furthermore, we wanted to investigate whether there is a relation between the NDE and the pathological rightward spatial bias in patients with CN. To investigate these issues, we used controlled paragraph reading tests (cf Reinhart et al., 2010, 2011) instead of single word reading tasks which enables us to examine spatial *and* word-based reading errors within the *same* task simultaneously. Even if the number of left- and right-sided omissions in cancellation tasks is a measure broadly used in former investigations, it might not be appropriate to reflect the specific spatial bias in CN as it contains no information about the spatial positions of the omissions. Therefore, we used the Center of Cancellation (CoC) first proposed by Binder et al. (1992) to examine the correlation between the severity of CN and ND. The CoC gives information about the spatial bias of omissions in cancellation tests and allows therefore a distinction between (left-sided) CN related and (distributed) errors which are driven by deficits in non-spatial attention. The CoC has been shown as a reliable measure of the severity of CN (Rorden & Karnath, 2010). In addition, we applied the same logic to our experimental paragraph reading tasks and computed the new measure of Center-of-Reading (CoR) errors obtained with the paragraph reading tests, and related this to the CoC derived from the cancellation task (see below).

2. Methods

2.1. Subjects

17 patients (seven female; mean age = 63.50 years; *SD* = 10.30) with right-hemispheric, vascular brain lesions (mean time post lesion = 14.41 weeks; *SD* = 8.43) and moderate to severe left-sided visuospatial neglect according to the results of 4 conventional neglect screening tests were included. The tests were very similar to those of the Behavioral Inattention Test (Halligan et al., 1989; Wilson, Cockburn, & Halligan, 1987): star cancellation, bisection of a 20 cm long line, clock drawing from memory and figure copy (star, flower, cube). All tests were shown at a distance of about 0.35 cm from the patient's eyes. All patients had a decimal visual acuity of at least 0.80 (= 80%) for the near viewing distance (0.4 m). All subjects had at least 9 years of education (see Table 1 for clinical and demographic details) and a decimal visual acuity of at least 0.70 (20/30 Snellen equivalent) for the near viewing distance (0.4 m) that was appropriately corrected during the experiment. The study was approved by the ethics committee of the Ludwigs-Maximilian-Universität, München/Germany, Project no. 352-09 in November 2009. All experiments were conducted in accordance to the Declaration of Helsinki II.

2.2. Experimental reading tests

Indented paragraph reading tasks are a highly sensitive measure of reading in neglect (Bachman, Fein, Davenport, & Price, 1993; Caplan, 1987; Towle & Lincoln, 1991) and are not confounded by differences in years of schooling (Bachman et al., 1993). We employed 45 short reading texts of different length (mean length: 51.7 words, range: 43–65; arranged in 8–10 lines) containing words of 2–11 letters from two story books (see Reinhart et al., 2010, 2011). The margins of each text were irregularly indented on both sides (see example in Fig. 1). Eight to ten words on every margin (left and right side) of each text were filler words (for example words as ''a'', ''but'', ''in'', ''very'', ''often'', etc.) and were not necessary for the semantic context of the text. The main message of the text could be understood even if most or all of these filler words were omitted. All texts were matched with respect to length (number of words, letters and lines) and spatial arrangement. The number of words displayed on each side of the reading texts was balanced (mean length left: 25.8 words, mean length right: 26.00 words). There was no statistical difference between the number of words presented on the left and right text side when all 45 texts were compared [$t(44) = 0.34$, $p = 0.76$]. Each text was displayed sequentially one by one within an $8 \times 24^{\circ}$ large rectangular white field on a 17″-computer screen. Texts were presented in black print (Arial, capital letters, point size 22) on a white background at a distance of 0.4 m to the patient's eyes. The midline of the computer screen was perpendicular to the patients' trunk midline.

Subjects were instructed to read out five to eight of the 45 texts sequentially displayed on the screen. All read texts were presented within one session of 30 min. Reading was simultaneously scored on a paper printout of the same texts displayed on the monitor. After each reading text a blank screen was presented and a short break of 1–2 min was given to the subject to avoid fatigue effects. No reading text was presented twice to any subject to prevent test repetition effects.

2.3. Line bisection task

Participants were asked to bisect (with a pencil in their dominant right hand) a 200 mm × 2 mm black line printed on white paper oriented horizontally to the patients' midsagittal plane of the body. The bisection error was measured in mm with negative values indicating leftward and positive values indicating rightward deviations with reference to the objective midpoint of the line (one trial).

2.4. Measurement of spatial neglect

To measure the severity of CN the CoC proposed by Binder et al. (1992) was calculated from the performance in the star cancellation task with a software developed by Rorden and Karnath (2010), (www.mricro.com/cancel/). The star cancellation test contains 56 targets (small stars) that are distributed between distractors (large stars and capital letters). The CoC takes the spatial position of every omitted target into consideration and therefore reflects the spatial bias of patients in cancellation tasks as a measure of the neglect severity. It can vary between −1 and +1 with values close to one indicating a severe rightward neglect in a patient who only canceled the rightmost targets in a cancellation task and vice versa. Performances with evenly distributed or without omissions reveal values of (close to) zero (Rorden & Karnath, 2010). As a continuous measure it can be used for parametric statistical analyses.

2.5. Scoring of reading errors in the experimental reading tasks

ND errors included omissions of left-sided letter(s), syllable(s) or half of a single word in compound words (i.e. 'keeper' instead of 'housekeeper') and part-word substitutions, when letter(s), syllable(s) or half of a word were substituted (i.e. 'house' instead of 'mouse') and were classified following Ellis et al. (1987). Omissions or substitutions were counted if the reading error was made on the left side of the word and when the read word and the target word were identical to the right of an identifiable neglect point within the word. Additions of letters were rare (< 1% of the reading errors) and were not counted as ND errors. Complete word substitutions were also excluded from the analysis as they may constitute a qualitatively different category of reading problem that is not typical for *unilateral* spatial neglect, since no clear left–right difference with respect to the substituted syllables within the word is evident. The extension of the neglected letter string (NDE) was calculated as the percentage of omitted or substituted letters of the misread word on the left side of the neglect point.

Omissions of entire words on the left and right side of the text respectively were scored as spatial reading errors (each omitted word counted as one error). Additionally, the mean ''center of reading'' (CoR) referring to Binder et al. (1992) was calculated as a continuous measure to define the spatial bias of text reading. To identify the CoR the software of Rorden and Karnath (2010), (www.mricro.com/cancel/) was applied to each text. The first letter of each word in a text defined the spatial location of the word. Read words (correct or with any reading error excluding complete word additions) were marked and the CoR was calculated for each read text separately and the mean CoR was calculated for each patient in analogy to the procedures for calculating the CoC.

Table 1
Clinical and demographic data of 17 patients with left visuospatial neglect (see text for further details).

Sub-ject	Age, Sex	Etio-logy	Weeks post Lesion	Lesion Location	Field defect/ Sparing (°)	Figure copy	Clock drawing	Cancel-lation	LBE	ND errors
1	63, m	MCI	12,00	Parietal	HH, <1°	+	+	+	+	+
2	57, f	MCI	23,00	Parietal, Temporal	HH, <5°	+	+	+	+	+
3	56, f	ICH	20,00	Parietal	HH, >5°	+	−	+	+	+
4	58, f	MCI	12,00	Parietal, Temporal	HH, >5°	+	+	+	+	+
5	53, m	MCI	12,00	Parietal, Temporal	HH, >5°	+	+	+	+	+
6	65, m	ICH, MCI	4,00	Parietal, Occipital	HH, >5°	+	+	+	+	+
7	51, m	ICB, MCI	14,00	Frontal, Parietal, BG	QA, >5°	−	−	−	+	+
8	77, f	ICH	6,00	BG	QA, >5°	−	−	+	+	+
9	69, m	MCI	4,00	Parietal, Occipital	HH, <1°	+	−	+	+	+
10	74, m	MCI	25,00	Frontal, Parietal	Normal	−	−	−	+	+
11	77, m	MCI	16,00	Parietal, Temporal	HH, <5°	−	−	+	+	+
12	55, f	MCI	31,00	Parietal, Temporal	HH, <1°	+	−	+	+	+
13	73, f	MCI	4,00	BG	Normal	−	+	+	+	+
14	72, m	ICH	3,00	Parietal, Occipital	HH, <1°	+	+	+	−	−
15	78, f	MCI	18,00	Parietal, Temporal	Normal	+	+	+	−	−
16	48, m	MCI	23,00	Parietal, Temporal	QA, >5°	+	+	−	−	−
17	53, m	MCI	18,00	Frontal	Normal	−	+	+	−	−
	Mean 63.5		**14.4 (3–31)**		**13/17 impaired**	**11/17 impaired**	**10/17 impaired**	**15/17 impaired**	**13/17 impaired**	**13/17 impaired**

Legend and abbreviations: ICH: intracerebral hemorrhage; MCI: middle cerebral artery infarction; BG: basal ganglia; MCA/PCA: middle cerebral artery infarction; L/R: left/right; HH: left-sided homonymus hemianopia; QA: quadrant anopia. Visual Field: Field sparing is indicated in (°) on the left horizontal meridian in the blind field. Neglect screening tests: Figure copy, clock drawing: + = pathological, neglect-related omissions or distortions observable, − = absent. Cancellation: Left-sided > right-sided omissions. LBE: Pathological line bisection error (right sided deviation > 5 mm). ND errors: + = observable, − = no ND errors (Cutoff: max 2 errors).

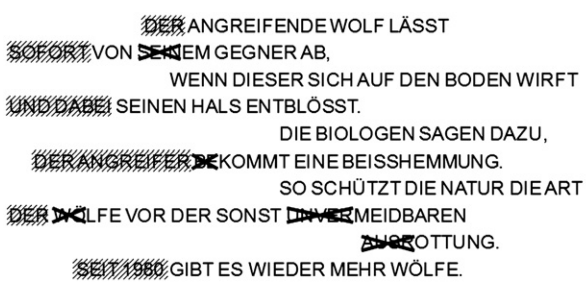

Fig. 1. Example of an indented paragraph reading text (A), and demonstration of a typical neglect patient (Nr 2) with a *CoR* = 0.170 for this single text. Omissions of entire words are shaded; ND errors (omissions or substitutions of letters) are crossed. The patient made two ND substitution errors (**SEIN**EM > **D**EM; **WÖ**LFE > **HI**LFE) and three ND omission errors (**BE**KOMMT > KOMMT; **UNVER**MEIDBAREN > MEIDBAREN; **AUSR**OTTUNG > OTTUNG) in this text.

3. Results

All statistics were computed with SPSS, version 19. Pearson's correlation coefficients were calculated between the performances in the different tasks. Correlations were compared with *t*-statistics as described in Field (2005).

3.1. Descriptive statistics

As can be seen in Table 1, four patients (patients 14–17) showed no signs of ND but were impaired in the figure copy or the clock drawing task. Three of them (14, 15, and 17) were additionally impaired in the star cancellation task. All these four patients showed no pathological rightward deviation in line bisection (*mean*: −0.25 mm; range: −2 mm to +3 mm; according to a normal cut-off of +/−5 mm deviations from the objective midline (Schindler & Kerkhoff, 2004). By contrast, all patients who made ND errors (1–13) showed a rightward deviation in the line bisection task. Four ND patients (7, 8, 10, and 11) made ND errors but were not impaired in figure copy or clock drawing. Two of them (7 and 10) also showed no omissions in star cancellation. However, all these patients showed a pathological deviation to the right (*mean* = +40.42 mm; *SD* = 25.36, range +13 mm to +90 mm) in line bisection as well as ND errors. ND patients omitted on average 30.16% of the words with a high variation within the group (*SD* = 28.28; *range* = 92% − 0% spatial omissions). ND errors varied between 1.03% and 38.89% of all read words (*mean* = 8.81%; *SD* = 12.17%). All patients with ND made at least 6 ND errors. There was no significant difference between omissions and substitutions in the group of patients with ND errors [*mean difference* = 11.35%; $t(12) = 0.760$; $p = 0.462$]. All ND patients made omission errors and substitution errors except patient 10 whose reading errors were all substitutions.

3.2. Relations of CN measurements

To examine if our CoR is a valid measure of contralesional spatial neglect (assessed with omissions of entire words), we calculated the correlation between the CoR (mean CoR = 0.22; *SD* = 0.28; *range* = −0.01 to +0.88) and the percentage of neglected words. This analysis revealed a high correlation ($r = 0.98$, $p < 0.001$). The correlation between the CoC (mean CoC = 0.43; *SD* = 30; *range* = 0.00–0.83) and the frequency of omissions was also significant ($r = 0.59$, $p = 0.013$), but smaller [$t(13) = 8.32$, $p < 0.001$]. There was a significant correlation between the CoC and the CoR ($r = 0.51$, $p = 0.028$).

3.3. Relations between LBE and CN measurements

There were significant correlations between the LBE (mean *LBE* = +30.82 mm; *SD* = 28.32; *range* = −2 mm to +90 mm) and the CoR ($r = 0.77$, $p < 0.001$) and the CoC ($r = 0.59$, $p = 0.013$).

3.4. Relations between ND, LBE and CN

There were high significant correlations between the NDE (mean NDE = 28.61; *SD* = 16.87; *range* = 0.00–44.12) and the LBE ($r = 0.73$, $p = 0.001$) and the percentage of ND errors ($r = 0.61$, $p = 0.009$), but no significant correlation between the CoC and the NDE ($r = 0.28$, $p = 0.272$) and the percentage of ND errors ($r = 0.41$,

$p=0.102$). To examine whether the high correlation between the LBE and neglect dyslexia (assessed with the NDE and percentage of ND errors) was artificially overestimated by the four patients without ND errors and no pathological LBE (as the slope of the regression line increases when it passes closer to the zero point) we run separate analyses excluding these 4 patients from further analysis. There was still a highly significant correlation between the LBE and the NDE in the reduced ND patient group ($r=0.65$, $p=0.017$, $N=13$). The correlation between the LBE and the frequency of ND errors just failed to reach significance ($r=0.54$; $p=0.055$). Correlations of measurements of the whole sample are reported in Table 2.

4. Discussion

Several findings are apparent from our investigation. Firstly, there was a high and meaningful correlation between the CoR and the frequency of entire word omissions ($r=0.98$) whereas the correlation between the CoC and word omissions was also significant, but smaller ($r=0.59$). Secondly, we found that the LBE predicted the frequency of ND errors and the extent of the neglected letter string within single words (NDE). Finally, there was no prediction of the severity of ND (NDE and percentage of ND errors as well) by the CoC. We will discuss these findings in detail below.

4.1. Word omissions and the CoR

The higher correlation between the CoR and word omissions than between the CoC and word omissions indicates that the CoR is a better predictor for neglect-related (spatial) omissions of entire words in paragraph reading than the CoC. The results may be task-related: in cancellation tests the starting point is not relevant for performing the task. Neglect patients typically start searching for the targets – that are distributed between distractors – on the upper right side and prefer a leftward search direction (Rabuffetti et al. 2012). Furthermore, the attention is moved inappropriately across the page, without a spatially ordered search strategy and with a tendency for perseverations on right-sided target stimuli. Weintraub and Mesulam (1988) found that the search strategy of neglect patients tend to be erratic when the stimuli are in an unstructured array, leading to more omissions on the left side of the worksheet compared to structured stimulus arrays. In contrast, as the reading direction is from the left to the right in western cultures and the starting point is relevant for comprehending the text, neglect patients typically start reading further to the left as compared to the starting point in a cancellation task, despite their attentional bias to the right. In contrast to cancellation tasks, distractors are lacking in reading as every word is a relevant target. Hence, the patient's reading strategy with saccades from one word to the next is spatially more organized (at least in the horizontal domain) than their exploration strategy, leading to fewer omissions of and perseverations on words as compared to cancellation of targets. Therefore, the task to read a text may operate as a cue for directing spatial attention to the left side, which in turn leads to fewer omissions of words as compared to omissions of cancellation targets. As the patients' performance in a spatial cancellation task was only a weak and non-significant predictor for reading as a relevant everyday ability, paragraph reading tasks should be included in clinical neglect assessments.

Table 2
Pearson correlation coefficients of different measures in 17 patients with left visuospatial neglect.

Measure	NDE	ND%	LBE	CoC
ND%	0.42 (0.09)			
LBE	0.73** (0.001)	0.61** (0.009)		
CoC	0.28 (0.27)	0.41 (0.10)	0.59* (0.013)	
CoR	0.54* (0.27)	0.91** (< 0.001)	0.77** (< 0.001)	0.51* (0.035)

Abbreviations: NDE: Extension of neglected letters in relation to the word. ND%: frequency of neglect dyslexia errors. LBE: line bisection error (deviation to the objective middle of the line). CoC: center of cancellation. CoR: center of reading. Significance level.

* $p<0.5$.
** $p<0.01$.

4.2. Line bisection error predicts neglect dyslexia (ND) and neglect dyslexia extension (NDE)

In line with the results of Ptak et al. (2012) we found that the LBE predicts the frequency of ND errors. Additionally, we found that the LBE is also a good predictor for the extent of the neglected letter string of words in ND as another measure of ND severity besides the frequency of reading errors. Furthermore, *all* patients of our sample with ND errors showed a pathological rightward deviation in the line bisection task. By contrast, there was no significant correlation between spatial neglect assessed with the CoC and the severity of ND (NDE and percentage of ND errors as well). In our sample there were three patients (14, 15, and 17) who made neither ND errors nor showed a pathological rightward line bisection error. However, as these patients were impaired in the cancellation task this reflects a clear dissociation of spatial and word-based neglect related impairments. Our results suggest that ND and CN frequently occur together but are dissociable impairments which are due to two different pathological mechanisms.

Four of our patients (1,9,12, and 14) had a left-sided hemianopia with a visual field sparing of $<1^{\circ}$. Therefore, it could be argued that in these cases left-sided word based errors were caused directly by the visual field defect and were not related to neglect. However, there are several points that speak against this interpretation. Even if patients with left-sided hemianopia with a visual field sparing of less than 5° make left-sided word based reading errors, these errors are rare in patients without additonal neglect (Schuett, Heywood, Kentridge, & Zihl, 2008). In contrast, our patients with a visual field sparing $<1^{\circ}$ made left-sided word based reading errors (cases 1, 9, and 12) with a much higher error frequency (32.50%, 8.61%, and 3.80%). Furthermore, all these patients showed the neglect related ipsilesional and not the hemianopia related contralesional bias in the line bisection task which argues for a neglect-related origin of the reading errors. By contrast, in patient 14 the line bisection error was absent and he showed no left-sided word based errors, even with a visual field sparing $<1^{\circ}$. Therefore it can be concluded that the neglect syndrome was probably the main contributing factor for the reading errors in the patients with leftsided hemianopia (1, 9, and 12). However, we cannot entirely rule out that the reading performance of these patients was *additionally* impaired by their leftsided visual field defects.

A plausible explanation for the close relation between the LBE and the NDE is that lines and words share some physical features that could lead to (partly) similar visual processing. For example, the LBE as well as the number of omitted or substituted letters increases with the length of the stimuli (Bisiach et al., 1983; Halligan & Marshall, 1988; Hillis & Caramazza, 1991; Marshall, 1998; Tegner & Levander, 1993; Subbiah & Caramazza, 2000).

Another similarity is that lines and words both are elongated objects with a canonical left to right orientation. Therefore it can be speculated that neglect impairs reading and line bisection in the same way by shifting the patients' attention to the right side of the stimulus. This hypothesis is provided with evidence by oculomotor investigations. Angeli, Benassi, and Ladavas (2004) found that normal subjects systematically directed their saccades halfway between the beginning and the center of a word, in contrast patients with ND fixate about two letters more to the right compared to the control group. Ishiai, Koyama, Seki, Hayashi, and Izumi (2006) found a similar rightward deviation of the fixation point in neglect patients performing a line bisection task. These results suggest that patients with ND as well as patients who show a rightward deviation in line bisection do not explore the left, contralesional part of the stimulus properly.

Contrary to the results of Binder et al. (1992) but in line with Azouvi et al. (2002) we found a significant correlation between the LBE and CN. However, there were 3 patients (14, 15, and 17, cf Table 1) in our sample who showed no LBE but severe CN related deficits in the cancellation task. Furthermore, two patients (7, 10) showed a pathological rightward biased LBE (>5 mm; Schindler & Kerkhoff, 2004) but no impairments in star cancellation indicating a clear dissociation. Therefore, even if some neglect patients were impaired in both tasks (possibly through large lesions involving crucial areas for both tasks) the double dissociations in our study suggest independent pathological mechanisms.

As a limitation of our study, we could not analyze the lesion images of our patients as these were not available. This issue has to be addressed in future investigations.

5. Conclusions

The horizontal LBE predicts the presence (or absence) and the frequency of errors in patients with neglect dyslexia in a paragraph reading task. Moreover, it also predicts the extent of omissions or misspellings of letters or letter strings within single words in these patients, thus rendering it a highly useful diagnostic test in addition to cancellation, drawing or more functional tasks in the assessment of patients with visuospatial neglect (Azouvi et al., 2002; Halligan et al., 1989). Finally, the application of the CoC technique to paragraph reading tasks with a similar spatial layout as cancellation tasks proves to be a sensitive and reliable index of ND, which may complement the contribution of the CoC in cancellation tasks and thus give a more complete picture of the multiple deficits in neglect patients.

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Anhang D

Reinhart, S., Schaadt, A. K., Adams, M., Leonhardt, E., & Kerkhoff, G. (2013). The frequency and significance of the word length effect in neglect dyslexia. *Neuropsychologia*, *51*(7), 1273-1278.

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The frequency and significance of the word length effect in neglect dyslexia

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ABSTRACT

Neglect patients often omit or misread initial letters of single words, a phenomenon termed neglect dyslexia (ND). Omissions of whole words on the contralesional side of the page during paragraph reading are generally considered as egocentric or space-based errors, whereas misreading of the left part of a word can be viewed as a type of stimulus-centred or word-based, neglect-related error. The research of the last decades shed light on several effects of word features (such as written word frequency, grammatical class or concreteness) that modulate the severity of ND. Nevertheless, almost all studies about those modulating factors were case studies and some of them have not been replicated yet. Therefore, to date we do not know how relevant such effects of different word stimuli are for a *population* of ND patients. Knowing their incidence would improve our theoretical understanding of ND and promote the development of standardized ND assessments, which are lacking so far. In particular, case studies have shown that ND error frequency increases systematically with word length (word length effect, WLE) while other single case studies found contrary results. Hence, the existence of the WLE in ND is unsettled and its incidence and significance in stroke patients is unknown. To clarify this issue we evaluated the relation between word length and the extent (number) of neglected or substituted letters within single words in ND (neglect dyslexia extent, NDE) in a group of 19 consecutive ND patients with right hemisphere lesions. We found a clear WLE in 79% (15 of 19) of our ND patients, as indicated by significant correlations between word length and NDE. Concurrent visual field defects had no effect on the WLE in our sample, thus showing no influence of early visual cortical processing stages on the WLE in neglect dyslexia. In conclusion, our results suggest a clear relationship between word length and reading errors in ND and show that the WLE is a frequent phenomenon in ND.

1. Introduction

Patients with visual neglect after unilateral right brain lesions do not report, respond, or orient to contralesional stimuli (Heilman, Watson, & Valenstein, 2012; Kerkhoff, 2001). Neglect patients typically show left-sided omissions in cancellation or visual search tasks and a rightward deviation in horizontal line bisection (Schindler & Kerkhoff, 2004; Utz, Keller, Kardinal, & Kerkhoff, 2011) as well as conspicuous reading impairments (Lee et al., 2009; Ptak, Di Pietro, & Schnider, 2012). Left-sided visuospatial neglect can impair reading in different ways. Patients typically omit entire initial words of a text line (text or space related omissions; cf. Reinhart, Keller, & Kerkhoff, 2010; Reinhart, Schindler, & Kerkhoff, 2011). Additionally, several patients omit or substitute initial letters of (horizontally presented) *single* words to the left of an identifiable "neglect point", an impairment termed neglect dyslexia (ND; Ellis, Flude, & Young, 1987; Kinsbourne & Warrington, 1962). A recent study with neglect patients and normal controls (Weinzierl, Kerkhoff, van Eimeren, Keller, & Stenneken, 2012) found that even healthy subjects frequently produced omissions and substitutions of letters, when the task difficulty was adapted by reducing presentation time of the word. In contrast to matched healthy control subjects, a high frequency of omissions and high error rates at initial (left-sided) letter positions of the word were found to be neglect-specific in this study.

Even though ND is mostly related to contralesional hemispatial neglect (further termed CN; Vallar, Burani, & Arduino, 2010) the relationship between the two disturbances is unclear. Lee et al. (2009) found the severity of CN to be a significant predictor for the frequency of ND errors. In contrast, several double dissociations have been reported in group studies (Behrmann, Black, McKeeff, & Barton, 2002) and single case studies (Cantoni & Piccirilli, 1997; Costello & Warrington, 1987; Haywood & Coltheart, 2001; Patterson & Wilson, 1990; Patterson & Wilson, 1990). In a recent investigation we found that the line bisection error (LBE) predicted the presence as well as the severity of ND, indicated by the extent of the neglected letter string and the frequency of ND errors. In contrast, we found no significant correlations between these reading-related measures and visuospatial neglect measures in a cancellation task

Abbreviations: ND, Neglect dyslexia; NDE, Neglect dyslexia extent; CN, Contralesional spatial neglect; WLE, Word length effect.

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(Reinhart, Wagner, Schulz, Keller, & Kerkhoff, 2013). Moreover, in two further investigations we found that a manipulation of the egocentric reference frame by head rotation (Reinhart et al., 2010), or optokinetic stimulation (Reinhart et al., 2011) selectively reduced *egocentric* word errors such as omissions whereas the *stimulus- or word-based* ND errors remained completely unaffected by these manipulations in the same text reading task. These results suggest two different types of reading errors: egocentric versus word-centric errors. Taken together, there is some evidence that reading impairments in neglect can occur independently in the viewer-centered (left-sided omissions of whole words) and object-centered (left-sided letter omissions/substitutions within a single word) reference frames.

To date, ND was mainly investigated in several single case reports or few group studies with small sample sizes. Therefore, the incidence of ND is unclear. In the few studies with larger sample sizes incidences of approximately 20% (Lee et al., 2009; McGlinchey-Berroth et al., 1996) up to 50% (Bisiach, Meregalli, & Berti, 1990; Ptak et al., 2012) were reported. This rather broad variance of the reported incidences might be attributable to differences in the number of presented stimuli (e.g. 12 words (McGlinchey-Berroth et al., 1996) versus 40 words (Ptak et al., 2012)). or to lexical effects of different word stimuli. The presentation of compound words where reading only the second (right) part of the compound and omitting the first (left) part of it already makes sense by itself is likely to provoke more left-sided ND errors (Ptak et al., 2012) and the use of stimuli controlled for word frequency (Lee et al., 2009) might influence error frequency in yet another way.

The research of the last decades shed light on several effects of word features that contribute to ND (for a review see Vallar et al., 2010). Nevertheless, almost all studies about those contributing factors were single cases and some of them have not been replicated yet. Therefore, to date we do not know how relevant these effects of different word stimuli are for a *population* of ND patients. Without having incidences for effects of different word stimuli, it is difficult to determine critical factors contributing to ND that could explain several dyslexic symptoms of ND patients. Knowing those factors could deepen our theoretical understanding of ND and facilitate the development of appropriate, standardized ND assessments, which are lacking so far.

1.1. Word length effect (WLE) in neglect dyslexia (ND)

Several single case studies found a correlation between word length and error frequency in ND (Behrmann, Moscovitch, Black, & Mozer, 1990; Ellis et al., 1987; Di Pellegrino, Ladavas, & Galletti, 2001; Nichelli, Venneri, Pentore, & Cubelli, 1993; Riddoch, Humphreys, Cleton, & Fery, 1990; Subbiah & Caramazza, 2000; Tegner & Levander, 1993; Vallar, Guariglia, Nico, & Tabossi, 1996). Other single case studies reported contrasting results (Behrmann et al., 1990; Cantoni & Piccirilli, 1997; Costello & Warrington, 1987; Hillis & Caramazza, 1991; Miceli & Capasso, 2001). To the best of our knowledge, only one group study evaluated the word length effect on ND error frequency in seven brain damaged patients. Takeda & Sugishita, (1995) reported that only two of their seven patients had a (non significant) tendency to make more ND errors in longer words. However, as the authors noted, only these two patients made enough errors at all in the 50 presented words in order to enable a statistical analysis of this issue.

In most studies ND error frequency was exclusively used as a measure of the severity of ND investigating the word length effect. A word length effect on the *position of the neglect point* within the word as another measure of ND severity has been reported merely in four case studies (Ellis et al., 1987; Hillis & Caramazza, 1991; Riddoch et al., 1990; Tegner & Levander, 1993). To our knowledge, the only study investigating the relation between the position of the neglect point and word length in a large sample size ($n=64$) ND was that of Schwartz, Ojemann, and Dodrill (1997) in patients with complex partial seizures receiving a right hemisphere injection of sodium amobarbital. The authors reported a significant correlation of $r=0.65$ between the position of the neglect point in a word and the length of the letter string in this sample. However, no study has investigated this issue in a larger sample of *stroke patients* with ND.

All in all, the significance and incidence of the WLE in ND in right hemisphere stroke is unclear at present. Therefore, in this study we investigated the effect of word length on the *spatial extent of the neglected initial letter string* (termed neglect dyslexia extent; NDE), in a larger group of 19 consecutive ND patients with right hemispheric stroke. The obtained results would inform us about whether the word length is a critical factor for increasing the probability of ND errors.

2. Methods

2.1. Subjects

19 consecutive patients (seven female; mean age=60.79 years; SD=9.41) all with a single right-hemispheric, vascular brain lesion (mean time post lesion=14.21 weeks; SD=7.50) and moderate (at least 1.03% ND errors) to severe left-sided ND were included (Table 1). All patients had a moderate to severe left-sided contralesional spatial neglect according to the results of two tests (star cancellation and bisection of a 20 cm long horizontal line) comparable to those of the behavioral inattention test (Halligan, Marshall, & Wade, 1989; Wilson, Cockburn, & Halligan, 1987). All patients had a visual acuity of at least 0.80 (=80%) for the near viewing distance (0.4 m) – in which all experimental reading tasks were performed – and at least 9 years of education. The study was approved by the ethics committee of the Ludwigs-Maximilian-Universität, München/Germany, Project Nr. 352-09 in November 2009. The experiment was conducted in accordance to the Declaration of Helsinki II. All patients gave their informed consent prior to investigation. Binocular visual fields were mapped perimetrically with a Tübingen or Goldmann perimeter in all patients (details see Kuhn, Heywood, & Kerkhoff, 2010; results see Table 1). Dynamic visual perimetry was performed with a circular white target (Tübingen perimeter, luminance: 102 cd/m^2; size: 1.02°) or the V4 stimulus (Goldmann perimeter) in a completely dark room (see Weinzierl et al., 2012 for a more detailed description).

2.2. Experimental reading tests

We employed 45 short reading texts of different lengths (mean length: 51.7 words, range: 43–65; arranged in 8–10 lines) containing words of 2–11 letters from two story books (see Reinhart et al., 2010, 2011). The margins of each text were irregularly indented on both sides (see example in Fig. 1A). Indented paragraph reading tasks are a highly sensitive measure of the reading performance in neglect patients (Bachman, Fein, Davenport, & Price, 1993; Caplan, 1987; Towle & Lincoln, 1991) and are not confounded by differences in years of schooling (Bachman et al., 1993). Eight to ten words on every margin (left and right side) of each text were filler words (for example words as “a”, “but”, “in”, very”, often”, etc.) and were not necessary for understanding the semantic context of the text. The main message of the text could be understood even if most or all of these filler words were omitted. All texts were matched with respect to length (number of words, letters and lines) and spatial arrangement. The number of words displayed on each side of the reading texts was balanced (mean length left: 25.8 words, mean length right: 26.00 words). There was no statistical difference between the number of words presented on the left and right text side when all 45 texts were compared [$t(44)=0.34$, $p=0.76$]. The texts were displayed sequentially one by one within an $8\times24°$ large rectangular white field on a 17″—computer screen in 0.4 m distance to the observer. Texts were presented in black print (Arial, capital letters, point size 22) on a white background at a distance of 0.4 m to the patient's eyes. The midline of the computer screen was perpendicular to the patients' trunk midline.

Subjects were instructed to read out aloud five to eight of the 45 texts displayed sequentially on the screen. These texts were presented within one session of 30 min. Reading performance was scored simultaneously during the task on a paper printout of the same text displayed on the monitor. After each reading text a blank screen was presented and a short break of 1–2 min was given to the subject to avoid fatigue effects. No reading text was presented twice to any subject to prevent test repetition effects.

Table 1
Clinical and demographic findings of 19 patients with right hemispheric stroke and neglect dyslexia (see text for details). Correlations (Pearson's *R* or Spearman's rho[a]) between the position of the neglect point and the length of the letter string as an indicator for a word-length effect in ND.

Subject	Etiology	Lesion location	CoC	LBE	Field defect/field sparing (°)	Number of ND errors	Persons r/Speamans rho[a]	*p*-value
1	MCI	Parietal	+++	+++	HH; 5°	16	**0.83****	< 0.001
2	MCI	Parietal, temporal	+++	+	HH; 5°	13	**0.75**^{**,a}	0.003
3	MCI	Parietal, temporal	++	+	HH; < 1°	10	**0.98**^{**,a}	< 0.001
4	ICH, MCI	Parietal, occipital	++	++	HH; > 5°	21	**0.59****	0.005
5	ICH	Parietal	++	+++	HH; 5°	13	**0.67**^{*,a}	0.012
6	MCI	BG	++	+	Normal	6	0.16[a]	0.77
7	MCI	Temporal	++	++	Normal	21	**0.64****	0.002
8	MCI	Parietal, occipital	++	++	HH; < 1°	13	**0.58**^{*,a}	0.038
9	MCI	Parietal, temporal	++	++	HH; > 5°	24	0.33	0.11
10	MCI	Temporal	++	+	HH; < 1°	26	**0.69****	< 0.001
11	MCI	Parietal, temporal	+	++	HH; 5°	20	**0.77****	< 0.001
12	ICH	BG	+	+	QA; > 5°	13	0.37[a]	0.22
13	MCI	Thalamus, parietal	+	+	Normal	7	0.49[a]	0.26
14	MCI	Parietal, temporal	+	+	HH; > 5°	22	**0.59****	0.004
15	MCI	Parietal, temporal	+	+	HH; 5°	9	**0.66**^{*,a}	0.054
16	MCI	Parietal	+	+	HH; > 5°	13	**0.67**^{*,a}	0.013
17	MCI	Parietal, temporal	+	–	Normal	18	**0.54***	0.02
18	ICH, MCI	BG, frontal, parietal	–	+	QA; 5°	19	**0.56***	0.013
19	MCI	Frontal, parietal	–	+	Normal	6	**0.93**^{**,a}	0.008

Abbreviations: ICH: intracerebral haemorrhage; MCI: middle cerebral artery infarction; BG: basal ganglia. Visual field: Field sparing is indicated in (°) on the left horizontal meridian in the blind field for hemianopic field defects and on the oblique median in the patients with quadrantic field defects. Left HH: left homonymous hemianopia, left QA: left homonymous quadranopia. Classification of LBE severity according to the deviation in mm: – = 0 mm deviation, + = 1–33 mm; ++ = 34–66 mm; +++ > 66 mm rightward deviation (cf. < 1/3, < 2/3, or > 2/3 of the half line). Classification of CoC severity: – = 0; + = < 0.33; ++ = < 0.66; +++ > 0.66 (cf. < 1/3, < 2/3, or > 2/3 of the leftward cancellation bias).

[a] Spearman's rho was calculated when the number of ND errors was < 15, Pearson's *R* when > 15. Significance level:
* = $p < 0.05$.
** = $p < 0.01$.

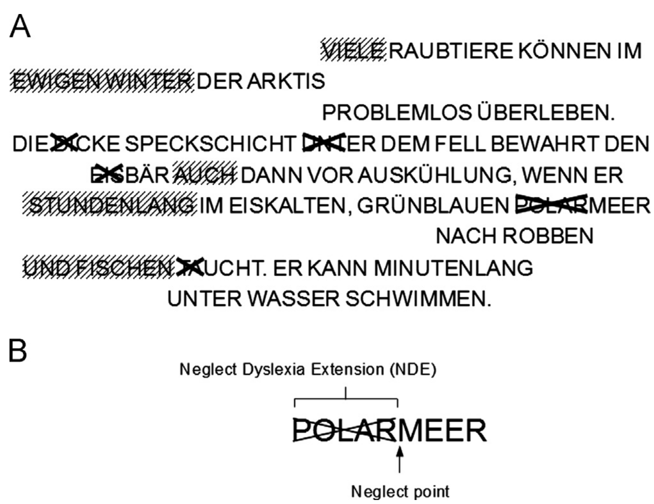

Fig. 1. (A) Example of an indented paragraph reading text. The patient made three ND substitution errors (**DI**CKE > **BA**CKE; **UNT**ER > **D**ER; **TA**UCHT > **S**UCHT) and two ND omission errors (**EIS**BÄR > BÄR; **POLAR**MEER > MEER) in this text. (B) Illustration of the neglect point (NP) and the neglect dyslexia extent (NDE) in a compound word with an omission error (**POLAR**MEER > MEER).

2.3. Scoring of reading errors in the experimental reading tasks

ND errors included omissions of left-sided letter(s), syllable(s) or half of a single word in compound words (i.e. 'keeper' instead of 'housekeeper') and part-word substitutions, when letter(s) or syllable(s) word parts were substituted (see Fig. 1A; i.e. 'house' instead of 'mouse'). The errors were classified following Ellis et al. (1987): Omissions or substitutions were counted as neglect dyslexia errors when the reading error was on the left side of the word and when the read word and the target word were identical to the right of an identifiable neglect point within the word. Additions of letters (0.48% of the reading errors) were rare and were not counted as ND errors. Complete word substitutions (0.81% of the read words) were also excluded from the analysis as they may constitute a qualitatively different category of reading problem that is not typical for *unilateral* spatial neglect, since no clear left–right difference with respect to the substituted syllables within the word is evident (Ptak et al., 2012). The extent of the neglected letter string (NDE) was calculated as the number of neglected (omitted or substituted) letters of the misread word on the left side of the neglect point (see Fig. 1 B).

3. Results

3.1. Word length effect

All statistics were computed with SPSS, version 19. ND errors varied between 1.03% and 38.89% (mean = 10.6%; SD = 10.9) across the patients. All patients made at least 6 ND errors. To examine whether there was a word length effect, correlations between the length of the misread word (mean = 7.86; SD = 3.24) and the position of the neglect point (mean = 3.14; SD = 1.89) were calculated for each patient. Nonparametric correlation coefficients (Spearman´s rho) were calculated for the individual word length effect if the number of ND errors was below 15; in all other cases parametric (Pearson) correlations were computed. A word length effect was significantly apparent in 15 of the 19 patients (Table 1). A significant WLE was even apparent in three of the five patients with intact visual fields (patients 7, 17, 19, see Table 1).

3.2. Subsequent analyses

To examine possible relations between neglect severity (performance in line bisection and star cancellation) and ND (error frequency and the percentage of omitted or substituted letters of the misread word on the left side of the neglect point) subsequent Pearson correlations were carried out for the whole group. The number of neglected targets in a cancellation task might not be an appropriate measure for the severity of CN as it gives no information about whether misses are evenly spatially distributed or whether there is a neglect-related contralesional spatial bias in the patient's performance. Therefore, the spatial bias in star cancellation was calculated with a procedure described in Binder, Marshall, Lazar, Benjamin, and Mohr (1992) and Rorden and Karnath (2010); center of cancellation, CoC. The CoC takes the spatial position of every omitted target into consideration and therefore reflects the spatial bias of patients in cancellation tasks as a continuous, reliable measure of the neglect severity (Rorden & Karnath, 2010). It can vary between −1 and +1 with values close to +1 indicating a severe rightward neglect in a patient who only canceled the rightmost targets (and vice versa for a score of −1). Performances with evenly distributed or without omissions reveal values of (close to) zero. As a continuous measure it can be used for parametric statistical analyses.

A similarity between the LBE and ND is that the line bisection error increases with the length of the line (Halligan & Marshall, 1988; Halligan et al., 1989). In a recent investigation (Reinhart et al., 2013) we found that the line bisection error predicts the severity of ND as indicated by the mean percentage of neglected initial letters relative to the length of the letter string. To examine whether this is true for the present sample the percentage of omitted or substituted letters of the misread word on the left side of the neglect point (further termed NDE%) was calculated by wordlength/position of the neglect point × 100 for further analyses.

The two measures of *visuospatial* neglect severity, CoC and LBE, correlated with $r=0.64$, $p=0.003$. There was a significant correlation between LBE and ND-error frequency ($r=0.48$, $p=0.039$) and a marginally significant correlation between LBE and NDE% ($r=0.43$, $p=0.063$). Correlations between CoC and ND-error frequency ($r=0.36$, $p=0.124$) as well as between CoC and NDE% ($r=0.30$, $p=0.207$) were not significant. The significant correlation between NDE% and ND-error frequency ($r=0.502$, $p=0.029$) indicates that patients who neglect more initial letters show also more ND-errors in total. Results are summarized in Table 2.

To examine whether the presence and the extent of the visual field defect (i.e. visual field sparing) interacts with ND severity (NDE% and ND error frequency), CoC in the star cancellation task, or the LBE, the group was split into patients with a residual visual field on the blind side ≤5° ($N=9$) versus >5° ($N=10$). There was no significant difference in any measure of neglect severity between the two groups of field defect severity (largest $t=1.31$, $p=0.206$; CoC in star cancellation). There was also no significant difference in the WLE correlations between the two groups [$t(17)=0.41$, $p=0.688$].

4. Discussion

We found a high incidence of the word-length effect in 79% of our ND patients, as indicated by a significant correlation between the length of the neglected letter string (NDE) and word-length. We will discuss these findings in the greater context of potential origins of the WLE in healthy readers, and will later propose a framework including three causative factors for the WLE in ND.

4.1. The origin and significance of the word-length effect in reading

The origin of the WLE is unclear so far. In healthy subjects without reading deficits the locations of the initial fixations on a word (landing position) are distributed around the center of the word (Di Pellegrino et al., 2001; Dunn-Rankin, 1978; Joseph, Liversedge, Blythe, White, & Rayner, 2009; Rayner, 1979). Inadequate landing positions are typically corrected with a re-fixation to a more optimal, central position (Joseph et al., 2009) and several studies demonstrated that readers refixate more often on low-frequency words as compared to high frequency words (Hyona & Pollatsek, 1998; Rayner, Sereno, & Raney, 1996; Rayner, 1998). As the focus of attention and the viewing direction of neglect patients are shifted to the right (Karnath & Rorden, 2011), a rightward deviation of the optimal landing position could be one factor causing ND. It seems plausible that, in longer words (as in bisecting longer horizontal lines), the initial landing position is shifted further to the ipsilesional, right side and therefore contributes to the WLE in ND. Pathological rightward deviations in the landing positions compared to healthy subjects were reported in a single case study of Di Pellegrino et al. (2001); patient F.C. They tracked the eye movements of F.C. during central single word reading and found that the landing positions for the first saccades were directed to the right side of the word. In contrast to healthy controls, where the landing positions fell slightly to *left* of the center of longer words, F.C.'s landing positions were displaced further to the *right* when the word lengths increased.

However, a pathological rightward landing position cannot be the sole explanation for ND errors as ND patients are able to read several (even long) words errorlessly. Lee et al. (2009) found that the probability of ND errors decreased when the word was frequent and meaningful (as compared to pronounceable nonwords and words with low written frequency). In contrast, ND patients make more ND errors when the stimulus is a compound and the right part forms a meaningful word (Ptak et al., 2012). Interestingly, beside the modulation by word length, the landing position of F.C. was also modulated by the lexical status of the presented letter string. It was displaced more towards the right for non words than for words (Di Pellegrino et al., 2001). Therefore, it can be assumed that the familiarity of the second (right-sided) part of a compound explains why a ND error is made in one word whereas the same patient reads another, comparably long compound errorlessly.

As a third factor, deficits in non-spatial attention (alertness and focused attention) might contribute to the severity of ND and the WLE. Several neglect patients suffer additionally from non-spatial attention impairments as those are also associated to right sided brain lesions (Husain & Rorden, 2003; Sturm et al., 2006). Impairments in alertness and focused attention should decrease error monitoring and therefore prevent corrective refixations. This idea is supported by (Behrmann et al., 2002) who found a strong relation between an accurate fixation of a word and the accuracy of the reading response.

In summary, we propose that (at least) three factors crucially increase the probability of ND errors as well as the severity of the WLE: (i) The pathological, rightward shifted landing position, which is (ii) not corrected when the residual right letterstring forms a familiar, regular word. (iii) Additionally, impaired non-spatial attentional functions may reduce error monitoring and thereby prevent corrections of misread words. We assume that the assessment or experimental manipulation of these three factors in

Table 2
Pearson correlation coefficients of neglect severity measures in 19 patients with left visuospatial neglect.

Measure	NDE%	ND%	CoC
ND% $M=10.63$ (SD=10.92)	**0.502*** ($p=0.029$)		
CoC $M=0.41$ (SD=0.28)	0.030 ($p=0.207$)	0.366 ($p=0.124$)	
LBE $M=29.56$ (SD=21.33)	0.434 ($p=0.063$)	**0.478*** ($p=0.039$)	**0.637**** ($p=0.003$)

Abbreviations: NDE%: Extent of neglected letters in relation to the word. ND%: frequency of neglect dyslexia errors. LBE: line bisection error (deviation to the objective middle of the line). CoC: center of cancellation. *M*: mean. SD: standard deviation. Significance level:

* $=p<0.5$.
** $=p<0.01$.

patient studies might increase our understanding of ND. However, as eye tracking data are lacking in our study and the words of the texts were not controlled in terms of the familiarity of residual word parts in compounds, this issue has to be addressed to further experiments.

4.2. Other issues

Not every patient showed a WLE in our sample. In fact, 4 patients did not exhibit the effect. A suitable explanation could be a lack of test power (as already hypothesized by Takeda & Sugishita, 1995) since the (non-parametric) correlation was calculated from only 6 or 7 ND errors in two of these patients. On the other hand, the remaining two patients made at least 13 ND errors without showing a WLE which indicates that the lack of statistical power due to few ND errors is unlikely to apply for all 4 cases without a WLE. Furthermore, there were 7 patients with a maximum of 13 ND errors in our sample who showed highly significant correlations of at least $r=0.58$ between NDE and word length. Another potential explanation could be that an additional visual field defect might moderate ND and thereby increases the WLE as found for pure alexia (Pflugshaupt et al., 2009). As a visual field of 3° to the left and 5° to the right of the fixation is sufficient for normal reading (Schuett, 2009) the WLE (i.e. correlation coefficients) should be smaller in patients with a sparing of the visual field $>5°$. Indeed, each of the 4 patients without a significant WLE had a normal left-sided visual field or a visual field sparing of $>5°$. However, we found no differences in ND error frequency, in NDE%, or in the WLE between patients with a residual visual field of $\leq 5°$ versus $>5°$. As can be seen in Table 1, there are several patients with a field sparing of 5° or beyond and even patients with intact visual fields who show a remarkable WLE. Therefore, visual field defects and field sparing appear to be unrelated to the presence or absence of a WLE in our sample of ND. This finding also suggests that the WLE in ND is probably not related to processing mechanisms in early cortical visual areas (probably close to V1), but emerges on higher processing stages where the length of the letter string is analyzed. A plausible anatomical explanation of the frequent co-occurrence of neglect and visual field defects might be that most of our patients, or ND patients in general (Ptak et al., 2012), had lesions that also disrupt the posterior visual pathways in the parietal, temporal, or more rarely also the occipital lobe.

We found that the LBE predicted ND severity (ND error frequency as well as – by trend – NDE%). However, there was no significant correlation between ND severity and CN severity as indicated by the spatial bias in a cancellation task (CoC). This is in line with several results (Behrmann et al., 2002; Ptak et al., 2012; Reinhart et al., 2013) and suggests that ND and CN are dissociable disturbances, underlying different attentional processes and/or spatial reference frames. Therefore, cancellation tests are not sufficient to assess all aspects of the neglect syndrome and specific tests of ND should be included in clinical assessment. More generally, these results support the view that neglect is no unitary disturbance but reflects a multi-componential, heterogenuous syndrome (Halligan, Fink, Marshall, & Vallar, 2003).

5. Conclusion

In summary, we found a high incidence of a WLE in our sample (15 out of 19 patients=79%) of ND patients, signifying it as a frequent phenomenon in right hemisphere stroke patients. Our findings replicate and extend earlier findings of Schwartz et al. (1997) in their epileptic patients obtained during Sodium Amobarbital injection. Furthermore, these results demonstrate that word length is a critical variable which influences the occurrence of ND errors in paragraph reading. As a practical consequence, longer words are more sensitive in eliciting ND errors and are therefore recommended for clinical use in assessment and rehabilitation.

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Anhang E

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Effects of head rotation on space- and word-based reading errors in spatial neglect

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ABSTRACT

Patients with right hemisphere lesions often omit or misread words on the left side of a text or the beginning letters of single words which is termed neglect dyslexia (ND). Two types of reading errors are typically observed in ND: omissions and word-based reading errors. The prior are considered as space-based omission errors on the contralesional side of the page, while the latter can be viewed as a kind of stimulus- or word-based reading errors where leftsided parts of a single perceptual entity (the word) are neglected. The head, trunk and eyes are part of a hypothetical egocentric reference frame that is aligned around our body and divides space into a left and right hemispace. Previous neglect studies have shown that head- and trunk-orientation significantly influence contralesional neglect. An open question is whether such egocentric manipulations also influence omissions and word-based errors in *paragraph* reading in ND. The current study investigated in a sample of right-hemisphere lesioned patients with ND vs. without ND and matched healthy control subjects the influence of head-rotation (HR) on both types of reading errors using controlled indented paragraph reading tests. Passive leftward HR significantly reduced omission errors on the left side of the text in ND, but had no effect on word-based reading errors. In conclusion egocentric manipulations like HR only appear to influence space-based attentional processes in neglect evident as omissions in paragraph reading but have no impact on those attentional processes involved in word identification evident as word-based errors in paragraph reading.

1. Introduction

Patients with unilateral brain lesions often show a conspicuous syndrome where they do not report or respond to stimuli presented in the contralesional hemispace in the absence of elementary sensory or motor deficits, termed neglect. Neglect is a multi-componential, heterogenuous syndrome that entails several different aspects (Halligan, Fink, Marshall, & Vallar, 2003). *Egocentric* neglect phenomena represent a category of various kinds of neglect where the reference frame is based on a midline projected from the body (Driver & Pouget, 2000). Importantly, there can be multiple frames of reference based on the body parts from where these midlines are projected (i.e. trunk, head, eyes, etc.). Hence, egocentric neglect phenomena concern the failure of the patient to attend to contralateral stimuli in space in relation to the mid-sagittal plane of the patient's body or certain body parts (Ventre & Flandrin, 1984). Typically, neglect patients show severe impairments in many egocentric tests of neglect that have been conducted so far (i.e. cancellation, visual and tactile exploration, writing, see for review Chokron, Dupierrix, Tabert, & Bartolomeo, 2007).

Another component of neglect is termed allocentric or object-centered neglect where the contralesional side of a single perceptual object is neglected irrespective of its location in space. Clinically, neglect patients often show impairments in object-centered neglect tasks such as drawing a symmetrical figure, perceiving or copying a face or eating from a plate (Halligan et al., 2003). Here, in contrast to egocentric neglect phenomena the patient's body (trunk, head, eyes, etc.) does not serve as a midline reference for the performance in these tasks, and therefore these impairments may occur with a similar frequency in both hemispaces.

Several studies have shown that ego- and allocentric neglect phenomena are dissociable and rely on different neural structures. Recent evidence has shown that allocentric or object-centered cancellation deficits (on the left side of *every* stimulus) were found after right superior temporal gyrus lesions whereas left egocentric neglect phenomena in the same cancellation task (omissions of stimuli in the left half of a page) were found after right pari-

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etal lesions (Hillis et al., 2005). In a related study (Ptak & Valenza, 2005) it was found that neglect patients with lesions involving the right inferior temporal cortex showed steeper left–right gradients in visual search for "object-like" displays. For these patients the left side of visual objects was more difficult to analyze, thus adding evidence to the role of right temporal cortex in object-centered visual processing. Convergent findings were obtained in another study (Grimsen, Hildebrandt, & Fahle, 2008). These authors studied visual search with specific displays and found that neglect-related impairments in an egocentric variant of their search tasks were associated with damage to the premotor cortex involving the frontal eye fields, while allocentric, object-centered neglect-related deficits were associated with lesions to ventral stream regions near the right parahippocampal gyrus. Taken together, these studies are consistent with the hypothesis that egocentric visual information processing is linked primarily to parieto-frontal brain areas in the dorsal stream (Vallar et al., 1999) whereas allocentric, object-centered visual processing is linked more closely to the areas in the ventral visual stream (Hillis et al., 2005; Honda, Wise, Weeks, Deiber, & Hallett, 1999; Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010).

In line with these dissociations based on different reference frames (egocentric vs. allocentric) task-dependent dissociations are often found in spatial neglect (Binder, Marshall, Lazar, Benjamin, & Mohr, 1992). These authors reported task-dependent anatomical dissociations in a group of 34 patients with right-hemisphere stroke. While patients with posterior lesions were mainly impaired in horizontal line bisection patients with frontal or deep lesions showed largely normal line bisection but impaired letter cancellation performance. Moreover, no significant correlation ($r = .39$) was obtained between both tasks in their patient group. These findings suggest separable components of the neglect syndrome which result from damage to discrete areas in the right cerebral hemisphere.

1.1. Neglect dyslexia (ND)

In addition to ego- and object-centered neglect phenomena in visual cancellation or visual search tasks, patients with spatial neglect often show impairments in reading termed neglect dyslexia (ND). During reading of *single* words these patients omit or substitute contralesional letters, syllables or half of a compound word (Behrmann, Moscovith, Black, & Mozer, 1990; Caramazza & Hillis, 1990; Ellis, Flude, & Young, 1987; Haywood & Coltheart, 2001; Ladavas, Umilta, & Mapelli, 1997; Riddoch, 1990). This feature of the neglect syndrome is considered to be a peripheral type of reading deficit induced by left-sided body-centered or object-centered inattention (Lee et al., 2009). During paragraph or text reading neglect patients often show omissions on the contralesional side of the text, and in addition word-based errors like omission of syllables or substitutes of leftsided letters within *single* words or substitutions of whole words.

The intensive research on single word reading in ND in the past two decades (see references above) has provided many important insights into the mechanisms of single word reading (Ellis et al., 1987), spared and impaired levels of performance in ND (Ladavas et al., 1997), the nature of object-centric "word-form" representations in the brain (Caramazza & Hillis, 1990), the identification of viewing-position effects (Stenneken, van, Keller, Jacobs, & Kerkhoff, 2008) as well as associations and dissociations with other forms of visuospatial neglect (Lee et al., 2009), to name only a few advancements in this field of research. In contrast to this huge progress in word-identification mechanisms in neglect dyslexia *paragraph reading* has been studied surprisingly rarely in ND up to now. Although paragraph or text reading subtests are often part of standard neglect screening batteries (see for instance the Behavioural Inattention Test, Halligan, Marshall, & Wade, 1989; Wilson, Cockburn, & Halligan, 1987) or the extensively validated French GEREN/GRECO neglect test battery (Azouvi et al., 2002), only few studies have so far dealt with the mechanisms of paragraph reading in comparable depth as those investigating single word reading in ND. Studies using the "Indented paragraph reading test" (Bachman, Fein, Davenport, & Price, 1993; Caplan, 1987; Towle & Lincoln, 1991) all have shown its high diagnostic sensitivity for neglect, partially because the indented margin on the left side requires frequent refixations by the patient. But even in these three studies mainly contralesional omissions were considered as dependent measures.

In an oculographic study of ND (Behrmann, Black, McKeef, & Barton, 2002) the authors had their patients read single words distributed randomly on a visual display comparable to a visual search task. Apart from reporting task-dependent dissociations of ND and visuospatial neglect they provided evidence that omitted (contralesional) words were often not fixated properly, while ipsilesionally presented words that were correctly read often were too often fixated. This dysfunctional oculographic pattern of results suggests a low-level visual impairment (i.e. eye-movement deficits) as one important source of reading errors in ND. Finally, in a recent treatment study we found that omissions in paragraph reading could be significantly reduced after repetitive optokinetic stimulation therapy whereas word-based neglect-related errors (i.e. substitutions, omissions of syllables within *single* words) persisted unchanged after treatment (Kerkhoff, Keller, Ritter, & Marquardt, 2006). This indicates that sensory stimulation do influence space-based or egocentric neglect phenomena as evident in the form of omission errors in reading but obviously failed to influence word-based errors in the same task in ND. This finding might also have implications for treatment because other novel therapies seem to be required if recent sensory stimulation techniques (Kerkhoff, 2003) are ineffective for the treatment of word-based errors in ND.

To sum up, much progress has been made in the past two decades in the understanding of the mechanisms involved in *single word reading* in ND. In contrast, less is known about the mechanisms involved in *paragraph reading* in ND apart from the fact that neglect patients are impaired in such tasks (see above). Even if one adopts the view that paragraph reading is not part of ND in a narrow sense but simply reflects spatial neglect it is indisputable that it is ecologically much more relevant for most of us than reading of single words presented in isolation. Paragraph or text reading is necessary in many different situations of daily living, including reading of a book, a newspaper, a journal article like this one, advertisements or a menu in a restaurant. Moreover, while studies involving single word reading have the clear advantage of allowing easy experimental control of relevant task variables (i.e. word length, frequency, etc.), paragraph reading allows to study both types of reading errors (omissions and word-based reading errors) in a more natural situation and may help to identify modulating factors. In turn, such findings might improve our understanding of the attentional mechanisms involved in paragraph reading in neglect patients.

The aim of the present study was therefore to analyse the influence of head-rotation (HR) – a well-known and effective manipulation of the egocentric reference (Chokron et al., 2007; Kerkhoff, 2001) – on omissions and word-based reading errors in right-hemisphere lesioned patients with ND, right-hemisphere lesioned patients without ND, and matched healthy normal subjects. While manipulations of the egocentric reference by modifications of head- or trunk-position (Karnath, Schenkel, & Fischer, 1991) or neck–muscle vibration (Schindler & Kerkhoff, 2004) have been shown to influence sensory neglect significantly only few experiments have investigated up to now their effect on reading. Interestingly, passive contralesional head-rotation by 20° as well as trunk-rotation by 20° significantly reduced ND in reading *single* words presented tachistoscopically in the center of the visual field (Schindler & Kerkhoff, 1997). Notably, the effects of head and trunk orientation were nearly equivalent in this study, suggesting comparable contributions.

The present study therefore addressed the following issues:

(i) Do modifications of the egocentric reference via manipulations of HR influence *both* types of reading errors (omissions and word-based errors)?
(ii) What is the quantitative relationship between the two types of reading errors in paragraph reading, and are there hemispace (left–right) differences in their frequency?

2. Methods

2.1. Subjects

Nine patients with right-hemispheric, vascular brain lesions and moderate to severe leftsided, visual neglect according to the results of conventional neglect screening tests (see below, Section 2.2) were included. Furthermore, another group of seven patients with vascular, right-hemispheric brain lesions without visual neglect in the same screening tests and comparable clinical and demographic criteria was investigated (see Table 1). In addition, 9 healthy subjects without brain damage (6 male, 3 female, age range: 33–67, mean age 46 years) were recruited. All subjects had a decimal visual acuity of at least 0.70 (20/30 Snellen equivalent) for the near viewing distance (0.4 m) and were appropriately corrected during the experiment. Moreover, all subjects had at least 9 years of education.

2.2. Visual field and visual neglect assessment

Kinetic monocular perimetry was performed in the majority of patients (N = 12) with a Tuebingen perimeter (Aulhorn & Harms, 1972) with a bright white stimulus (size: 106 min of arc of visual angle, luminance: 102 cd/m^2), a grey stimulus (106 min of arc of visual angle, 1.02 cd/m^2), a coloured target (green 525 nm, same size, 320 cd/m^2), and a form target (white light, same size, rhomboid, 320 cd/m^2). Kinetic perimetry was performed along all meridians in a pseudorandom order. Visual field sparing is indicated in Table 1 for the left horizontal meridian. In the remaining four patients kinetic Goldmann perimetry was performed monocularly with the largest test stimulus (V4) in the same way as described above.

Visual neglect was tested with three conventional tests, most of them very similar to those of the Behavioural Inattention Test (Halligan et al., 1989; Wilson et al., 1987): clock drawing from memory, figure copy (star, flower, cube) and paragraph reading of a 180-word reading test (Kerkhoff, Münβinger, Eberle-Strauss, & Stögerer, 1992). All screening tests were shown on a 29.7 cm × 20 cm white paper board – perpendicular to the patient's trunk midline – and at a distance of 0.33 m from the patient's eyes who wore his correction when required.

2.3. Experimental reading tests

As indented paragraph reading tasks are a highly sensitive measure of reading in neglect (Bachman et al., 1993; Caplan, 1987; Towle & Lincoln, 1991) and are not confounded by differences in education (Bachman et al., 1993) we constructed 45 short reading texts (mean length: 51.7 words, range: 43–65; arranged in 8–10 lines) of different length from two story books. The margins of each text were irregularly indented on *both sides* in order to enable comparisons of errors on the left vs. right text side; see examples in Appendixes A and B. Eight to ten words on every margin (left and right side) of each text were filler words and were not necessary for the semantic context of the text. This increases the sensitivity of the tests in ND. All texts were parallelized according to length (number of words, letters and lines), spatial arrangement and complexity as judged by the performance of the normal subjects. Each text was displayed sequentially one by one within a 8° × 12° large rectangular white field on a 17-in. computer screen. Texts were presented in black print (Arial, point size 22) on a white background at a distance of 0.5 m to the patient's eyes. The number of words displayed on each side of the reading texts was balanced (mean length left: 25.8 words, mean length right: 26.00 words). There was no statistical significant difference between the number of words presented on the left and right text side [$t(88) = 0.34$, $p = 0.73$].

2.4. Experimental conditions

The sequence of the experimental conditions was the following: the first and last experimental session served as baseline tests (Baseline 1, Baseline 2 with the head straight (0°)). This was done to control for possible learning effects throughout the study. The sequence of the second and third experimental session was balanced: in half of all subjects head-rotation to the left (20°) was followed by head-rotation to the right (20°), and vice versa in the other half of the subjects (see Fig. 1).

Under all conditions the subject's head was fixed in a head- and chin-rest and held there by one experimenter while the other preceded with the stimulus presentation. The subjects were instructed to read aloud everything they saw on the monitor in front of them. Reading was recorded with a tape-recorder for later off-line analysis, and simultaneously scored on a paper printout of the same texts displayed on the monitor. Five reading texts were presented during each experimental condition, their data were collapsed for each condition. Before starting the experiment two sample texts were presented to familiarize the subject with the procedure; these trials were not scored. No reading text was presented twice to any subject to exclude memory effects.

Table 1
Clinical and demographic data of 9 patients with left visual hemineglect due to a single vascular lesion of the right cerebral hemisphere (A, subjects $N+1$ to $N+9$), and 7 patients with a single right hemispheric infarction without leftsided visual neglect (B, $N-1$ to $N-7$). *Abbreviations*: ICB: intracerebral bleeding; MCI: middle cerebral artery infarction; BG: basal ganglia; MCA/PCA: middle cerebral artery infarction; L/R: left/right; Visual field: field sparing is indicated in (°) on the left horizontal meridian in the blind field. Neglect screening tests: paragraph reading of a 180 word reading test: cutoff max 2 errors, figure copy: − = omissions or distortions; + = normal performance; cancellation: number of omissions on the left/right side of the page; normal cutoff: max 1 omission per side.

Subject	Visual neglect	Age, sex	Etiology	Months post lesion	Lesion location	Field defect, field sparing (°)	Figure copy Left/right side	Clock drawing Left/right side	Reading (% errors)
A: Right brain damaged patients with left visual neglect									
$N+1$	Yes	55, f	ICB	9	Parietal	Left hemianopia, 5°	−/+	−/+	20
$N+2$	Yes	55, m	MCI	4	Thalamus, parietal	Normal	−/−	−/+	33
$N+3$	Yes	61, m	MCI	3	Temporal	Left hemianopia, 1°	−/+	−/+	10
$N+4$	Yes	55, f	MCI	3	Parietal, temporal	Left hemianopia, 5°	−/+	−/+	8
$N+5$	Yes	60, m	MCI	4	Parietal	Left hemianopia, 30°	−/+	+/+	22
$N+6$	Yes	68, m	MCI	4	Parietal, temporal	Left hemianopia, 20°	−/+	−/+	25
$N+7$	Yes	39, m	MCI	5	Parietal, temporal	Normal	−/+	−/+	35
$N+8$	Yes	45, f	MCI	9	Frontal, temporal	Normal	−/+	−/+	11
$N+9$	Yes	50, m	MCI	2	Temporal	Normal	−/+	−/+	8
Mean		54.2 years		4.9 (2–9)		5/9 impaired	9 impaired	8 impaired	19.1%
B: Right brain damaged patients without visual neglect									
$N-1$	No	29, f	MCI	1	Temporal	Normal	+/+	+/+	0
$N-2$	No	62, f	MCI	4	Frontal, parietal	Normal	+/+	+/+	1
$N-3$	No	44, m	MCI	6	Temporal	Normal	+/+	+/+	0
$N-4$	No	62, m	MCI	3	Temporal, basal ganglia	Left hemianopia, 5°	+/+	+/+	0
$N-5$	No	57, f	MCI	12	Parietal, occipital	Normal	+/+	+/+	1
$N-6$	No	50, f	MCI	4	Parietal, occipital	Left hemianopia, 20°	+/+	+/+	0
$N-7$	No	62, m	MCI	4	Temporal	Left hemianopia, 4°	+/+	+/+	1
Mean			52.2 years	4.8 (1–12)		3/7 impaired	0 impaired	0 impaired	0.1%

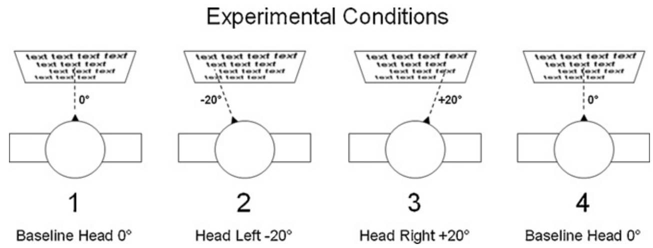


Fig. 1. Illustration of the four experimental conditions (see text for details). The rectangles indicate the subject's trunk, the circle the subject's head, and the black triangle the subject's nose. The head orientation is indicated by the stippled lines.

The testing room was dark and quiet to minimize distraction and the influence of other visual or auditory cues on reading. The observer distance was 0.5 m (from the subject's eyes to the monitor surface) in all experimental conditions, with all subjects wearing corrective glasses if necessary. After each reading text a blank screen was presented and a short break of 1–2 min was given to the subject. The whole experiment included frequent breaks and did not last longer than 30 min to reduce fatigue effects. To counter effects of spontaneous recovery all investigations were completed within 3 days in all patients, and within one session in the normal subjects.

2.5. Scoring of reading errors

The following two types of neglect-related reading errors were scored: (1) omissions of single words (each omitted word counted as 1 error). Completely omitted lines of text were not scored because they might represent a qualitatively different category of errors more related to oculomotor disorders (i.e. resulting from the left-sided field defect and/or saccadic disturbances) than to reading processes per se. (2) Word-based errors (errors on the left or right side of single words): these included omissions of leftsided letter(s), syllable(s) or half of a *single* word in compound words (i.e. keeper instead of housekeeper) and part-word substitutions, when letter(s), syllable(s) or half of a word was substituted (i.e. house instead of mouse). Whole-word substitutions were also excluded from the analysis as they might represent a qualitatively different category of reading problem that is not related to neglect. Appendixes A and B show an example of a representative patient with ND.

2.6. Data analysis

Data analyses were computed with SPSS, version 17. As there were ceiling effects in the RBD-control and the normal control group (see Sections 3.1 and 3.2 below), only the data of the neglect group were examined in analyses of variance for repeated measures (ANOVA). The dependent variables omission of words and word-based errors were calculated as relative errors (reading-errors divided by the *number of read words*). Note that for the calculation of relative word based errors the omitted words were not counted. Greenhouse–Geisser corrections of degrees of freedom were applied if appropriate.

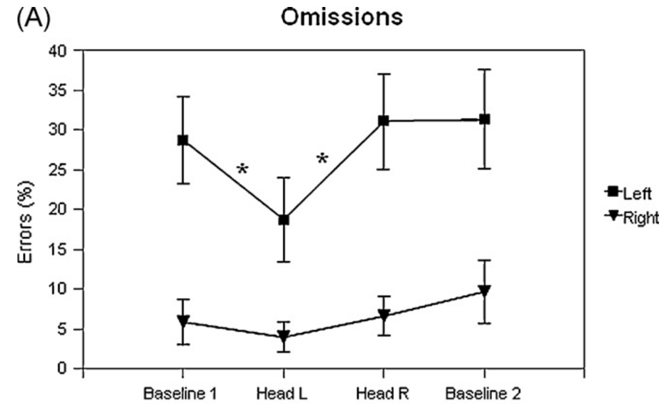
A Wilcoxon Ranks Test was computed to compare the change of relative reading errors across the experimental conditions. Therefore, the relative change of reading errors in each condition was calculated as first baseline (errors) minus head turned to the left side (errors) and this result was divided by the number of reading errors in the first baseline. This calculation was made to control for the differences in error frequency between word-based and space-based errors. The adopted level of significance was 5%.

3. Results

3.1. Distribution of errors in paragraph reading

Within the neglect patient group omissions accounted for 90.2% of all reading errors in ND, whereas word-based errors accounted for 9.8% of the errors. Omissions in the ND group showed a clear left–right-gradient, being significantly more frequent on the contra- as ipsilesional side of the text in the first baseline (56.4% vs. 15.8%). The same left–right-gradient was found within the category of the word-based reading errors (6.9% leftsided vs. 0.9% rightsided omissions *within* the word).

Although we excluded completely omitted lines during reading in the neglect group from our analysis (see Section 2.5, above), it may be qualitatively interesting to note that they accounted for only 1.8% of total errors and occurred in two neglect patients only. Finally, whole-word substitutions – which we also excluded from our analysis (see Section 2.5, above) – accounted for only 0.2% of all errors in paragraph reading.



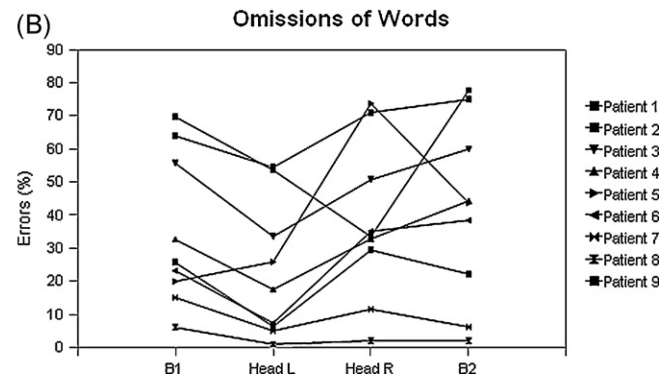


Fig. 2. (A) Mean percentage of spaced-based omission errors on the left and the right side of the text in the neglect patient group across the four experimental conditions. Error bars indicate standard error of the mean (SEM). The results of the two other subject groups (RBD patients without neglect and healthy control subjects) are not shown due to a floor effect in performance (<1% errors in any task). (B) Individual error percentages for left-sided omissions of the 9 neglect patients across all experimental conditions. Note that 8 out of 9 patients show a reduction of omissions selectively during left-ward head rotation in comparison to Baseline 1.

3.2. Omission of words

As only the neglect patient group committed a significant number of reading errors while the two non-neglect samples performed nearly errorless (see Appendix C for a survey of the mean number of omissions and word-based-errors) we limited the ANOVAs reported here and in Section 3.2 to the neglect patient group. The dependent variable omission of words was examined in an ANOVA with the within-subject factors Head Orientation (left, central, right) and Word Position (words presented in right or left hemispace). The main effects of Head Orientation [$F(1.62, 12.92) = 4.78$; $p = 0.034$], Error Position [$F(1, 8) = 31.17$, $p = 0.001$] and the Head Orientation × Error Position interaction [$F(3, 24) = 4.36$; $p = 0.014$] were significant.

Pairwise comparisons showed significant differences between Head Position left (Head Left) and all other head positions (Baseline 1; $p = 0.003$, Head Right; $p = 0.015$, Baseline 2; $p = 0.002$) for left sided omissions of whole words. Other comparisons (Baseline 1–Baseline 2, Head Right–Baseline 1; Head Right–Baseline 2) were not significant ($p > 0.27$ for each comparison). For the right text side, only the comparison between Head Left and Baseline 2 was significant ($p = 0.023$). Fig. 2 summarizes the results.

In addition to presenting group data (Fig. 2A) we present individual data of all neglect patients for leftward omission errors across all experimental conditions.

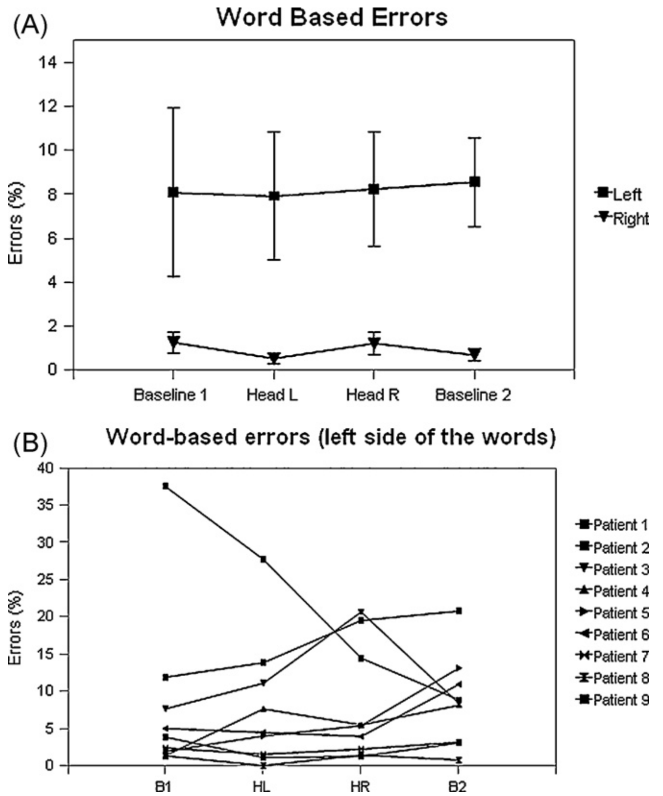


Fig. 3. (A) Mean percentage of word based reading errors on the left and the right side of single words in the neglect patient group across the four experimental conditions. The results of the two other subject groups (RBD patients without neglect and healthy control subjects) are not shown due to a floor effect in performance (<1% errors in any task). Note the different scaling of the *y*-axis in comparison to Fig. 2. Error bars indicate SEM. (B) Individual error percentages for word-based errors on the left side of words of the 9 neglect patients across all experimental conditions. Note that 8 out of 9 patients show no reduction of word-based errors during left- nor rightward head rotation in comparison to Baseline 1. Rather, a (non-significant) deterioration of performance is seen in Baseline 1 as compared to the other experimental conditions. Subject 2 showed a continuous reduction in word-based errors across all conditions and showed fewer errors in Baseline 2 vs. Baseline 1.

3.3. *Word-based reading errors*

Word based errors were examined in an ANOVA (which included only the neglect patient group, see Section 3.1, above) with the within-subject factor Head Orientation and Error Position (errors on the left or the right side of the word). The main effects of Head Orientation [$F(1.64, 13.14) = 4.89$; $p = 0.68$] and the Head Orientation × Error Position interaction [$F(3, 24) = 0.41$; $p = 0.74$] were not significant. Only the main effect of Error Position [$F(1, 8) = 16{,}74$; $p = 0.003$] was significant, showing that the neglect patients made more errors on the left side of the word (see Fig. 3).

In addition, we list individual error rates for omissions and word-based errors of every neglect patient and mean errors of the two nonneglecting samples in Appendix C. This shows that *each* of the 9 neglect patients committed more such leftsided word-based errors than both nonneglecting samples.

In addition to presenting group data (Fig. 3A) we present individual data of all neglect patients for leftward omission errors across all experimental conditions.

3.4. *Word-based errors compared with omission errors*

Here, we directly compared the modulatory effect of leftward HR in comparison to the first baseline on omissions and word-based reading errors. An ANOVA with the within-subject factors Head Orientation, Error Type (word-based error or spaced

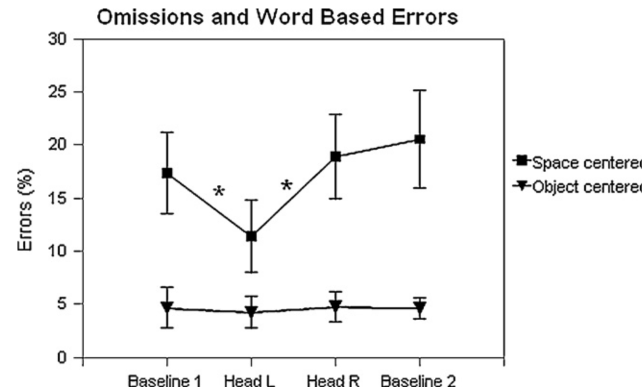


Fig. 4. Mean percentage of omissions and word based reading errors in the neglect group across the four experimental conditions. Error bars indicate SEM.

based error) and Error-Position (left or right side of the text or word) was computed. The main effects of Head Orientation [$F(3, 24) = 3.59$; $p = 0.028$], Error Type [$F(1, 8) = 22.47$; $p = 0.001$], Error Position [$F(1, 8) = 26.08$; $p = 0.001$] and the interactions (Head Orientation × Error Type [$F(3, 24) = 3.39$; $p = 0.034$] and Error Type × Error Position [$F(1, 8) = 17.89$; $p = 0.003$]) were significant. The interactions Head Orientation × Error Type × Error Position [$F(2.09, 16.78) = 2.31$; $p = 0.13$] and Head Orientation × Error Position [$F(1.43, 11.51) = 1.62$; $p = 0.23$] were not significant.

To examine whether HR affected the error types (word based vs. space based/omission errors) in a differential way, we examined the Head Orientation × Error-Type interaction more closely with pairwise comparisons. There were differences between Head Position left (Head Left) and all other head positions (Baseline 1; $p = 0.003$, Head Right; $p = 0.043$, Baseline 2; $p = 0.001$) *only* for omission errors. In contrast there was no significant effect of Head Orientation on word-based errors (all $ps > 0.53$).

A nonparametric (Wilcoxon Ranks) test was run to compare the change of error percentages (Head Left in relation to the first baseline) between the two error types (word-based and spaced-based/omission errors). The significant difference between the error types ($Z = -2.66$, $p = 0.008$) indicates that the reduction of space based errors (omissions) induced by HR was significantly higher than the reduction of word-based errors by leftward HR. Remember that we already showed in Section 3.2 (see above) that there was no significant difference in the frequency of word-based errors across the four experimental conditions in the neglect group. Together, these analyses underline the result that leftward HR significantly reduced omissions but not word-based reading errors in neglect. Fig. 4 summarizes the results of the neglect group when the two types of reading errors are considered independently of the side on which they occurred.

3.5. *Individual analyses of reading errors*

Finally, we evaluated whether the lack of any statistical effect of HR on word-based reading errors in our study might simply result from a lack of statistical power if only a minority of neglect patients in our sample actually might have shown such errors. Appendix C lists both types of reading errors (omissions and word-based errors) *individually* in every neglect patient in comparison to the minimum, maximum, and mean values of the two non-neglecting subject groups for the first baseline examination. As is evident from inspection of Appendix C, *every* neglect patient showed *both* types of reading errors. Second, although omission errors were more prominent than word-based errors in most of the patients, *every* neglect patient showed a higher rate of word-based errors in comparison to the mean error rates found in the

RBD-group without neglect and the healthy control group. These word-based errors are considered by some theorists as the “true” neglect dyslexia errors. Put differently: the lack of a statistically significant modulation of word-based errors by HR in the neglect group neither resulted from a scarcity of such errors nor from the theoretical possibility that only a minority of our neglect patients might have shown such word-based errors. In fact, none of the neglect patients performed normally with respect of word-based errors and therefore showed no ceiling-effect like the two non-neglecting subject groups. Hence, they could have improved their performance with respect to word-based errors significantly due to leftward HR but this did not occur. Appendixes A and B neatly illustrate this fact in a representative neglect patient: while leftward HR significantly reduced leftsided and in part also rightsided omissions the number of word-based errors (four) was identical during the baseline (straight head position, Appendix A) and during leftward HR (Appendix B). As no text was read twice during the experiments these word-based errors shown in Appendix B do not symbolize perseverations from a previously read text reading but stand for a specific problem in identifying the initial (hence leftsided) letters or syllables of words correctly in paragraph reading.

4. Discussion

Several findings are apparent from our study:

(i) Passive HR to the left, contralesional hemispace in the ND group significantly reduced omissions in the left hemispace and also in the right hemispace in comparison with Baseline 2. None of these results can be explained by learning effects or adaptation to testing procedures as the first and final baseline reading tests with a straight head position showed comparable performance in all subjects groups.
(ii) In contrast to the strong effect of HR on contralesional omissions, HR failed to influence word-based reading errors significantly. This non-effect was not due to a scarcity of word-based errors (some 8% of leftsided errors within single words were found in the neglect group vs. <1% errors in the two other samples). Furthermore this null-effect did not result from a lack of statistical power in the total neglect group as would have been the case if only a few patients had shown word-based reading errors. In fact, *all* 9 neglect patients showed omissions *and* word-based errors that were in *every* case more frequent than in any other person of the two nonneglecting samples (see Appendix C).
(iii) Omissions showed a clear left–right gradient in their frequency being more frequent on the contralesional vs. ipsilesional side. No hemispace difference was found for word-based reading errors but a clear left–right gradient was found with respect to the side of the errors *within* single words.

In the following we will discuss these findings and relate them to current theories of neglect and ND.

4.1. *Egocentric mechanisms affect omissions in paragraph reading in neglect*

HR had a powerful influence on omissions in ND, as can be seen from the significant reduction of nearly 35% in left hemispace when compared with the first baseline. The improvement in right hemispace was comparable (33% reduction) but it was only significant in comparison with the second baseline where the patients committed slightly more omissions than in the first baseline. These results corroborate previous findings which showed significant modulatory effects of head- and trunk-position on numerous neglect phenomena (for review see Chokron et al., 2007; Kerkhoff, 2001). The improvements of ND in right hemispace – though not significant in comparison to Baseline 1 – may result from two factors. First, ND was so severe in some patients, that they read only some 40–50% in right hemispace. In such cases HR may significantly improve performance in *both* hemispaces when we assume that their egocentric reference is shifted markedly to the ipsilesional side. In addition or alternatively, HR may have improved ND in right hemispace by activating nonlateralized attentional mechanisms which in turn might have improved ND in ipsilesional hemispace. Given the fact that HR is likely to influence neuronal functioning in parietal cortex (Duhamel, Bremmer, Benhamed, & Graf, 1997) and that human parietal cortex is also concerned with *nonlateralized* spatial attentional mechanisms (Husain & Rorden, 2003) it might be expected that contralesional HR could act on such mechanisms thereby leading to improvements of ND in ipsilesional hemispace. This hypothesis might be tested empirically in subsequent studies. Together, our present results extend the earlier findings mentioned above to paragraph reading in ND thus corroborating the importance of the head saggitale as one important physical “anchor” for spatial orientation on the page during paragraph reading. A contralesional, passive rotation of this body part shifts the egocentric reference towards the neglected hemispace which in turn reduces leftsided omission in ND. Animal studies support the view that the monkey parietal cortex is crucially involved in such egocentric computations as shown by the significant modulation of neural activity induced by manipulations of eye-, head- or trunk-position as obtained from single-cell recordings in parietal neurons (Andersen, Snyder, Bradley, & Xing, 1997; Brotchie, Andersen, Snyder, & Goodman, 1995; Duhamel et al., 1997). Functional imaging and human patient studies also corroborate this view and highlight the importance of the fronto-parietal network for egocentric spatial processes (Hillis et al., 2005; Vallar et al., 1999).

Interestingly, rightward HR did not significantly aggravate the deficit in the neglect dyslexics as compared to a straight head position. This finding mirrors several previous findings in related studies (Karnath et al., 1991; Schindler & Kerkhoff, 1997), who both found no further deteriorating effect of rightward HR as compared to straight HR in neglect patients. The most likely explanation for this finding is that performance in many neglect patients with severe ND was already maximally deviated to the right, ipsilesional side in the straight head position, so that no further deterioration was possible with rightward HR. This was obviously the case in 5 out of 9 neglect patients from our sample who omitted more than 75% of the text in the left half of the presented reading tasks.

In summary, the head sagittale makes an important contribution to the egocentric reference in ND thus influencing the occurrence of omission errors during paragraph reading. This has implications for the treatment of deficits in paragraph reading because it appears likely that manipulations of the egocentric reference (via head- or trunk rotation) or via sensory stimulation (neck–muscle vibration, optokinetic stimulation, etc.) will influence omissions in paragraph or text reading in ND. In fact omissions in text reading can be significantly reduced with such methods (Chokron et al., 2007; Kerkhoff et al., 2006; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002) while word-based errors during text reading remain unchanged after optokinetic stimulation therapy (Kerkhoff et al., 2006). Hence, alternative, novel treatments may be required in order to treat word-based reading errors in ND.

4.2. *Egocentric mechanisms and word-based errors in paragraph reading in ND*

In contrast to the strong effect of HR on omissions in ND a null-effect of the same manipulation was obtained in the same reading tasks for word-based errors. Theoretically HR could have influenced the frequency of word-based errors in our neglect sample in both directions (i.e. increased it during rightward HR or decreased it during leftward HR), but no such effect was induced. Rather, the manipulation of the egocentric reference seemed to be irrelevant for the occurrence of word-based errors. In contrast to this null-effect a previous study (Schindler & Kerkhoff, 1997) investigating reading of centrally presented *single* words in neglect patients showed significant positive effects of leftward head- or trunk-rotation to the neglected hemispace. It is important to note, that in this previous study exactly the same manipulation of head position by 20° to the left or right side was adopted in an even smaller patient sample ($N = 5$). How can these two findings be reconciled? A related study by Behrmann and Tipper (1999) showed in a sophisticated experimental setup that contralesional neglect may co-exist simultaneously in a space- and an object-based reference frame with different degrees of severity. Interestingly, these authors also noted that the degree of contralesional neglect in both frames of reference was influenced by task contingencies and attentional strategies, and that the object-based spatial representation in their experimental setup was somewhat weaker (p. 85). A parsimonious explanation of our present results and those of Schindler and Kerkhoff (1997) in light of the findings by Behrmann and Tipper (1999) may therefore be, that ND in text reading expresses itself in at least two distinct reference fames – at the level of the whole text (global level) and at the level of single words (local level). In single word reading the global level and the local level are identical (both are determined by the word) and the two reference frames (space- vs. object-based are completely aligned). We therefore assume here, that HR is likely to affect primarily the *global* level (text in paragraph reading and single words in word reading), but fails to influence the *local* level (word identification during paragraph reading). It will be interesting to test in subsequent studies whether this represents a "fixed" mechanisms related to HR or whether specific task instructions inducing either a more global or a more local task strategy during reading are capable of manipulating the degree of ND in space- vs. word-based errors.

An alternative, not necessary excluding hypothesis for the non-modulation of word-based errors in paragraph reading in our study might be that such word-related information is not processed primarily in the *dorsal* visual stream which is more devoted to egocentric spatial processing (Hillis et al., 2005; Vallar et al., 1999). Instead, "object-like" visual information which might convey important clues to the length of a word may be preferentially processed in cortical areas of the ventral visual stream (i.e. occipito-temporal cortex). Lesions to such areas in the right hemisphere give rise to contralesional deficits in visual search for object-like forms (Grimsen et al., 2008; Ptak & Valenza, 2005) and word-based reading errors in ND (Lee et al., 2009). HR may thus activate mainly parietal cortex in our patients which in turn leads to improvements in omissions but not in word-based errors as this latter error type may be preferentially processed in ventral stream areas which however are not influenced by head rotation.

Finally, another account of our results may be that our word-based reading errors are not to be considered as "true" object-centered neglect errors but rather as an indication of "relative egocentric neglect" (Driver & Pouget, 2000). These authors have argued that many claims of pure "object"- or allocentric neglect phenomena in fact can all be explained in purely egocentric terms, provided that relative egocentric position matters in addition to absolute egocentric position. In fact the dysfunctional eye fixation pattern reported in one ND study (Behrmann et al., 2002) according to which the lack of proper fixation of the word beginning is tightly coupled with incorrect reading of this word would fit to this account. Fixating single words more on the right, ipsilesional side of words would exactly create such a *relative* egocentric neglect pattern where letters to the left of the landing position of the saccade on the word during reading would be incorrectly processed thus leading to word-based errors. However, regardless of whether we conceive word-based errors as an expression of object-centric or relative egocentric neglect the non-modulation of such errors by HR in paragraph reading is an interesting phenomenon which requires further study.

4.3. Error analysis in paragraph reading in ND

As stated above, omission errors accounted for the great majority of all errors committed during text reading in the neglect dyslexics and showed a clear left–right gradient in their frequency. This is comparable to similar left–right gradients of performance in visual search or cancellation tasks in patients with visual neglect (for review see Kerkhoff, 2001). The non-spatial relationship of word-based reading errors in ND – hence their comparable frequency on both sides of the page – is in accordance with the results of studies on object-centered visual neglect, which have demonstrated that object-centered perception operates independently of the hemispace where the stimulus is presented in Humphreys and Riddoch (1995). In line with the findings that egocentric visual neglect in a cancellation task was much more frequent than allocentric (object-centered) visual neglect in the same task (Hillis et al., 2005) we also found that omissions were more frequent than word-based reading errors during paragraph reading in ND.

5. Conclusions

In conclusion, the present study clearly demonstrates the dissociative, highly specific effects of HR on reading performance in a paragraph reading in ND. The egocentric manipulation used here effectively influenced omissions but not word-based errors which has implications for theory and treatment of ND. On a theoretical level, the results confirm the independence of these two types of errors and suggest the dissociability of the underlying attentional processes. With respect to the treatment of ND it follows from our results that omissions can be cured with treatment approaches using manipulations of the egocentric reference (Chokron et al., 2007) while the less frequent but nevertheless relevant word-based reading errors probably require the development of alternate therapy approaches that specifically influence object-/word-centered attention in ND.

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Appendixes A and B.

Example of the reading performance of a neglect dyslexic patient in the first baseline (A) and with head turned to the left (B). Omissions are outlined, word-based errors encircled.

Appendix C.

Individual error data for left- vs. rightsided omissions (%) and left- vs. rightsided word-based reading errors (%) during the first baseline tests in the neglect patients (patient numbers correspond to those in Table 1). At the bottom of the table, the minimum, mean and maximum percentages of the Right-Brain-Damaged Control Group without neglect and the Normal control Group are indicated for comparison. Note that *every* neglect patient committed more omissions and more word-based errors than the worst subject (=max. error percentage) in any of the two nonneglecting control groups.

Patient	Space-based errors		Word-based errors	
	Left	Right	Left	Right
1	23.73	1.94	3.82	0.00
2	43.50	26.23	37.50	0.00
3	42.51	13.22	7.63	0.69
4	32.12	0.50	1.35	0.00
5	17.52	2.46	1.91	0.47
6	22.85	0.37	4.99	1.36
7	15.09	0.00	2.36	1.80
8	4.83	1.22	1.30	3.89
9	57.00	7.00	11.88	3.13
Controls				
Mean RBD (min–max)	0.17 (0–0.8)	0.00 (0–0)	0.34 (0–0.8)	0.63 (0–1.6)
Mean normal (min–max)	0.00 (0–0)	0.00 (0–0)	0.13 (0–0.4)	0.07 (0–1.2)

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Smooth Pursuit Eye Movement Training Promotes Recovery From Auditory and Visual Neglect: A Randomized Controlled Study

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Abstract

Background. No treatment for auditory neglect and no randomized controlled trial evaluating smooth pursuit eye movement therapy (SPT) for multimodal neglect are available. *Objective*. To compare the effects of SPT and visual scanning therapy (VST) on auditory and visual neglect in chronic stroke patients with neglect. *Methods*. A randomized, prospective trial was conducted. Fifty patients with left auditory and visual neglect were randomly assigned. Twenty-four patients completed SPT therapy and 21 patients VST. Five patients (4 VST, 1 SPT) were lost. Each group received 1-hour sessions of neglect therapy for 5 consecutive days totaling 5 hours. Outcome measures in visual neglect (digit cancellation, visuoperceptual- and motor line bisection, paragraph reading) and auditory neglect (auditory midline) were assessed twice before therapy, thereafter, and at 2-week follow-up. The SPT group practiced smooth pursuit eye movements while tracking stimuli moving leftward. The VST group systematically scanned the same but static stimuli. Both groups were divided into subgroups, and effects were separately investigated for mild and severe neglect. *Results*. Both groups did not differ before therapy in clinical/demographic variables or neglect severity (auditory/visual). After treatment, the SPT group showed significant and lasting improvements in all visual measures and normal performance in the auditory midline. Neither visual nor auditory neglect impairments changed significantly after VST. Moreover, the treatment effect sizes (Cohen's *d*) were considerably higher for visual and auditory neglect after SPT versus VST, both for mild and severe neglect. *Conclusions*. Repetitive contralesional, smooth pursuit training induces superior, multimodal therapeutic effects in mild and severe neglect.

Keywords

stroke rehabilitation, spatial neglect, auditory neglect, visual field, smooth pursuit eye movement

Introduction

Spatial neglect is a challenging and complex disorder.[1] Typically, it is characterized by an inability to respond to sensory stimuli (visual, auditory, tactile, olfactory) in the contralesional hemispace of a neurological patient.[1] Despite spontaneous recovery, approximately a third of all neglect patients present chronic neglect 1 year after stroke with major impairments in attention and perception.[2] Moreover, associated awareness deficits impair recovery[3] and interfere with treatment of hemiparesis.[4] Nevertheless, the past decade has seen substantial advances in neglect therapy, with studies showing that optokinetic stimulation (OKS) with pursuit eye movements,[5-7] attention training,[8,9] visuomotor feedback,[10] neck-proprioceptive training,[11] prism adaptation,[12] and transcranial magnetic stimulation[13,14] all effectively reduce *visual* neglect. However, few randomized controlled trials (RCTs) are available,[15,16] and the results of such trials do not necessarily confirm therapeutic effects of some interventions, such as prism adaptation.[17] In addition, no established treatment is available for *auditory* neglect, which is surprising given its frequency.[18] Only recently have researchers begun to investigate potential treatments for auditory neglect.[19,20]

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Recent studies using OKS with *s*mooth *p*ursuit eye movement *t*raining (SPT) via moving displays to the contralesional side showed substantial and lasting improvements in *visuospatial*[5,6,21] and *tactile* neglect.[7] These positive effects may result from the fact that pursuit eye movements are easier for subacute neglect patients than saccadic eye movements to the neglected hemispace.[22] Moreover, this type of stimulation activates multiple cortical and subcortical regions in healthy subjects (temporoparietal cortex, basal ganglia, brain stem, cerebellum[23-25]), some of which are involved in eye movements and gaze shifts. Primate studies[26] found largely congruent and overlapping receptive fields of neurons in the monkey's ventral intraparietal cortex. Crucially, these neurons have been shown to have bimodal properties by responding to visual *and* auditory spatial stimuli, thereby enabling the audiovisual integration of information into a modality invariant representation of external space. Accordingly, right temporoparietal lesions frequently cause visual *and* auditory neglect.[19] Recently, we showed a rapid but transient normalization of the subjective auditory midline in neglect patients after 20 minutes of SPT, persisting several hours poststimulation.[19] Moreover, 20 sessions of SPT induced lasting recovery from visual *and* auditory neglect in 3 patients.[19] In the present RCT, we attempted to clarify 2 issues: (*a*) Does repetitive SPT of 5 treatment sessions reduce visual *and* auditory neglect to a significantly greater extent than 5 sessions of standard visual scanning therapy (VST)? (*b*) Do these improvements remain stable for at least 2 weeks posttreatment?

Methods

Participants

Fifty stroke patients with left-sided neglect (time postlesion ≥ 1 month) were consecutively recruited provided they met the following inclusion criteria: right-hemispheric stroke with no previous history of cerebrovascular disease; signs of left neglect in at least 3 out of the 5 used visual neglect tests (perceptual/motor line bisection, single/double digit cancellation, paragraph reading; for description see Assessment, below, results in Table 1) and in the auditory midline test; no psychiatric disorder and no peripheral hearing deficit. In addition, only patients who were able to sit in a wheelchair for 50 minutes were selected. Finally a minimum stay in the clinic for 6 weeks was required to complete the study protocol. Sensorimotor disturbances were assessed by a neurologist, and visual fields were mapped perimetrically.[27] All subjects had at least 9 years of education and a corrected visual acuity of at least 0.70 (20/30 Snellen equivalent) for the near viewing distance (0.4 m). In total, 45 patients completed the study including the follow-up phase (Table 1). Five patients (4 VST group, 1 SPT group) were discharged before completing the study because health insurance providers declined further funding of the patients' hospitalization.

Study Design

Patients were allocated randomly to a treatment group by a person not involved in the study who drew cards from a sealed envelope after baseline 2. Every patient was examined in a single subject baseline design with a treatment-free interval of 2 weeks *before* treatment and an identical follow-up period of 2 weeks after treatment ended. Four assessments were carried out: 2 pretests resulting in 1 averaged baseline before treatment, a posttest, and a follow-up 2 weeks after the posttest. The treatment started immediately after the second pretest (Baseline) and consisted of five 50-minute sessions, held over a period of 7 to 9 days. Apart from this treatment all patients received standard occupational therapy and physiotherapy, but no other neglect or attentional training. Informed consent according to the Declaration of Helsinki II was obtained from all participants, and the study was approved by the local ethics committee (Bavarian Medical Association). Figure 1 summarizes the patient recruitment and retention.

Assessment and Outcome Measures

Cancellation. Patients were instructed to cancel with a pen in their right hand, all target digits (eg, all 20 number "8" items) distributed randomly among 200 single distractor digits ranging from "0" to "9" and presented on a 29 × 21 cm white piece of paper in front of the patient. This cancellation task was administered 3 times with a different target item at each measurement date. The number of omissions in the left and right hemifields was counted (maximum 10 per hemispace and task) and added across all 3 tasks resulting in a maximum of 30 omissions for each hemifield. In a more demanding dual cancellation version, 2 types of target digits (ie, all "1" and "9" numbers) had to be cancelled on 3 different sheets of paper that were identical to those in the single cancellation task (maximum 20 targets per hemispace). Cancellation tasks are reliable during repeated testing.[28] Moreover, dual cancellation tasks increase attentional load, produce more omissions, and are therefore more sensitive.[29]

Paragraph reading. Indented reading texts are highly sensitive for neglect in daily life[30] and were included to examine treatment transfer to a nontrained but important activity of daily living. Twenty parallel versions of a paragraph reading test were used.[31] Fifty-five words were arranged in 6 double-spaced lines with irregularly indented margins on both sides. Each text was printed in Arial 12 point font on a 25 cm × 9 cm sheet of paper. Five texts were presented successively in each session. The mean number of omissions across the 5 reading tests was calculated.

Table 1. Demographic/Clinical Data and Assessment Scores for Both Groups at Pretreatment 1 (Baseline 1).[a]

Sample Size	Visual Scanning Training (n = 21)	Smooth Pursuit Training (n = 24)	Statistical Comparison (*P*)
Stroke etiology	17 ischemic, 4 hemorrhagic	20 ischemic, 4 hemorrhagic	—
Parietal lesion	10	9	—
Temporal lesion	7	9	—
Frontal lesion	1	1	—
Occipital lesion	1	2	—
Subcortical lesion (thalamus, BG)	2	3	—
Months since stroke (mean, median)	Mean: 5.24 (1-34), Mdn: 3	Mean: 3.58 (1-10), Mdn: 3	.29
Age (years; range)	59.86 (36-73)	58.50 (37-74)	.64
Sex (male/female)	14/7	16/8	1.00*
Hemiparesis	19 left	23 left	.47*
Visual field defect; field sparing (°)	15/5°	19/6°	.55*
Neglect test 1: Perceptual line bisection (deviation in mm)	+18.99 right-sided (−15 to 65)	+25.15 right-sided (−2 to 94)	.47
Neglect test 2: Visuomotor line bisection (deviation in mm)	+15.93 right-sided (−13 to 60)	+19.54 right-sided (−2 to 88)	.57
Neglect test 3: Digit cancellation, single target (omissions left/right, max 10/10)	6.52/2.61 (0-10/0-9)	5.98/1.81 (0-10/0-9)	.59/.30
Neglect test 4: Digit cancellation, dual targets (omissions left/right, max 20/20)	11.11/5.00 (0-20/0-17)	11.77/4.64 (2-20/0-20)	.75/.81
Neglect test 5: Reading (omissions, max 55)	12.90 (0-44)	12.97 (0-47)	.99
Neglect test 6: Auditory midline (deviation from midline in °, max 90° left/right)	+13.71° right-sided (1-28)	+10.53° right-sided (−3 to 33)	.13

Abbreviations: BG, basal ganglia, Mdn, median.
[a]Mean values and ranges (in brackets) are reported. Neglect tests: Single/double digit cancellation: number of omissions on the left/right side of the page (cutoff: max 10% per hemifield); Perceptual/motor line bisection: horizontal deviation from true midline in mm (cutoff: ±5 mm); Reading: omissions and substitutions in a 55 word indented reading test; Auditory midline (cutoff: <−7° and >+4° deviation). *P*: 2-tailed statistical significance (*t* test, respectively, *chi-square test for categorical data). Note that only the primarily affected lobe is indicated in the table and that all patients had additional lesion locations in other lobes. For more details see Methods.

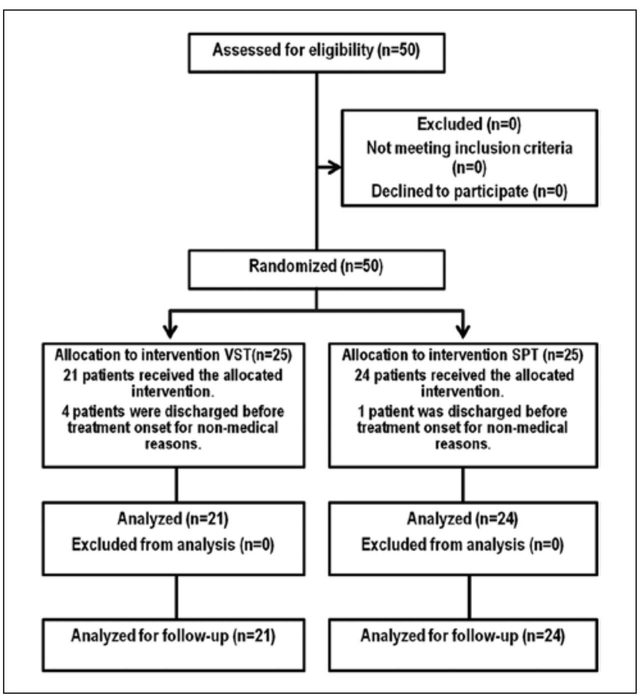

Figure 1. Flow chart of recruitment and retention.
Abbreviations: SPT, smooth pursuit training; VST, visual scanning training.

Line bisection. Two versions were used. In the perceptual version (10 trials) a 24 × 1 cm yellow horizontal bar against black background was presented centrally on a PC screen at a distance of 0.4 m from the patient. On the right side of the bar a small vertical black slit was visible (2 × 10 mm) that had to be positioned in the center of the bar. The objective center of the bar was aligned with the patient's body sagittal plane. The examiner moved the slit by key-press on the keyboard based on the patient's verbal feedback into the subjective midline position. In the motor version (3 trials) a 200 mm long and 5 mm wide black horizontal line was presented centrally on a 29 × 21 cm large white sheet of paper. The patient was instructed to bisect the line with the right hand using a pencil. The purpose of both tasks was to assess the possible transfer of treatment effects into perceptual and motor domains of visual neglect.

Auditory tests. The peripheral hearing functions in all patients were screened with a Philips HP 8741/31 pure-tone audiometer in a sound-shielded room. Hearing sensitivity (loss in dB) was within normal limits and showed no significant difference between the 2 ears and both treatment groups (all *P*s >.05). Auditory neglect was assessed with the auditory subjective midline test (details and normative values[19]). Subjects listened to *sound* stimuli (3 seconds of white noise, sound pressure level: 75 dB) sequentially presented over headphones (AKG K240), with a spatial resolution of 5° in front space. The starting position was pseudo-randomized between the 2 hemispaces to control for any bias. The subject's head rested on a head/chinrest while viewing a red central fixation spot (0.5°, 30 Lux). Subjects indicated whether the sound came from the left, right, or directly from their subjective midline position. Following each "left" or "right" response a new stimulus located 5° more toward the opposite direction of the perceived sound position was presented. This adjustment procedure was repeated until the subject indicated that the sound represented his subjective midline. Each session consisted of 20 trials with an equal number of 10 starting positions per hemispace.[19]

Treatments

SPT stimuli were presented on a 17-in. PC monitor (eccentricity: 44.8° horizontal, 34.8° vertical, refresh rate 75 Hz) in a distance of 0.4 m from the patient. The patients were instructed to look at computer-generated random displays of 30 to 70 dots (of all colors, size: 2° to 4°) on a dark background, all moving coherently toward the left, contralesional hemispace with a speed varying from 2.6° to 11.2°/s. Movement speed and the number of stimuli on the display changed from trial to trial to keep patients alert. Subjects were encouraged to make smooth pursuit movements toward the direction of the motion and return with their eyes to the ipsilesional side of the screen each time they reached the (contralesional) border of the screen. Eye movements were monitored by the therapist for the duration of the session from the side. No head movements were allowed and controlled by the therapist. Patients in the VST group received treatment using the same setup, device, and stimuli as for SPT. However, all visual stimuli were displayed *stationary.* Patients were instructed to scan the array systematically (horizontally, vertically) by starting on the top left corner and ending at the bottom right of the screen. Patients searched for specific target symbols on the display (ie, all red circles). Scanning strategies were repeatedly explained to the patients and the timing of treatment and breaks was identical to the SPT group. Patients were encouraged repeatedly to make (saccadic) eye movements to the left side. No head movements were allowed. Each SPT/VST therapy session consisted of 4 runs of 10 minutes duration, with short breaks (2 minutes) between these runs. Thus, the only crucial difference between the 2 treatments was in the moving versus stationary presentation of the visual stimuli, and in the type of eye movements exacted from the patient (voluntary saccades during VST vs pursuit eye movements and saccades during SPT).

Statistical Analysis

A series of mixed ANOVAs was carried out with Treatment (SPT vs VST) as between-group factor and Measurement Point (Baseline 1, Baseline 2, Posttest, Follow-up) as within-group factor. The chosen α level of .05 was Bonferroni-corrected for multiple comparisons (t tests). Additionally, both treatment groups were split into moderately versus severely impaired subgroups, and effects sizes in these subgroups were computed.

Results

Demographic Comparison of the 2 Treatment Groups at Treatment Onset

The 2 neglect groups did not differ significantly with respect to sex ($\chi^2 = 0.00$, $P = 1.00$), frequency of visual field defects ($\chi^2 = 0.36$, $P = .55$), presence of paresis ($\chi^2 = 0.52$, $P = .47$), age ($t[43] = -0.48$, $P = .64$), or time since lesion ($t[43] = -1.08$, $P = .29$). The clinical and demographic data are shown in Table 1.

Group Comparisons at Baseline

Separate univariate ANOVAs with the factors Group (VST and SPT) and Time (first and second baseline) were performed for each task to rule out spontaneous remission, repetition, or unspecific training effects between the 2 baselines as well as preexisting group differences. There were no significant main effects of Group in any of the measured variables (largest $F[1, 43] = 2.45$, $P = .124$ [Auditory Midline] and no significant Group × Time interactions [largest $F[1, 43] = 2.05$, $P = .16$ [Reading Omissions]). Therefore, the pretreatment performances of the SPT and the VST groups can be assumed to be comparable. A (marginally) significantly *deteriorated* second baseline compared to the first was found for the Dual Cancellation Test with less targets detected on the left side of the array ($F[1, 43] = 4.01$, $P = .052$). All main effects of Time were not significant either (largest $F(1, 43) = 1.10$, $P = .30$ [Reading Omissions]). These results indicate neither significant *improvements* from the first to the second baseline (indicative of spontaneous remissions) nor significant differences between the 2 experimental groups, nor significant Group × Time interactions. Based on these findings, all subsequent analyses ware carried out using data that were collapsed across both baseline measures.

Treatment Comparisons

Separate 2 × 3 ANOVAs with the factors Group (SPT and VST) and Time (pooled baseline, posttest, follow-up) were carried out for reading omissions, deviations in perceptual and motor line bisection, and the auditory midline task. The

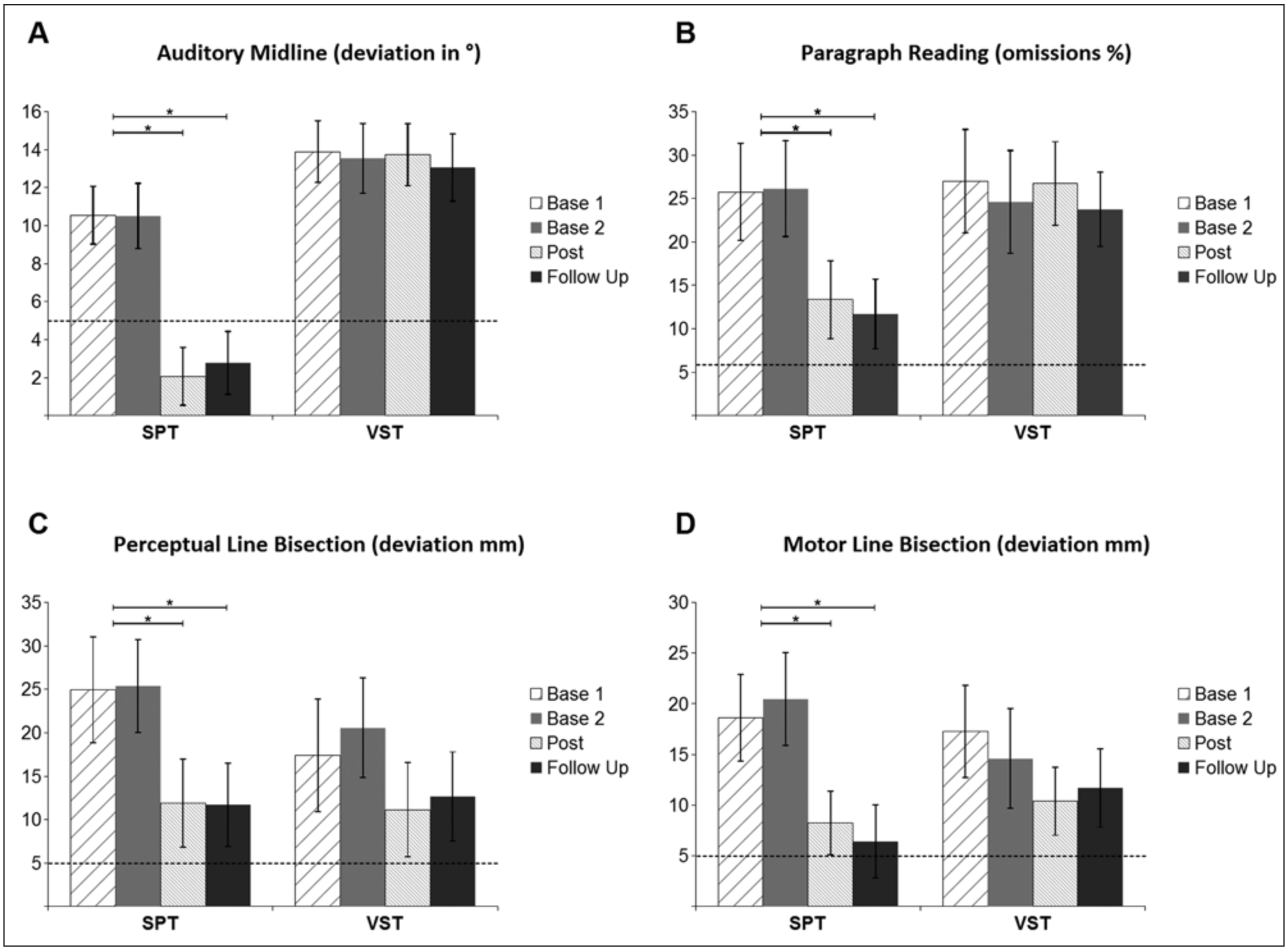

Figure 2. Effects of smooth pursuit training (SPT) and visual scanning training (VST) on the auditory midline task (A), paragraph reading (B), perceptual line bisection error (C), and motor line bisection error (D).
Mean values and standard errors (black error bars) of the mean are reported.*Significant with $P < .05$ (see statistics for details). Dashed lines: normal cutoff.

omissions in the Single and Double Cancellation tasks were analyzed using 2 × 2 × 3 ANOVAs with the factors Group (SPT and VST), Side (left or right sided omissions), and Time (pooled baseline, posttreatment, and follow-up). Greenhouse–Geisser corrections were performed if the sphericity assumption had been violated.

Auditory Midline

There were significant main effects of Time ($F[2, 86] = 7.22$, $P = .001$) and Group ($F[1, 43] = 25.10$, $P = .001$) as well as a significant Group × Time interaction ($F[2, 86] = 6.29$, $P = .003$). A further simple main effect analysis revealed a significant effect for SPT ($F[2, 42] = 15.31$, $P < .001$, $\eta^2_p = 0.422$) but not for VST ($F[2, 42] = 0.08$, $P = .919$, $\eta^2_p = 0.004$). Paired comparisons showed a significant reduction of the rightward deviation in the auditory midline after SPT from baseline to posttest (mean difference = 8.45, $P < .001$) and from baseline to follow-up (mean difference = 7.75, $P < .001$; Figure 2A), but no difference from posttest to follow-up ($P > .05$).

Paragraph Reading

The ANOVA yielded a significant main effect of Time ($F[1.58, 68.16] = 14.41$, $P < .001$) as well as a significant Group × Time interaction ($F[1.58, 68.16] = 11.37$, $P = .052$). There was no significant effect of Group ($F[1, 43] = 1.60$, $P = .213$). The main effect analysis was significant for SPT ($F[2, 42] = 22.20$, $P < .001$, $\eta^2_p = 0.515$), but not VST ($F[2, 42] = 1.27$, $P = .30$, $\eta^2_p = 0.057$). Paired comparisons revealed a significant reduction of omissions after SPT from baseline to posttest (mean difference = 6.30, $P < .001$) and to follow-up (mean difference = 7.12, $P < .001$; Figure 2B). Posttest and follow-up measures did not differ significantly ($P > .05$).

Perceptual Line Bisection

There was a significant main effect of Time (F[1.39, 59.88] = 10.47, P = .001) but no significant effect of Group (F[1, 43] = 0.09, P = .77), nor a significant Group × Time interaction (F[1.39, 59.88] = 1.04, P = .34) were found. The main effect analysis was significant for SPT (F[2, 42] = 5.90, P = .006, η_p^2 = 0.219) but not for VST (F[2, 42] = 1.47, P = .24, η_p^2 = 0.065). Paired comparisons revealed a significant reduction of the rightward deviation after SPT from baseline to posttest (mean difference = 13.27, P = .009) and to follow-up (mean difference = 13.42, P = .004; Figure 2C), while posttest and follow-up were not different (P > .05).

Motor Line Bisection

For motor line bisection there was a significant main effect of Time (F[2, 86] = 11.37, $P \leq$ .001). There was neither a significant Group effect (F[1, 43] = 0.69, P = .79) nor a significant Time × Group interaction (F[2, 86] = 2.38, P = .10). A simple main effect analysis was significant for SPT (F[2, 42] =8.07, P = .001, η_p^2 = 0.278) but not for VST (F[2, 42] = 1.37, P = .26, η_p^2 = 0.061). Paired comparisons revealed a significant reduction of the rightward deviation after SPT from baseline to posttest (mean difference = 11.29, P = .002) and to follow-up (mean difference = 13.12, P = .001; Figure 2D), while posttest and follow-up did not differ (P > .05).

Single Digit Cancellation

For the single digit cancellation task, a 3 × 2 × 2 ANOVA revealed significant main effects for Time (F[2, 86] = 14.37, P < .001), Side (F[1, 43] = 90.09, P < .001), and Group (F[1, 43] = 5.22, P = .027) as well as significant Group × Time (F[2, 86] = 5.91, P = .004) and Side × Time (F[2, 86] = 6.23, P = .003) interactions. The Group × Side (F[1, 43] = 0.96, P = .33) and the Group × Side × Time interactions (F[2, 86] = 2.16, P = .12) were not significant. A simple main effect analysis was performed to examine the effects of the different treatments separately. These analyses revealed significant effects for the SPT treatment on the left side (F[2, 42] = 19.47, P < .001, η_p^2 = 0.481) and on the right side (F[2, 42] = 6.23, P = .004, η_p^2 = 0.229) of the Single Number Cancellation task. Paired comparisons yielded a significant reduction of left-sided (mean difference = 2.78, P < .001) and a nonsignificant trend for a reduction of right-sided (mean difference = 0.90, P = .081) omissions after SPT from baseline to posttest. Both comparisons between baseline and follow-up were significant as well (left-sided: mean difference = 2.94, P < .001; right-sided: mean difference = 1.02, P = .003). No significant change was observed between posttest and follow-up (left/right side P > .05). There was no significant simple main effect after VST, neither for left-sided (F[2, 42] = 1.02, P = .37, η_p^2 = 0.046) nor for right-sided (F[2, 42] = 0.30, P = .74, η_p^2 = 0.014) omissions (Figure 3A and B).

Double Digit Cancellation

For double digit cancellation, a 3 × 2 × 2 ANOVA revealed significant main effects for Time (F[1.53, 65.79] = 22.07, P < .001), Side (F[1, 43] = 69.03, P < .001), Group (F[1, 43] = 4.08, P = .050), and significant Group × Time (F[1.53, 65,79] = 16.22, P < .001), Side × Time (F[1.76, 75.55] = 7.08, P = .002), and Group × Side × Time interactions (F[1.76, 75.55] = 3.66, P = .036). The Group × Side interaction (F[1, 43] = 1.08, P = .30) was not significant. A simple main effect analysis revealed significant effects for the SPT treatment on the left side (F[2, 42] = 24.04, P < .001, η_p^2 = 0.537) and on the right side of the array (F[2, 42] = 7.39, P = .002, η_p^2 = 0.260). Paired comparisons revealed a significant reduction of left-sided (mean difference = 7.23, P < .001) and right-sided (mean difference = 2.94, P = .001) omissions after SPT from baseline to posttest. Both comparisons between baseline and follow-up were also significant (left-sided: mean difference = 5.90, P < .001; right-sided: mean difference = 2.27, P = .007). No significant change was observed between posttest and follow-up (left/right side P > .05).

Again, there was no significant simple main effect for VST observable, neither for left-sided (F[2, 42] = 2.34, P = .11, η_p^2 = 0.10) nor for right-sided (F[2, 42] = 0.280, P = .76, η_p^2 = 0.013) omissions (Figure 3C and D).

Comparison of Effect Sizes for Subgroups With Mild Versus Severe Neglect

To compare whether the efficacy of the treatments was modulated by the severity of neglect, the groups were divided by median split into mild or severe neglect for each dependent variable. Cohen's d was computed for the posttreatment and the follow-up measurements as compared to the pooled baselines before treatment, separately for all split dependent variables. Effect sizes were considerably higher for SPT than VST therapy, both in the visual *and* auditory modalities, and for both severity subgroups. Importantly, all effects of SPT remained stable at follow-up (Figure 4).

Discussion

This first RCT of pure SPT showed widespread therapeutic effects on visual neglect, which generalized across perceptual and visuomotor tasks. Importantly, SPT also reduced auditory neglect. Immediate transfer of SPT to daily life tasks was observed for the paragraph reading test although reading was not trained. Interestingly, the improvements

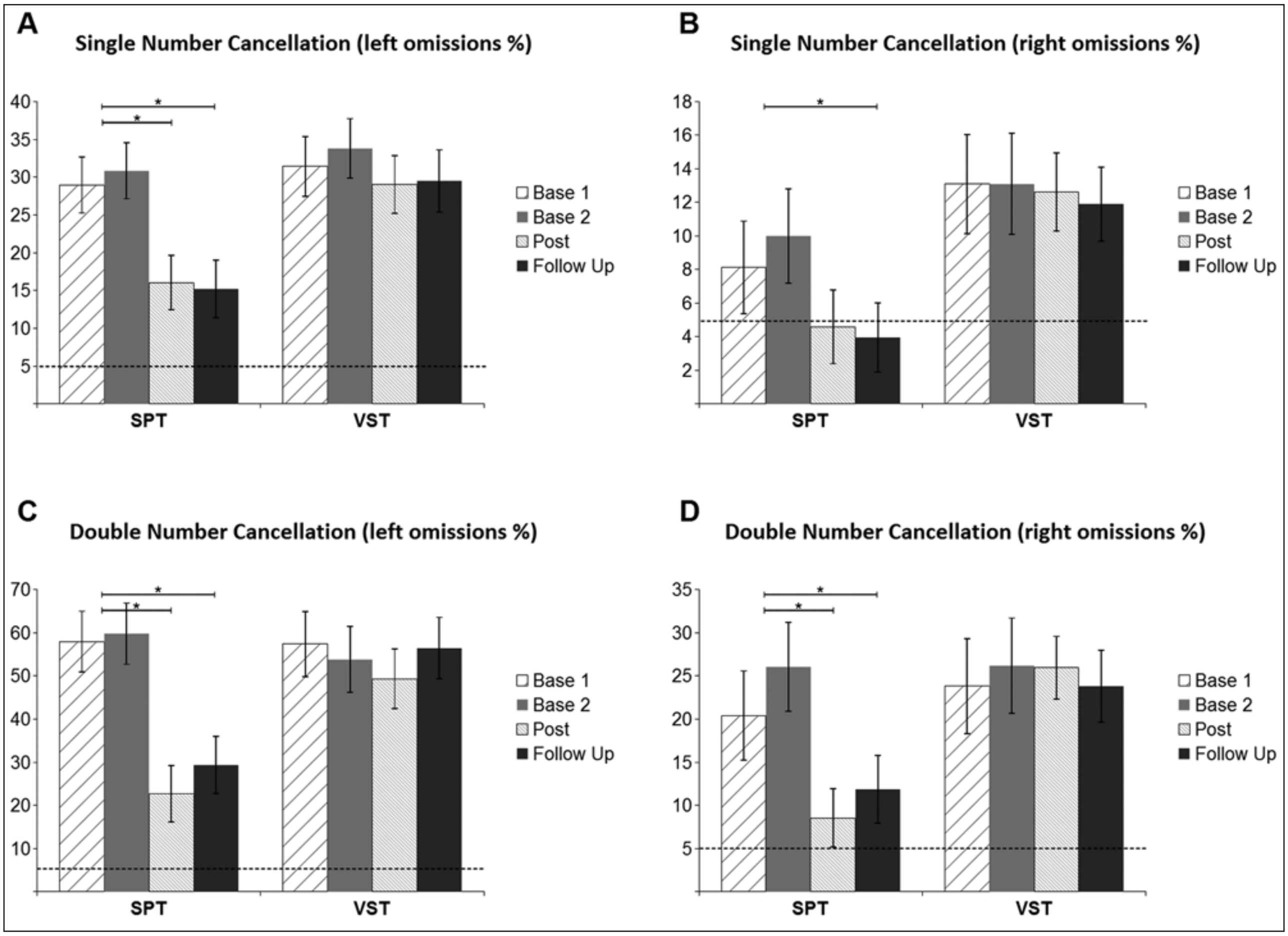

Figure 3. Effects of SPT and VST on the percentage of left-sided (A; contralesional) and right-sided (B; ipsilesional) omissions in single digit cancellation during 2 baseline measurements (Base 1, Base 2), after treatment (Post) and at follow-up. Analogue results for *dual* digit cancellation are shown for left-sided (C) and right-sided (D) omissions, respectively.
Mean values and standard errors of the mean (black error bars) are displayed. *Significant with $P < .05$ (see statistics for details). Note different scaling of *y*-axis in B, D as in A, C. Dashed lines: normal cutoff.

were strongest (Figure 3C and D) in the *dual* cancellation task, which may indicate improved attentional resources after SPT. In terms of efficacy, SPT was clearly more effective within this short treatment duration (5 hours) than conventional VST. Importantly, all effects of SPT remained stable at follow-up (Figure 4). Moreover, comparable treatment effects were obtained for moderately and severely impaired patients. By and large, these results concur with previous studies using similar methods for visual and tactile neglect,[5-7,19,21] and show for the first time that SPT significantly improves one component of auditory neglect: the auditory midline.

Functional imaging studies suggest a widespread activation of a cortico-subcortical network during OKS inducing smooth pursuit eye movements in healthy participants,[24,32] and hemianopia.[33] This network includes the occipitotemporal, parietal, insular and occipital cortex, basal ganglia, cerebellum, and the brain stem.[23,24,32] Moreover, this network is involved in gaze and attentional shifts,[23-25] which were explicit features of SPT. SPT may thus have improved neglect by recalibrating egocentric spatial orientation,[34] thus correcting the pathological, ipsilesional neglect bias into a more symmetrical midline position, and facilitating attention shifts to the neglected side.[35] Additionally, SPT may have activated the vestibulo-ocular system via optokinetic nystagmus. The cross-modal effect is probably related to multimodal space representations.[36] The parietal cortex is involved in visual/auditory space representations[26] *and* auditory-spatial attention shifts.[37] It also contains a modality-independent priority map, which is believed to be involved in spatial neglect.[38,39] Visual motion may induce stronger treatment effects because of dynamic features contained in moving displays eliciting smooth pursuit[40] and the multiple brain regions involved in visual motion processing.[41]

Figure 4. Mean effect sizes (Cohen's *d*) for the treatments and their stability in visual and auditory outcome measures, separately for mild versus severe neglect in the 2 treatment groups (VST = grey bars vs SPT = black bars). Negative bars indicate (nonsignificant) worsening of the performance.

A few limitations of our study should be mentioned: First, graphical overlays of MRI-lesion scans were not available, and functional outcome measures were not included. VST is the most often evaluated treatment for visuospatial neglect in neurorehabilitation.[15] Unfortunately, VST has several shortcomings such as no effect on *nonvisual* neglect (haptic[11]; auditory: current study), and the large number of necessary treatment sessions (20-40).[34] Moreover, no RCT is available documenting long-term efficacy of VST on functional disability. Therefore, more time- and modality-effective therapies are required to accelerate behavioral recovery from visual neglect, and also from auditory neglect, body-related neglect,[42,43] and extinction phenomena.[44] SPT is one such candidate because it acts multimodally, quickly, and is easily applicable.

Declaration of Conflicting Interests

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