Multiple Neglectphänomene und

Störungen der Vertikalenwahrnehmung

Neuromodulation durch GVS und deren klinische Implikationen

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Zusammenfassung

Der Schlaganfall ist die am meisten vertretende Erkrankung in der neurologischen Rehabilitation und stellt die häufigste Ursache von chronischen Einbußen in den westlichen Ländern dar. Infolge eines rechtsseitigen zerebrovaskulären Ereignisses (Hirninfarkt, Hirnblutung) können multiple Neglectphänomene und Störungen der Vertikalenwahrnehmung resultieren.

Unter einem Neglect (synonym Hemineglect, multimodaler Neglect, räumlicher Neglect) versteht man das Vernachlässigen von Reizen in der kontraläsionalen Raum- bzw. Körperhälfte. Es lassen sich unterschiedliche Phänomene, wie der egozentrische, objektzentrierte Neglect und Kombinationen daraus ebenso wie Einbußen in lebenspraktischen Fähigkeiten, wie beispielsweise beim Lesen und Schreiben, beobachten. Aktuelle Erklärungsmodelle sprechen für den therapeutischen Einsatz von "Bottom-Up"-Verfahren zur Symptomreduktion. Es konnten bereits unter Anwendung sensorischer Stimulationen längerfristige Therapieeffekte nachgewiesen werden. Allerdings eigenen sich nur wenige dieser Verfahren für den Einsatz in der Rehabilitation, da sie teilweise unangenehme Nebenwirkungen haben oder vom Klinikpersonal nicht angewendet werden können.

Die Störungen der Vertikalenwahrnehmung können den Raumorientierungsstörungen zugeordnet werden. In der Regel kommt es bei entsprechender kortikaler Schädigung zu einer kontraläsionalen Kippung der frontalen Hauptraumachsen, welche sich in diversen Modalitäten (visuell, haptisch, postural) nachweisen lässt. Auf der Verhaltensebene zeigen sich meist Einschränkungen in räumlichen Anforderungen des alltäglichen Lebens, wie dem Orientieren, Bewegen sowie Handeln im Raum. Zudem können Gleichgewichts- sowie Haltungsprobleme mit Fallneigung bei den Betroffenen beobachtet werden. Obgleich auch hier Erklärungsmodelle für einen Einsatz von Stimulationstherapie zur Reduktion der Symptomatiken sprechen, gibt es hierfür bislang kaum Wirksamkeitsstudien und klinische Anwendungen.

Bei beiden Störungen scheint das vestibuläre System, welches bei der Verarbeitung von Raum- und Körperinformationen zentral ist, eine wichtige Rolle zu spielen. Dieses kann als komplexes Strickleitersystem beschrieben werden, welches von den peripheren Vestibularorganen zum Hirnstamm führt, dortige Kernregionen sowie den Thalamus passiert und mit diversen multisensorischen Kortexarealen in Verbindung steht. Bei Schädigung kortikaler vestibulärer Kernzentren, die mit dem "multisensorischen Integrationssystem" assoziiert werden und am ehesten dem aus dem Tiermodell bekannten multisensorischen PIVC entsprechen (wie posteriorer insulärer Kortex und parietales Operculum), und angrenzender temporo-parietaler multisensorischer Regionen (wie superiorer temporaler

Gyrus und temporo-parietale-Junction) resultieren meist multiple Negectphänomene und Störungen der Vertikalenwahrnehmung.

Die galvanisch vestibuläre Stimulation (GVS) beinhaltet eine schwache elektrische Stimulation des Vestibulärsystems, bei der mittels zweier Elektroden (Kathode, Anode) hinter den Ohren des Probanden kutan subliminal Gleichstrom appliziert wird. Dadurch erfolgt eine "Bottom-Up"-Stimulation entlang der gesamten Projektionsbahnen des Vestibulärsystems, die bis in multisensorische vestibuläre Kortexareale reicht. Die GVS ist somit eine einfache, kostengünstige und sichere Methode zur „kognitiv-sensorischen“ Neuromodulation, die vernachlässigbare Nebenwirkungen aufweist und hinsichtlich möglicher Placeboeffekte gut kontrolliert werden kann.

Gegenstand der vorliegenden Dissertation ist es, das Potential der GVS als Stimulationsmethode zur Neuromodulation und/oder dauerhaften Behandlung „kognitiv-sensorischer“ Störungen bei Schlaganfallpatienten zu evaluieren. Dies erfolgt anhand von drei bereits publizierten Originalarbeiten. Publikation Nr. I ist eine ausführliche Übersichtsarbeit über die Transkranielle Gleichstromstimulation und die GVS und ihres jeweiligen Potentials zur Neuro- sowie Funktionsmodulation und Symptomreduktion kognitiver, sensorischer und emotionaler Störungen. Die zweite Studie ist eine Patientenstudie zur Modulation unterschiedlicher visueller Neglectphänomene (allozentrisch, egozentrisch, objektzentriert) durch die GVS (Publikation Nr. II). Publikation Nr. III evaluiert den Effekt von GVS auf die Störungen der Vertikalenwahrnehmung (visuell und haptische subjektive Vertikale) nach Schlaganfall. Studie I zeigt, dass die GVS in der Tat ein gewisses Potential für die Modulation kognitiver und sensorischer Störungen nach Schlaganfall hat. Allerdings sind hier auch noch zahlreiche Fragen ungelöst, wie etwa die Wirkung der unterschiedlichen Polarität (Kathode/Anode links vs. rechts), die optimale Intensität und Frequenz der GVS, mögliche Effekte von repetitiver GVS und wie die GVS mit anderen Therapieverfahren im klinischen Setting kombiniert werden kann. Studie II zeigt, dass die GVS nicht nur – wie aus theoretischen Überlegungen zum Vestibulärsystem naheliegend – *egozentrische* visuelle Neglectphänomene reduziert, sondern einen ebensolchen, kurzzeitigen therapeutischen Effekt auf objektzentrierte und allozentrische visuelle Neglectphänomene hat. Studie III zeigt – ebenfalls an Schlaganfallpatienten- dass subliminale GVS einen unmittelbaren positiven (Online)-Effekt hat auf die konstanten Fehler und die perzeptuellen Unsicherheitsbereiche bzw. variablen Fehler sowohl in der Subjektiven Visuellen als auch der Subjektiven Taktilen Vertikalen in der Frontalebene. Zusammenfassend zeigen die drei Studien, dass die GVS ein sowohl theoretisch interessantes als auch klinisch relevantes und praktikables Instrument zur Neuromodulation kognitiver und sensorischer Einbußen nach einem Schlaganfall darstellt. Mögliche Implikationen, offene Fragen und Limitierungen der drei Studien werden diskutiert.

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

Inhaltsverzeichnis

Liste der drei Originalarbeiten

Utz, K. S., Dimova, V., **Oppenländer, K.,** & Kerkhoff, G. (2010). Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology - a review of current data and future implications. *Neuropsychologia, 48*(10), 2789-2810.

Oppenländer, K., Keller, I., Karbach, J., Schindler, I., Kerkhoff, G., & Reinhart, S. (2015a). Subliminal galvanic-vestibular stimulation influences ego-and object-centred components of visual neglect. *Neuropsychologia*, *74*, 170-177.

Oppenländer, K., Utz, K. S., Reinhart, S., Keller, I., Kerkhoff, G., & Schaadt, A. K. (2015b). Subliminal galvanic-vestibular stimulation recalibrates the distorted visual and tactile subjective vertical in right-sided stroke. *Neuropsychologia*, *74*, 178–183.

Abbildungsverzeichnis

Abkürzungen

fMRT	funktionelle Magnetresonanztomographie
GS	galvanische Stimulation
GVS	galvanisch vestibuläre Stimulation
INC	Nucleus interstitialis Cajal
ISO-map	integrated Space-Object map
KVS	kalorisch vestibuläre Stimulation
LBA	longitudinale Body Axis
NET	Neglect-Test
OKS	optokinetische Stimulation
OTR	ocular tilt Reaction
PIVC	parieto-insulärer-vestibulärer Cortex
rACM	rechte Arteria cerebri media
SPV	subjektive posturale Vertikale
SV	subjektive Vertikale
SVV	subjektive visuelle Vertikale
STG	superiorer temporaler Gyrus
STV	subjektive taktile Vertikale
tDCS	transcranial direct current Stimulation
TPJ	temporo-parietale-Junction
VN	Nuclei vestibularis
VOR	vestibulo-okulären Reflex

1 Multiple Neglectphänomene

1.1 Störungsbild

Der Neglect als neuropsychologisches Störungsbild umfasst ein komplexes, multimodales und multiphänomenales Syndrom. Die klassische Ätiologie ist ein Schlaganfall, bei dem das Stromgebiet der rechten Arteria cerebri media (rACM) betroffen ist und daraus ausgedehnte Läsionen in rechtshemisphärischen Arealen resultieren (Vallar et al., 1986, Leibovitsch et al., 1998). Typischerweise zeigt sich der Neglect (Synonyme: halbseitige Vernachlässigung, räumlicher Hemineglect) als eine neuronal bedingte Verhaltensstörung, bei der die Patienten nicht mehr in der Lage sind, sensorische Reize in der zur Schädigung kontralateralen Raum- bzw. Körperseite wahrzunehmen bzw. auf diese ihre Aufmerksamkeit zu lenken und adäquat zu reagieren (Karnath, 2012). Die halbseitige Vernachlässigung kann verschiedene Sinnesmodalitäten (visuell, taktil, somatosensibel, auditorisch, olfaktorisch) sowie motorische Funktionen betreffen, ohne dass ursächlich eine primäre Störung, wie Hemianopsie, Hemiparese oder Hemianästhesie vorliegt (Kerkhoff, 2004).

1.2 Diagnostik

Die multiplen Neglectphänomene manifestieren sich in diversen diagnostischen Untersuchungen. Bei sogenannten egozentrischen Tests werden raumbasierte Aufmerksamkeitsleistungen erfasst. Typische Aufgaben sind etwa das Explorieren, Bearbeiten und Kopieren von visuellen und taktilen Vorlagen sowie Lesen und Abschreiben. Die egozentrischen Neglectphänomene äußern sich in einem kontralateral zur Läsion lokalisierten Aufmerksamkeitsdefizit beim Erfassen von Stimuli, welche sich in der kontraläsionalen Raumhälfte befinden (Ferber et al., 2002). Das egozentrische Referenzsystem stellt hierbei der Körper dar, wobei die sagittal verlaufende Körpermittelachse (hier vor allem Augen, Kopfmitte und Rumpfmitte als "Anker") den Raum in eine kontraläsionale und eine ipsiläsionale Hälfte teilt (siehe Abb. 1.1).

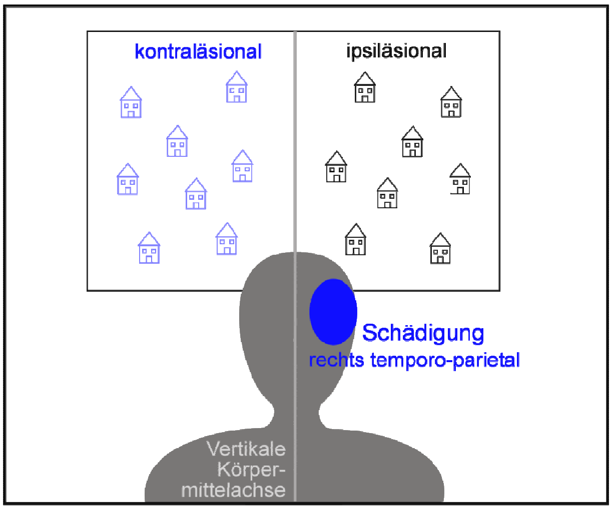

Abb. 1.1 Bei einem Patienten mit rechts temporo-parietaler Läsion wird der egozentrische Raum durch die sagittal verlaufenden Körpermittelachse in zwei Hälften (ipsi-, kontraläsionale) geteilt. Während auf einer visuellen Vorlage die ipsiläsional gelegenen Objekte (schwarze Häuser) bearbeitet werden können, kommt es zu Auslassungen (blaue Häuser) auf der kontraläsionalen Seite.

Ein davon abzugrenzendes Phänomen stellt der objektzentrierte Neglect dar. Dieser zeigt sich beim Wahrnehmen, Bearbeiten und Kopieren von *einzelnen* perzeptuellen Objekten im Raum. Soll ein Patient beispielsweise symmetrische Objekte wie Uhren, Blumen oder Häuser abzeichnen, kommt es zu Auslassungen von kontraläsionalen Objektdetails (Karnath, 2002). Befindet sich dieses Objekt immer an derselben Position im egozentrischen Referenzsystem des Betrachters, z.B. auf der Körpermittelachse, so kann der objektzentrierte Neglect unabhängig von egozentrischen Neglectphänomenen festgestellt werden. Das Referenzsystem stellt hierbei das Objekt selbst dar und die vertikale Objektmittelachse teilt dieses in zwei Hälften (kontraläsionale, ipsiläsionale) (siehe Abb. 1.2).

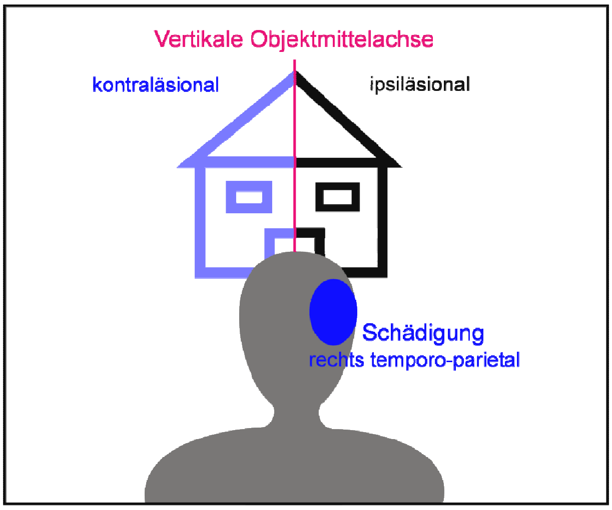

Abb. 1.2 Ein Patient mit rechts temporo-parietaler Schädigung soll ein bestimmtes Objekt im Raum explorieren. Hierbei stellt das Objekt selbst das Referenzsystem dar und wird durch die vertikale Objektmittelachse (pinke Linie) in zwei Hälften (ipsi- und kontraläsional) geteilt. Während die rechten Objektdetails (schwarz markiert) wahrgenommen werden, kommt es zur Vernachlässigung von links gelegenen Objektteilen (blau markiert).

Die Kombination aus egozentrischen und objektzentrierten Wahrnehmungs- bzw. Aufmerksamkeitsleistungen ermöglicht uns im Alltag das Zurechtfinden im Raum sowie das

Erfassen von für uns bedeutsamen Stimuli, wie Gegenstände, Personen oder Gefahrenquellen im Raum. Es gibt neuropsychologische Untersuchungsmethoden, welche dieses Zusammenspiel aus egozentrischem und objektzentriertem Neglect (auch bekannt als allozentrischer Neglect) erfassen. Hierbei wird das Ausmaß der Vernachlässigung von kontraläsionalen Objektdetails durch die Positionierung der Objekte im egozentrischen Raum bestimmt. Ein häufig verwendeter Test ist die im NET (Fels, Wilson & Geissner, 1997) enthaltene Linienhalbierungsaufgabe, bei der auf einem DIN A4 Blatt (Querformat) drei waagerechte Linien treppenförmig angeordnet sind. Der Patient soll jeweils die Mitte dieser Linien schätzen. Die objektzentrierte Vernachlässigung zeigt sich in einer ipsiläsionalen Verschiebung der subjektiven Linienmitte und vergrößert sich, je weiter die Linie im kontraläsionalen egozentrischen Raum liegt (siehe Abb. 1.3). Eine andere Methode zur Untersuchung dieser beiden Neglectkomponenten (ego- vs. objektzentrisch) ist beispielsweise der „Apples-Test“, bei dem der Patient Äpfel auf einem Blatt ausstreichen muss, manche mit einem Wurm drin, manche ohne einen solchen (Bickerton et al., 2011).

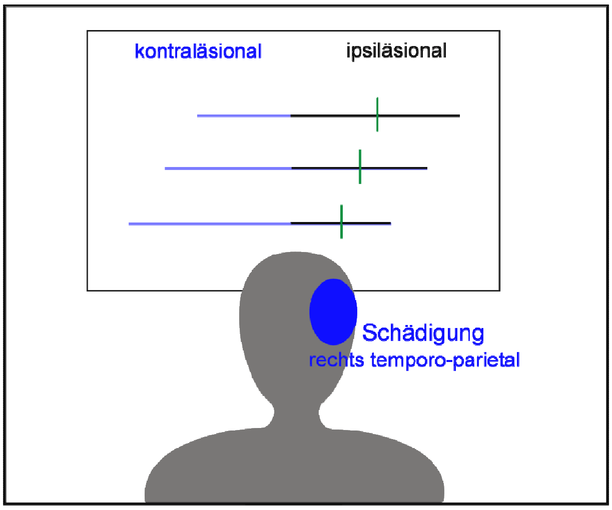

Abb. 1.3 Ein Patient mit rechts temporo-parietaler Schädigung bearbeitet die Linienhalbierungsaufgabe aus NET (Fels, Wilson & Geissner, 1997). Dadurch, dass der hier blau markierte kontraläsionale Bereich nicht ausreichend wahrgenommen werden kann, kommt es zu einer Verschiebung der subjektiven Linienmitte (grün markiert) in ipsiläsionaler Richtung. Je weiter die Linie im kontraläsionalen Raum positioniert ist, desto größer der Schätzungsfehler.

1.3 Aktuelle Erklärungsmodelle und Lokalisationen

Es gibt eine Fülle an Versuchen, Phänomene, Mechanismen und Ursachen des Neglects zu erklären. Einen Überblick über die gängigsten Theorien bieten Kerkhoff (2001) sowie Karnath (2012). Im Folgenden sollen zwei aktuelle Erklärungsmodelle, das "integrated Space-Object map (ISO-map)" Modell und das "integrative Modell des räumlichen Neglects", kurz vorgestellt.

1.3.1 "Integrated Space-Object map (ISO-map)"

Um die direkte Interaktion zwischen körperzentrierten und objektbasierten Aspekten des räumlichen Neglects zu beschreiben, entwickelten Niemeier und Karnath (2002) ein "integrated Space-Object map (ISO-map)" Modell. Bei der willentlichen Exploration einer räumlichen Vorlage postulieren die Autoren eine glockenförmige Aufmerksamkeitsverteilung, welche bei Neglectpatienten nicht wie in Karnath und Fetter (1995) beschrieben primär gestört ist, sondern lediglich eine Transformation aufweist. Der Aufmerksamkeitsvektor weist dabei eine Rotation in ipsiläsionaler Richtung um die vertikale Körperachse des Betrachters auf (siehe Abb. 1.4). Beim objektzentrierten Neglect nehmen sie einen linearen Aufmerksamkeits- bzw. Salienzgradienten an, welcher vom kontraläsionalen zum ipsiläsionalen Objektende ansteigt. Die Steigung dieser Salienzkurve hängt von der Position des fokussierten Objektes im egozentrischen Raum ab. Je weiter kontraläsional das Objekt liegt, desto steiler die Salienzkurve für ipsiläsionale Objektdetails und desto mehr kontraläsionale Vernachlässigung. Wandert die Objektposition in den ipsiläsionalen Raum, beschreibt die Funktion des Aufmerksamkeitsgradienten zunehmend eine Parabel, d.h. die Exploration wird ausgewogener und die kontraläsionalen Objektdetails werden zuverlässiger wahrgenommen. (siehe Abb. 1.4)

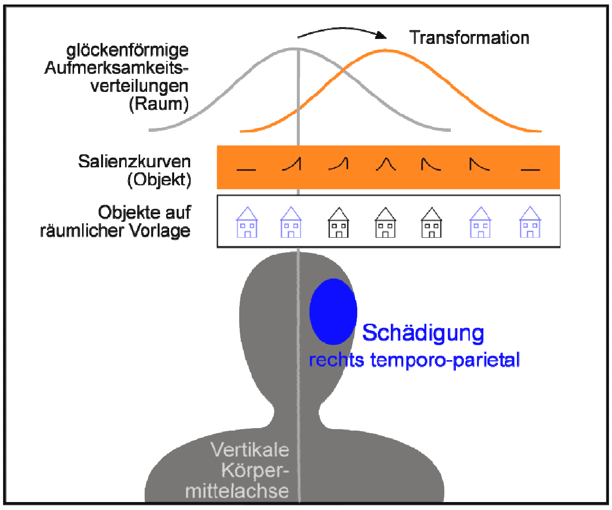

Abb. 1.4 Vereinfachte Darstellung des "integrated Space-Object map (ISO-map)" Modells von Niemeier und Karnath (2002). Exploriert ein Patient mit einer rechts temporo-parietalen Läsion eine räumliche Vorlage, so kommt es zu einer Transformation der glockenförmigen Aufmerksamkeitsverteilung. Dabei wird die Kurve, welche ihre Form beibehält, um die vertikale Körpermittelachse in ipsiläsionaler Richtung verschoben. Die Form der Salienzkurven für die Objekte bzw. Objektdetails (oranges Feld) hängen von der Position des fokussierten Objektes (hier Häuser) im Raum ab. Je weiter kontraläsional das Haus (blau markierte) liegt, desto steiler die Salienzkurve für ipsiläsionale Details und desto mehr kontraläsionale Vernachlässigung zeigt sich. Wandert die Objektposition in den ipsiläsionalen Raum und zur Mittellinie der räuml. Aufmerksamkeitsverteilung (schwarze Häuser), beschreibt die Funktion des Aufmerksamkeitsgradienten zunehmend eine Parabel, d.h. die Exploration wird ausgewogener und die kontraläsionalen Details werden zuverlässiger wahrgenommen. An den Rändern der räumlichen Aufmerksamkeitsverteilung (kontra-, aber auch ipsiläsional) werden die Häuser, wie beim Gesunden, nicht mehr wahrgenommen (blau markierte Häuser) und die Salienzkurve beschreibt eine liegende Gerade.

1.3.2 "Integratives Modell des räumlichen Neglects"

Karnath (2015) kombiniert in seinem sogenannten "integrativen Modell des räumlichen Neglects" Neglect- und Aufmerksamkeitstheorien mit neuronalen Strukturen, um die Mechanismen und Ursachen der halbseitigen Vernachlässigungsphänomene verständlicher zu machen. Die Transformationstheorie nach dem Jeannerod-Biguet Modell (Jeannerod & Biguer, 1987) besagt, dass ein Orientieren und Handeln im Raum eine erfolgreiche Transformation und Integration sensorischen Inputs (visuell, auditive, taktil, propriozeptiv, vestibulär) voraussetzt. Bei Neglectpatienten ist dieser Transformationsprozess für kontraläsionale Reize aus den unterschiedlichen Modalitäten gestört und das egozentrische Referenzsystem wird nicht ausreichend mit sensorischen Informationen über den kontraläsionalen Raum versorgt. Nach Karnath (2015) führt dieser Informationsmangel zu einer ipsiläsionalen Rotation des Raumes um die egozentrische Körpermittelachse. (siehe Abb. 1.4). Aus Studien mit bildgebenden Verfahren (Corbetta & Shulmann, 2002, Peterson & Posner, 2012) geht hervor, dass die "dorsale Bahn" assoziiert werden kann mit egozentrischer räumlicher Aufmerksamkeitssteuerung, die "ventrale Bahn" mit stimulusgeleiteter, automatischer Aufmerksamkeitszuwendung und dass diese miteinander über auf- ("Bottom-Up") und absteigende ("Top-Down") Bahnen kommunizieren. Läsionsstudien zeigen, dass die größte Überlappung in Regionen vorliegen, die am ehesten der "ventralen Bahn" zugeschrieben werden können: TPJ (temporo-parietale-Junction, STG (superiorer temporaler Gyrus) (Heilman et al., 1983; Vallar et al., 1986; Leibovitch et al., 1998; Mort et al., 2003) und Insel (Karnath et al., 2001, 2004). Nach Karnath (2015) kommt es durch Stimulation sensorischer Kanäle zu einer Aktivierung von Kernregionen in der "ventralen Bahn" und über "Bottom-Up"-Prozesse zur Rekalibrierung des egozentrischen Referenzsystems, was über "Top-Down"-Steuerungen zu einer zuverlässigeren Zuwendung zu Reizen in der kontraläsionalen Raumhälfte führt.

1.4 Therapiemethoden

Abgeleitet aus obigem Erklärungsmodell sollten in der Therapie weniger top-down Therapiestrategien (wie visuelles Explorationstraining, Förderung der Awareness) angewendet werden, sondern vielmehr "Bottom-Up"-Stimulationen sensorischer Kanäle eingesetzt werden. Transiente und längerfristige Therapieeffekte konnten für folgende sensorische Stimulationen nachgewiesen werden: optokinetische Stimulation (OKS) (Kerkhoff, 2003; Kerkhoff et al., 2012; Kerkhoff & Schenk, 2012; Kerkhoff et al., 2013, 2014), Prismenbrille (Dimova et al., 2009; Jacquin-Courtois et al. 2013), Nackenmuskelstimulation (Schindler et al. 2002), Kopf- und Körperrotationstraining (Reinhart et al. 2010), kalorisch vestibuläre Stimulation (KVS) (Rubens, 1985; Vallar et al., 1999; Karnath et al. 1994) und galvanisch vestibuläre Reizung (GVS) (Utz et al. 2010, 2011b). Allerdings können nicht alle diese Verfahren in der Praxis für die Rehabilitation eingesetzt werden, da sie teilweise unangenehme Nebenwirkungen haben oder vom Klinikpersonal aufgrund fehlender Fachkenntnisse nicht angewendet werden können (Kerkhoff & Schenk, 2012).

2 Vertikalenstörung

2.1 Störungsbild

Die Vertikalenstörung wirkt sich im Gegensatz zum oben beschriebenen linksseitigen Neglect (siehe Kapitel 1) nicht in der horizontalen (Kerkhoff, 2004), sondern in der frontalen Raumebene aus (Kerkhoff, 2002). Das fehlerhafte Empfinden von Vertikalität, welches Ausdruck einer Raumorientierungsstörung ist und zu den räumlich-perzeptiven Störungen gezählt werden kann (Kerkhoff, 2012), wird vom Betroffenen nicht bewusst wahrgenommen (Kerkhoff & Zoelch, 1998). Dabei können diverse neurologische Erkrankungen (Anastasopoulos et al., 1999) periphere und zentrale (subkortikale, kortikale) Schädigungen vorliegen (siehe Abschnitt 3.2). Auch wenn noch Uneinigkeit über assoziierte kortikale Korrelate besteht (Baier et al., 2012a), zeigten mehrere Forschungsarbeiten einen Zusammenhang mit ausgedehnten zerebrovaskulären Ereignissen, welche temporo-parietale multisensorische Regionen betreffen (Brandt et al., 1995; Bender et al. 1948). In der Regel kommt es bei kortikalen Läsionen zu einer kontraläsionalen Kippung der frontalen Hauptraumachsen, d.h. bei rechtsseitiger Schädigung ist eine Verdrehung gegen den Uhrzeigersinn zu erwarten (Baier et al., 2012a; Pérennou et al., 2008; Karnath & Dieterich, 2006). Dieses neuropsychologische Phänomen lässt sich in diversen Modalitäten (visuell, haptisch, postural) nachweisen (Pérennou et al., 2014; Volkening et al., 2014). Auf der Verhaltensebene zeigen sich meist Einschränkungen in räumlichen Anforderungen des alltäglichen Lebens, wie dem Orientieren, Bewegen sowie Handeln im Raum (Kerkhoff, 2012). Zudem können Gleichgewichts- sowie Haltungsprobleme mit kontraläsionaler Fallneigung bei den Betroffenen beobachtet werden (Barra et al., 2009; Bonan et al., 2015).

2.2 Diagnostik

Da die Vertikalenstörung alle Orientierungen (vertikal, horizontal, oblique) in etwa gleich beeinflusst, kann bei einer gekippt wahrgenommenen vertikalen Raumachse eine komplette Verdrehung der Raumachsen in der Frontalebene angenommen werden (Kerkhoff, 2001). Die subjektive Vertikale (SV) hat sich aufgrund ihrer Sensitivität bezüglich Ausmaß und Richtung als Messinstrument für diese spezifische räumlich-perzeptive Störung bewährt (Brandt et al., 1994). Kerkhoff (1999) fand eine pathologische Verdrehung der SV sowohl auf visueller (SVV) als auch auf taktiler (STV) Ebene, wobei er anhand von Vergleichswerten mit Gesunden den Cutoff-Wert für eine pathologische Abweichung (konstanter Fehler) bei der SVV größer 2° (s. auch Bender et al., 1948, Yelnik et al., 2002) und bei der STV größer 2,5° (beidseitig) festlegte. Abbildung 2.1 veranschaulicht die bei rechts temporo-parietaler Schädigung und Vertikalenstörung zu erwartende kontraläsionale Kippung der SVV (links) und STV (rechts). Zur Untersuchung der SVV eignet sich beispielsweise der Untertest "Subjektive Achsen" aus dem computergestützten Programm "VS-WIN" (Kerkhoff et al., 1993). Hierbei soll der Patient in mehreren Durchgängen verbal angeben, wann eine vom Untersucher rotierte Linie exakt senkrecht steht. Das "Taktile Brett" (Kerkhoff, 1999) hingegen ermöglicht die Erhebung der subjektiven Vertikalen in der taktilen Modalität. Bei dieser haptischen Untersuchung bekommt der Patient die Augen verbunden und hat die Aufgabe, mit einer Hand (in der Regel die nicht paretische, ipsiläsionale Hand) einen Stab mehrfach senkrecht einzustellen. Beide Messinstrumente können sowohl den zu erwartenden konstanten kontraläsionalen Fehler als auch die erhöhte perzeptuelle Unsicherheit in der subjektiven Einschätzung quantitativ erfassen. Einen Überblick über diagnostische Verfahren zur Untersuchung räumlich-perzeptiver Störungen bzw. der Raumorientierungsstörung geben Kerkhoff & Utz (2014).

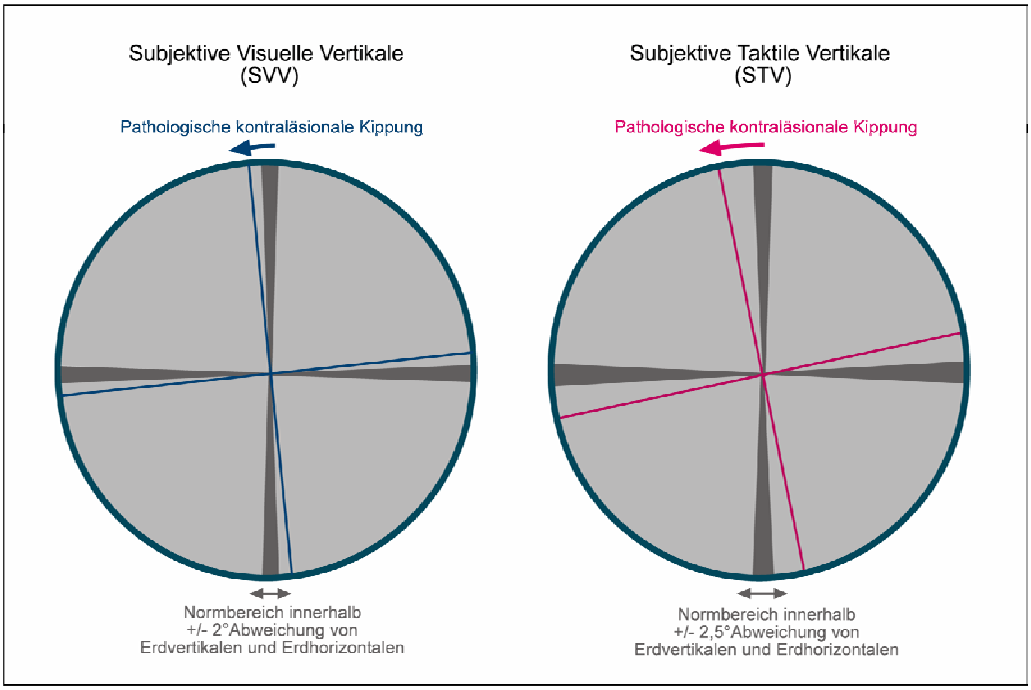

Abbildung 2.1 Schematische Darstellung der Vertikalenstörung infolge einer rechts temporo-parietalen Schädigung und kontraläsionaler Kippung der subjektiven Hauptraumachsen in der Frontalebene (modifiziert nach Kerkhoff, 2004). *links* subjektive visuelle Vertikale (SVV): hellgraue Sektoren kennzeichnen den Normbereich (+/-2° um die Erdvertikale/Erdhorizontale); blaue Achsen zeigen eine zu erwartende pathologische Kippung des Raumes bzw. der SV; *rechts* subjektive taktile Vertikale (STV): hellgraue Sektoren stellen den Normbereich (+/-2,5° um die Erdvertikale/Erdhorizontale) dar; pinke Achsen veranschaulichen eine zu erwartende pathologische Kippung des Raumes bzw. der SV.

2.3 Aktuelle Erklärungsmodelle und Lokalisationen

Barra und Kollegen (2010) sprechen von sogenannten "internalen Modellen", welche beim Beobachter das Gefühl von Vertikalität durch Bündelung und stetiger Aktualisierung vestibulärer und somatosensorischer Informationen über die Schwerkraft konstruieren. Diese "internalen Modelle" dienen laut den Autoren der sensorischen Verarbeitung, der sensomotorischen Integration und der motorischen Kontrolle. Während dieser theoretische Ansatz noch nicht hinreichend belegt wurde, besteht allgemeiner Konsens über das Vorliegen eines "multisensorischen Integrationssystems", welches visuelle, vestibuläre und somatosensorische (propriozeptive) Informationen kombiniert und damit eine Raumrepräsentation ermöglicht. Lopez und Kollegen (2005) bezeichnen das "multisensorische Integrationssystem" als vermittelnde "zentrale Instanz" zwischen Sensorik

(Afferenzen) und motorischen Funktionen (Efferenzen). Weiterhin wird von den Autoren angenommen, dass die zentralen Repräsentationen des extrapersonellen (allozentrischen) und des körperbezogenen (egozentrischen) Raumes mit den zentralen Referenzen der Schwerkraft (Gravitation) eng zusammenarbeiten. In Anlehnung an Lopez und Kollegen (2005) könnte demnach eine Störung aufgrund einer Schädigung innerhalb der räumlichen Repräsentationen zu einer Kippung folgender subjektiver Vertikalen führen: SVV (Lopez et al., 2005) sowie STV (Funk et al., 2010) (allozentrisches Referenzsystem) und SPV (Posturalen Asymmetrie, Bonan et al., 2015) sowie LBA (longitudinal Body Axis), Barra et al., 2009) (egozentrisches Referenzsystem) (siehe Abbildung 2.2).

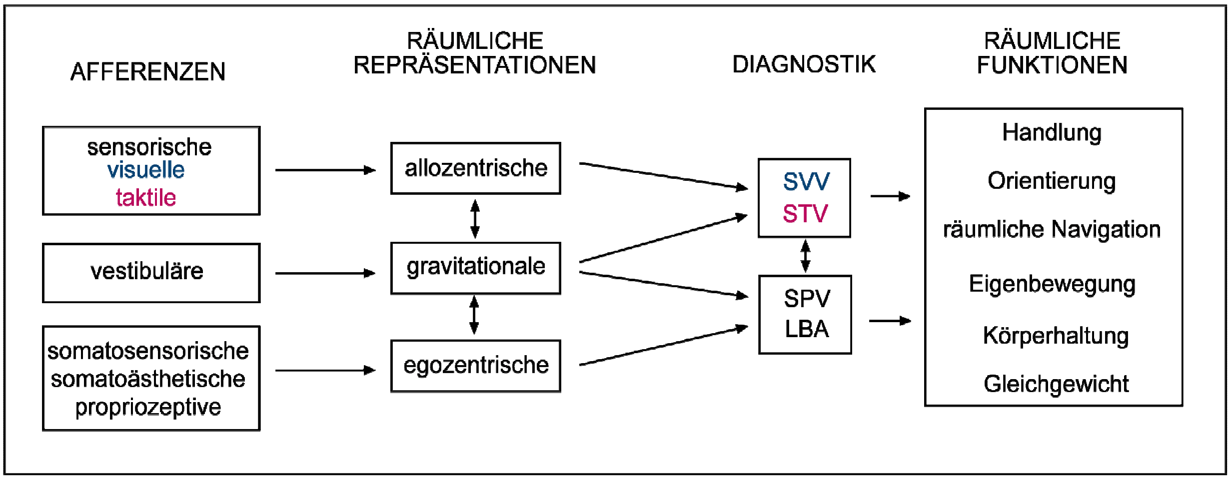

Abb. 2.2 Modifiziertes und erweitertes Modell der Repräsentation von Vertikalität nach Lopez und Kollegen (2005). Es werden die Afferenzen aus diversen Modalitäten verschaltet und ermöglichen räumliche Repräsentationen (allozentrische, gravitationale und egozentrische), welche eng miteinander zusammenarbeiten und somit die Voraussetzung für adäquate räumliche Funktionen liefern. Bislang konnten sich Störungen der räumlichen Repräsentationen in einer Kippung der subjektiven Vertikalen als SVV (subjektive visuelle Vertikale), STV (subjektive taktile Vertikale), SPV (subjektive posturale Vertikale) und LBA (longitudinal Body Axis) nachweisen lassen.

Dieses komplexe Zusammenspiel räumlicher Repräsentationen als vermittelnde Instanzen zwischen Sensorik und Motorik, wie sie bei diversen räumlichen Anforderungen benötigt werden, wäre eine mögliche Erklärung für die heterogenen Befunde kortikaler Korrelate der Vertikalenwahrnehmung aus den unterschiedlichen Läsionsstudien (Baier et al., 2012a). Weitaus mehr Einigkeit über Lokalisationen besteht auf subkortikaler Ebene. Hierbei übernimmt das vestibuläre System mit seinen multimodalen Schaltzentralen eine wichtige Rolle. In Kapitel 3 wird auf Funktion und Bau des vestibulären Systems, ebenso wie auf Auswirkungen von Systemschädigungen eingegangen.

2.4 Therapiemethoden

Da die Vertikalenstörung mit Problemen in räumlichen Anforderungen des alltäglichen Lebens (Kerkhoff & Utz, 2014) sowie Haltungs- und Gleichgewichtsstörungen (Pérennou et al., 2008, Bonan et al., 2007) einhergehen kann und darüber hinaus mit weiteren räumlichen Störungen, konstruktiven Apraxien (Funk et al., 2013) sowie häufig mit einem multimodalem Neglect (Kerkhoff, 1999) assoziiert ist, kommt in der neurologischen Rehabilitation in der Regel ein multidisziplinäres Team aus Ergo-, Physio-, Kognitions- und Sehtherapeuten zum Einsatz. Obgleich die Prognose für Schlaganfallpatienten bei Vorliegen einer Raumorientierungsstörung mit assoziierten Einbußen eher schlecht ist, gibt es bislang nur wenige spezifische, effektive Methoden in der Funktionstherapie (Funk et al. 2013). Einen Überblick über gängige Therapien räumlich-perzeptiver Störungen bietet (Kerkhoff & Utz, 2014). In einer aktuelleren Forschungsarbeit von Funk und Kollegen (2013) konnte eine Reduktion der pathologischen SVV und STV bei Patienten mit einer Raumorientierungsstörung nach Schlaganfall nachgewiesen werden. In dieser Studie kam ein feedbackbasiertes visuelles Training zur Unterscheidung von Linienorientierungen aus dem oben erwähnten computergestützten Programms "VS-WIN" (Kerkhoff et al., 1993) zum Einsatz. Im Vergleich zum Neglect gibt es für die Vertikalenstörung noch kaum Forschungsarbeiten, welche die Effektivität der sensorischen Stimulation auf die Symptomreduktion untersuchten. Neben einer vielfach zitierten Studie von Saj und Kollegen (2006), welche einen bedeutsamen Zusammenhang zwischen GVS (galvanisch vestibulärer Stimulation) und einer Reduktion einer pathologischen SVV (subjektive visuelle Vertikale) nachwies, zeigte eine aktuelle Arbeit von Bonan und Kollegen (2015) erstmals einen positiven Therapieeffekt von OKS (optokinetischer Stimulation) und GVS auf die SPV (subjektive posturale Vertikale). Nach derzeitigem Forschungsstand haben bislang Stimulationstherapien zur Reduktion der Vertikalenstörung noch kaum Einzug in die Rehabilitation gefunden.

3 Vestibuläres System

Der menschliche Gleichgewichtssinn, an manchen Stellen als "sechster Sinn" bezeichnet, basiert ebenso wie die Fähigkeit zum Navigieren im Raum auf der Verarbeitung von vestibulären Informationen. Kennzeichnend für das vestibuläre System ist ein enges Zusammenspiel mit anderen Sinnen, insbesondere dem visuellen, dem somatosensorischen, sowie dem propriozeptiven, und der Motorik (Brandt & Dieterich, 1999). Es spielt eine einzigartige Rolle bei der sensomotorischen Kontrolle und Wahrnehmung (Lopez & Blanke, 2011), was uns die aufrechte Haltung und den Gang auf zwei Beinen ebenso ermöglicht, wie das Orientieren und Handeln im Raum. Im Folgenden werden bewährte und neuere Erkenntnisse zu Funktion und Bau des vestibulären Systems vorgestellt und anhand von aktuelleren Läsionsstudien Zusammenhänge zwischen Systemausfällen und Vertikalenstörung sowie multisensorischem Hemineglect aufgezeigt.

3.1 Funktion und Bau

3.1.1 Peripheres vestibuläres System

Das Vestibularorgan hat die Aufgabe, Rotations- und Translationsbeschleunigungen über Informationen der Schwerkraft (Gravitation) zu detektieren. Es befindet sich jeweils auf der rechten und linken Seite (bilateral) im harten Knochen des Schädels. Abbildung 3.1a zeigt das rechte Vestibularorgan (gelb) im Innenohr gelegen und eingebettet in das Felsenbein des Schädelknochens. Es steht über den Nervus vestibularis (orange) mit dem Gehirn und zum anderen über die Zellen des Mastoides (türkis) mit dem Processus mastoideus (Warzenfortsatz, hinter dem Ohr) in Verbindung.

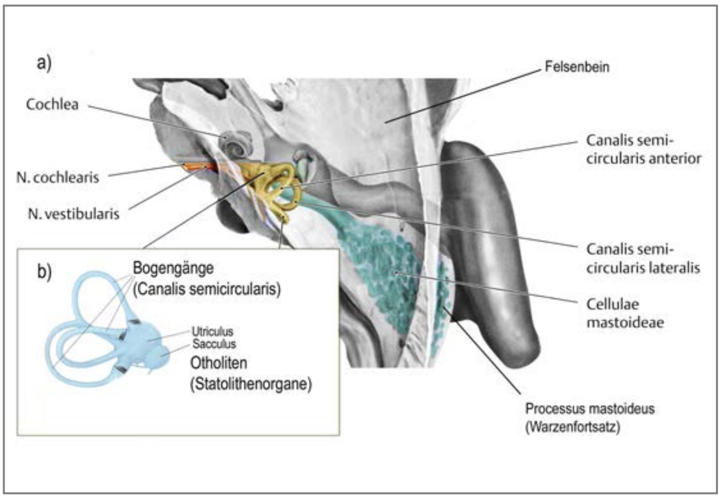

Abb. 3.1 a) Lage des Vestibularorgans b) Bogengänge und Otolithen (modifiziert nach Schünke et al., 2006)

Das periphere vestibuläre System besteht neben den drei häutigen Bögengängen (Canalis semicirculares), welche für das Erfassen von Rotationsbeschleunigungen zuständig sind, aus den beiden Otolithen (Statolithenorgane), Sacculus und Utriculus, die Translationsbeschleunigungen wahrnehmen (siehe Abb. 3.1b). Innerhalb des Systems der

Vertikalenwahrnehmung scheint die Otolithenfunktion eine dominierende Rolle einzunehmen (Baier & Dieterich, 2014). Das periphere (Vestibularorgan) ist mit dem zentralen vestibulären System über den Nervus vestibularis, welcher sich mit dem Nervus cochlearis zum Nervus vesibulochochlearis (VIII. Hirnnerv) vereint, verbunden (Kretschmann et al., 2003).

3.1.2 Zentrales subkortikales vestibuläres System

Die Informationen über Vertikalität aus den beiden Vestibularorganen erreichen zunächst die vestibulären Kerne im Hirnstamm. Über mehrere aufsteigende Bahnen, die unterschiedliche Kernregionen passieren, gelangen die Informationen in diverse kortikale Regionen. Bisher ist das komplexe vestibuläre Netzwerk noch nicht vollständig verstanden. Folgende subkortikale Regionen wurden nach aktuellem Forschungsstand als bedeutsam identifiziert: Nucleus vestibularis, als erste zentrale Station, in der vestibulärer mit sensorischer (visueller, somatosensorischer, propriozeptiver) und motorischer Information verschaltet wird (Schünke et al., 2006), Kleinhirn, welches mit dem vestibulären Kerngebiet kommuniziert (Baier et al., 2008), und posteriolateraler Thalamus, der als weitere multisensorische Schaltzentrale fungiert (Barra et al., 2010).

Im Folgenden werden zwei aktuelle Theorien zu möglichen Verarbeitungswegen zwischen den vestibulären Kernen und dem Kortex kurz vorgestellt.

Baier und Dietrich (2014) beschreiben folgenden Verarbeitungspfad für die Vertikalenwahrnehmung (siehe Abb. 3.2a). Im vestibulären Kernkomplex (blauer Kreis) werden die Informationen aus dem Vestibularorgan mit denen aus dem Kleinhirn (grüner Kreis) verschaltet. Aufsteigende Pfade passieren den posterolateralen Thalamus und führen zum insulären Kortex und anderen multisensorischen Regionen.

Kirsch und Kollegen (2015) gelang es mittels struktureller und funktionaler Bildgebung einen detaillierteren Überblick über einen interhemisphärischen Kreislauf gravizeptiver vestibulärer Bahnen zwischen den vestibulären Kerngebieten im Hirnstamm und der operculären-insulären Region (entspricht dem PIVC, siehe Abschnitt 3.1.3) zu beschreiben. Dieses von den Autoren als "Strickleiter" bezeichnete interhemisphärische Netzwerk (siehe Abb. 3.2b) umfasst fünf Pfade (zwei gelbe, rosa, blau, grün). Zudem postulieren sie vier Kreuzungen im Hirnstamm: Zwischen den Nuclei vestibularis (VN) (lila), auf Höhe der Pons (blau), zwischen den interstitiale Nuclei of Cajal (INC) des Mittelhirns (grün) und einer interhemisphärischen Kreuzung zwischen den PIVCs (rot). Als weitere wichtige Schaltzentralen wurden der posterolaterale und der paramediane Kern des Thalamus identifiziert, diese werden sowohl von ipsilateralen als auch von kontralateralen Bahnen passiert (zwei gelbe, grün, blau). Ein weiterer ipsilateraler Pfad umgeht den Thalamus und projiziert direkt in den inferioren Teil der Insel (rosa).

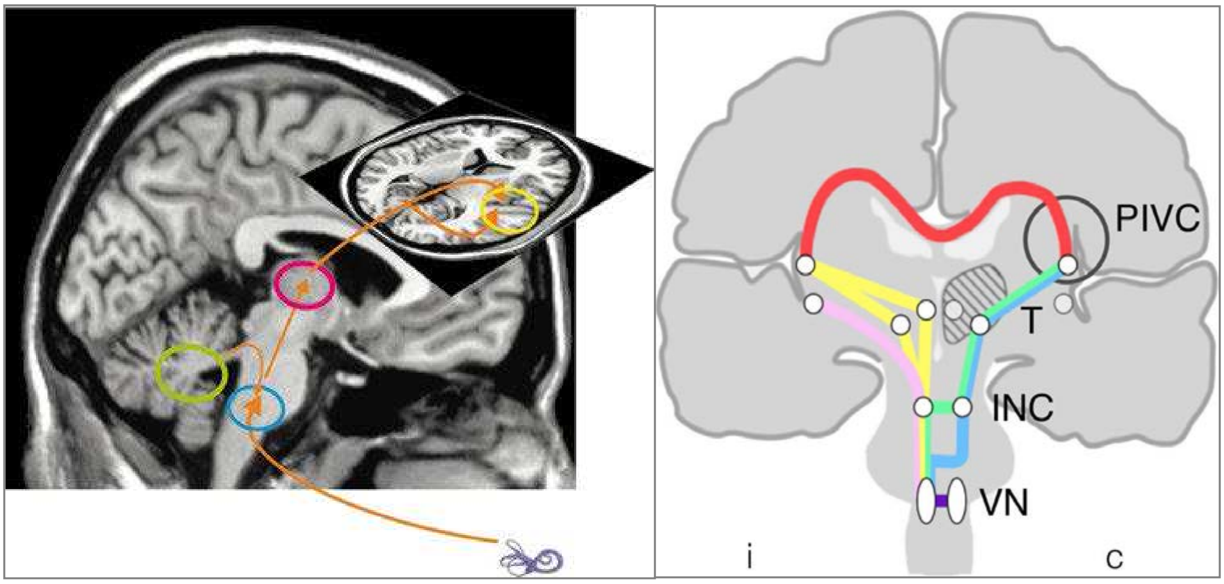

Abb. 3.2 a) Schematische Darstellung der zentralen Gebiete und Projektionswege, welche von Baier & Dieterich (2014) als bedeutsam für die Verarbeitung der Otolithen-dominierenden vertikalen Wahrnehmung identifiziert wurden. Input aus Otolithen und Kleinhirns (grüner Kreis) werden primär im vestibulären Kernkomplex (blauer Kreis) verarbeitet. Weitere aufsteigende Bahnen durch den Hirnstamm passieren posterolateralen Thalamus (roter Kreis) und führen nach entsprechender Umschaltung weiter zum insulären Kortex und anderen multisensorischen Regionen im temporo-parietalen Kortex wie dem superiorer temporaler Gyrus (gelber Kreis).

b) Schematischer Überblick des vestibulären Systems aus der Studie von Kirsch und Kollegen (2015). Fünf unterschiedliche vestibuläre Bahnen wurden von den Autoren identifiziert: drei Bahnen verlaufen ipsilateral (gelb, rosa) und zwei kreuzen, eine auf Höhe der Pons (blau) und die andere im interstitialer Nucleus of Cajal (INC) des Mittelhirns (grün). Zwei der ipsiläsionalen Projektionen passieren den Thalamus, eine den posterolateralen und die andere den paramedianen Kern (gelb) während eine weitere den inferioren Teil des insulären Cortex direkt erreicht (rosa). Beide kontralateral verlaufende Signalwege führen durch den postereolateralen Thalamus (blau, grün). Auf kortikaler Ebene sind die operculären-insulären Regionen (PIVCs) beider Hemisphären mit einer rechtshemisphärischen Dominanz beteiligt. Diese stehen über das anterior caudale Splenium des Corpus Callosum in Kontakt (rot). Mit der Verbindung der beiden vestibulären Kernregionen (lila) beschreibt dieser bilaterale vestibuläre Kreislauf, laut den Autoren, die Form einer "Strickleiter".

3.1.3 Zentrales kortikales vestibuläres System

Auf kortikaler Ebene ließen sich bisher keine primär vestibulären Kortexareale identifizieren. Frühere Studien mit funktioneller Bildgebung (Bottini et al., 1994; Bucher et al., 1998; Bense et al., 2001) an Gesunden konnten während Stimulation des peripheren Vestibularorgans in der posterioren Insel ein Areal entdecken, welches als das menschliche Homolog des multisensorischen parieto-insulären-vestibulären Cortex (PIVC) beim Affen fungieren könnte (Grüsser et al., 1990; Guldin et al., 1996, 1998; Brandt et al., 1999). Es folgte eine Fülle weiterer Forschungsarbeiten zu kortikalen Korrelaten der vestibulären Verarbeitung. Folgende Strukturen wurden bisher als kortikale vestibuläre Kernzentren diskutiert und könnten derzeit am ehesten dem aus dem Tiermodell bekannten multisensorischen PIVC sowie dem oben beschriebenen "multisensorischen Integrationssystem" (siehe Abschnitt 2.3) entsprechen: posteriorer insulärer Kortex (Brandt et al., 1994, Lopez & Blanke, 2011), operculäre-insuläre Region (Kirsch et al., 2015) und parietales Operculum (Lopez et al. 2012, Zu Eulenberg et al. 2012). Zudem werden die angrenzenden temporo-parietalen multisensorische Regionen, wie superiorer temporaler Gyrus (STG) (Baier et al. 2012b), inferiorer parietaler Lobus (Baier & Dieterich, 2014) sowie temporo-parietale Übergangsregion (TPJ) (Lopez & Blanke, 2011), und darüber hinaus etliche weitere kortikale Ariale und Faserverbindungen in Zusammenhang mit multisensorischer vestibulärer Verarbeitung gebracht. Einen Überblick über weitere Lokalisationen bietet ein Review von Lopez & Blanke (2011).

Einigkeit unter vielen Forschern besteht darin, dass die rechte Gehirnhälfte die dominante Rolle bei der vestibulären Verarbeitung spielt und eine Integrationsfunktion aufweist, welche aus den unterschiedlichen Modalitäten eine vertikale Raumrepräsentation konstruiert (Dieterich et al. 2003; Eickhoff et al, 2006; Pérennou et al., 2008).

Bedenkt man das breite Spektrum an sensomotorischen (im weiteren Sinne auch kognitiven (Brandt et al. 2005), emotionalen (Franke et al. 2012) Funktionen, bei der vestibuläre Informationen eine Rolle spielt, ist ein komplexes Netzwerk, wie es Kirsch und Kollegen (2015) vorstellen, ebenso nachvollziehbar, wie die bisher heterogenen Befunde zu kortikalen Strukturen aus den unterschiedlichen Forschungsarbeiten (Lopez & Blanke 2011; Baier et al. 2012b).

3.2 Auswirkungen zentral-vestibulärer Läsionen auf die Vertikalenstörung und den Hemineglect

Läsionsstudien zeigten, dass an unterschiedlichen Stellen im Verlauf vestibulärer Bahnen vom peripheren Vestibularorgan im Innenohr zum multisensorischen parietotemporalen Kortex, Störungen auftreten können, die zu einer Vertikalenstörung (Kapitel 2) führen. Sind das periphere Vestibularorgan oder die gravizeptiven Bahnen zum Hirnstamm unilateral beschädigt, können asymmetrische Otolithensignale den vestibulo-okulären Reflex (VOR) sowie die Blickstabilisierung beeinflussen und eine Kippung der SV auslösen (Dieterich & Brandt, 1993a, 1993b). Die SVV ist in diesem Fall das subjektive perzeptive Korrelat der OTR (ocular tilt reaction: skew deviation, head tilt, ocular torsion (Baier et al. 2012b). Baier et al. (2012b) zeigten in ihrer Läsionsstudie, dass sich abhängig von der unilateralen Läsionslokalisation im Hirnstamm die Richtung der SVV-Abweichung unterscheidet (ipsi- versus kontraläsional). Ab dem Thalamus wird die SV nicht mehr von einer OTR begleitet, sondern ist nun vielmehr Ausdruck einer fehlerhaften Integration multisensorischer gravizeptiver Informationen (Dieterich & Brandt, 1993a, Barra et al., 2010). Schädigungen in Regionen, die mit dem "multisensorischen Integrationssystem" (siehe Abschnitte 2.3 und 3.1.3) assoziiert werden, führen neben der Vertikalenstörung häufig auch zu einem multimodalen Hemineglect (Kapitel 2), was die hohe Koinzidenz der beiden Störungen zu erklären vermag (Baier und Kollegen, 2012a; Kerkhoff & Utz, 2014). Ein weiteres Indiz dafür, dass es sich bei beiden Störungen um eine fehlerhafte Integration multimodaler vestibulärer Rauminformationen handeln könnte, ist die Tatsache, dass bei Schädigungen der rechten Hemisphäre, welcher eine integrative Funktion mit vestibulärer Dominanz zugesprochen wird, im Vergleich zu links-hemisphärischen Läsionen beide Störungen in einer ausgeprägteren Form vorliegen und länger persistieren (Kerkhoff, 2001; Kerkhoff & Utz, 2014).

4 Galvanisch vestibuläre Stimulation (GVS)

Die sogenannte sensorische Stimulation nutzt "Bottom-Up"-Prozesse, um über die periphere Reizung sensorischer Kanäle (z.B. visueller, propriozeptiver und vestibulärer) auf kortikaler Ebene eine Neuromodulation zu erzeugen, die dann auf der behavioralen Ebene eine Symptomreduktion bestimmter sensorisch-kognitiver Störungen bewirken können (siehe Abschnitt 1.3, Karnath, 2015). Eine vielfach untersuchte Methode der vestibulären Stimulation (VS) stellt die kalorisch vestibuläre Stimulation (KVS) dar. Durch die Spülung des Innenohrs mit Wasser konnte einerseits eine Reizung der horizontalen Bogengänge und Aktivierung des vestibulären Systems, des Thalamus sowie multisensorischer temporo-parietaler Kortexareale hervorgerufen werden (Friberg et al, 1985; Fasold et al., 2002;

Dieterich et al., 2005; Lopez et al., 2012), und zum anderen eine temporäre Reduktion von Neglectsymptomen beobachtet werden (Vallar et al., 1999; Kerkhoff, 2001). Diese Methode eignet sich jedoch nicht für eine längere und wiederholte therapeutische Intervention im klinischen Kontext, da sie von unangenehmen Nebenwirkungen (wie Augenverdrehen, Nystagmus, Schwindel, Übelkeit) begleitet wird (Rode et al., 1998, Kerkhoff & Schenk, 2012; Utz et al., 2011c).

Eine für den Patienten angenehmere, nebenwirkungsarme vestibuläre Reizung ist die galvanisch vestibuläre Stimulation (GVS), auf die im Folgenden eingegangen wird. Nach einem kurzen historischen Abriss, Einführung in die Methode sowie Applikation und Überblick über die aktuelle Forschungslage wird anhand der Publikationen Nr. I-III die Effektivität dieser Methode hinsichtlich Neuromodulation und Symptomreduktion in Kapitel 5 diskutiert.

4.1 Kurzer historischer Abriss

Die galvanische Stimulation (GS) hat eine lange Geschichte und dient schon seit über einem Jahrhundert als Methode zur Erforschung der funktionellen Anatomie des vestibulären Systems. Das historische Fundament bilden Galvanis Tierversuche (Galvani, 1791) und Voltas Erfindung der Batterie (Volta, 1793). Seither wurde die Gleichstromstimulation auch für therapeutische Zwecke eingesetzt (z.B. Grapengiesser, 1801). Die ersten systematischen Untersuchungen zum vestibulären System und galvanisch induziertem Schwindel führte Purkyne (1820) in Selbstversuchen durch. Indem Breuer (1875) im Tiermodell die Labyrinthektomie mit der galvanischen Stimulation kombinierte, zeigte er, dass Nystagmus und Gleichgewichts- bzw. Haltungsunsicherheiten vestibulär verursacht sind. Aus der Arbeit von Camis (1930) ist zu entnehmen, dass Breuer und Volta die beiden Elektroden erstmals hinter den Ohren kutan auf den beiden Mastoiden platzierten und daraufhin das Gefühl auslöste, auf die Seite der Kathode (Minuspol) zu fallen. Mit Aufkommen der bildgebenden Verfahren in den 70er Jahren des letzten Jahrhunderts konnten über die beobachtbaren Auswirkungen der galvanisch vestibulären Stimulation (GVS) hinaus auch funktionale neuroanatomische Einblicke in das vestibuläre System von Tieren und Menschen gewonnen werden (siehe Review von Fitzpatrick & Day, 2004; Publikation I).

4.2 Einführung in Methode, Applikation und Wirkmechanismen der GVS

Die transkraniale Gleichstromapplikation wird als tDCS (transcranial direct current stimulation) bezeichnet. Hierbei werden zwei Elektroden (Anode, Kathode) auf der Kopfhaut direkt über die zu stimulierenden Gehirnareale angebracht und Gleichstrom appliziert. Die Sicherheit dieser Methode (Iyer et. al., 2005; Nitsche et. al., 2003) konnte ebenso wie deren Effektivität auf Neuroplastizität (Nitsche, 2016). Positive Effekte der tDCS auf Wahrnehmung (Lepecq et al., 2006), Kognition (Fregni et al., 2005), Sprache (Sparing et al., 2008), Motorik (Nitsche et al., 2000, 2001), Schmerz (Antal et al. 2008), Migräne (Liebetanz et al., 2006), psychischen (Fregni et al., 2006a, Boggio et al., 2008) und neuropsychologischen Störungen (Hummel et al., 2005a,b; Hesse et al., 2005; Quartarone et al., 2005; Ojardias et al. 2015, Valiengo et al., 2016) sowie neurologischen Erkrankungen (Fregni et al., 2006b; Boggio et al., 2012, Falconer et al., 2015) konnten bereits nachgewiesen werden. Einen umfassenderen Überblick über Forschungsarbeiten zur tDCS bietet Publikation Nr. I.

Eine spezielle Form der tDCS ist die galvanisch vestibuläre Stimulation (GVS), bei der nicht direkt über Gehirnarealen Gleichstrom appliziert wird, sondern das Prinzip der "Bottom-Up"-Signalverarbeitung genutzt wird (siehe Abschnitt 1.3 und 1.4). Hierbei werden mittels galvanischer Reizung an den beiden peripheren Vestibularorganen Informationen über diverse aufsteigende Bahnen des Vestibulären Systems zu kortikalen multisensorischen vestibulären Arealen geleitet.

Für die GVS wird lediglich eine Batterie (6 bis 9 Volt) und eine über einen Drehschalter variabel einstellbare Stromstärkeregulation im Milliampere-Bereich benötigt (abgesehen von den erforderlichen Prüfsiegeln für die Benutzung eines solchen Gerätes im medizinischen Kontext). Bei der bilateralen bipolaren GVS wird die kathodale Elektrode hinter dem einen Ohr und die anodale Elektrode hinter dem anderen Ohr auf der Haut über den Mastoiden fixiert (Rorsman et al., 1999, Saj et al., 2006). Polarisationseffekte bei Stromfluss lösen spezifische Reizmuster an den Bogengängen und Otholiten aus (Stephan et al., 2005), was im Vergleich zur KVS mit deutlich weniger unangenehmen Nebenwirkungen einhergeht (Bottini et al., 1994; Dieterich et al., 2003). Der Nervus vestibularis leitet die Reize weiter an das vestibuläre System und über den Thalamus an kortikale vestibuläre Projektionsareale (Fitzpatrick et al., 2004, Publikation I, Abschnitt. 3.1). Bei dieser Art der Stromapplikation im subliminalen (d.h. unterhalb der Wahrnehmungsschwelle) Bereich (ca. 0.7 mA, siehe Publikationen II, III) ist diese Methode als sicher und nebenwirkungsarm einzuschätzen (Wilkinson et al. 2009, Utz et al., 2011c, Publikationen I). Zudem konnten Balter und Kollegen (2004) nachweisen, dass bei mehrfacher Anwendung der GVS bereits nach der zweiten Applikation Habituationsprozesse vernachlässigbar sind. Inwiefern diese Methode als therapeutische Intervention genutzt werden könnte, wird anhand der Publikationen I, II und III im Abschnitt 5.4 diskutiert.

4.3 Aktueller Forschungsstand

Publikation I gibt einen umfassenden Überblick über die bis dato publizierten Forschungsarbeiten zur tDCS und GVS. Im Folgenden werden Ergebnisse der bis heute durchgeführten GVS-Studien zusammenfassend und unterteilt nach Neuro- sowie Funktionsmodulation und Symptomreduktion kurz dargestellt.

4.3.1 Neuro- und Funktionsmodulation

Mehrere Studien mit bildgebenden Verfahren konnten durch GVS ausgelöste neuronale Modulationen nachweisen. Bense & Kollegen (2001) und Bucher & Kollegen (1998) fanden ein Aktivitätsmuster in multisensorischen kortikalen Arealen, wie insulären und retroinsulären Regionen, im superioren temporalen Gyrus (STG), im temporaler-parietaler Kortex, in den Basalganglien und im anterioren cingulären Kortex. Lobel und Kollegen (1998) fanden Aktivierungen in der temporo-parietalen Übergangsregion (TPJ), im zentralen sowie intraparietalen Sulcus und in prämotorischen Regionen des Frontallappens, Dieterich und Kollegen (2003) wiesen Aktivität im PIVC und in der TPJ nach. Lopez und Kollegen (2012) identifizierten die Sylvischen Fissur und umliegenden temporo-parietale und retroinsuläre Regionen bei vestibulärer Stimulation. Zudem fanden Fink und Kollegen (2003) bei links-anodaler/rechts-kathodaler GVS eine unilaterale rechtshemisphärische Aktivierung des vestibulären Systems und bei links-kathodaler/rechts-anodaler GVS eine bilaterale Aktivierung vestibulärer Kortexareale. In dieser Dissertation werden in Abschnitt. 5.1 diese teilweise unterschiedlichen Befunde aus den Lokalisationsstudien und ein möglicher Einsatz von GVS als Tool zur Neuromodulation kognitiv-sensorischer Defizite unter Berücksichtigung von Publikationen Nr. I diskutiert.

Bei Gesunden ließen sich auf behavioraler Ebene während der GVS Veränderungen vestibulärer Funktionen wie Augenverrollungen (Zink et al., 1997, 1998), und darüber hinaus ein verbesserter visueller Gedächtnisabruf von Gesichtern (Wilkinson et al. 2008), bei der Linienhalbierungsaufgabe eine Verschiebung der subjektiven Linienhalbierung in Richtung

Anode (Fink et al., 2003) und zudem bei der Vertikalenwahrnehmung eine Verdrehung der subjektiven visuellen Vertikalen (SVV) zur Anode hin (Mars et al. 2001; Lenggenhager et al., 2008; Volkening et al., 2014) nachgewiesen werden.

4.3.2 Symptomreduktion

Neben der Frage, ob GVS sich als Tool zur Neuro- und Funktionsmodulation eignet, möchte diese Dissertation vor allem einen Beitrag zur Erforschung der GVS als mögliche Therapiemethode bei Neglectphänomenen und Vertikalenstörungen nach Schlaganfall leisten. In den folgenden Forschungsarbeiten wurde diese Methode hinsichtlich Reduktion unterschiedlicher Neglectphänomene (siehe Kapitel 1) bisher untersucht. Die Pioniere, Rorsman und Kollegen, berichteten im Jahr 1999 von temporären Verringerungen des egozentrischen Neglects ("line-crossing task") während rechts-kathodaler Stimulation. Eine signifikante Reduktion des Linienhalbierungsfehlers ("line bisection task") konnten Utz und Kollegen (2011a) unabhängig von der Polarität, jedoch mit größerem Effekt für rechts-kathodale GVS nachweisen. In einer Untersuchung von Schmidt und Kollegen (2013a) waren Neglectpatienten signifikant besser in der Lage, ihre Armposition des linken, kontraläsionalen Armes während und 20 Minuten nach links-kathodaler Stimulation (Nacheffekte) einzuschätzen. Wilkinson und Kollegen (2014) wiesen Langzeiteffekte (bis vier Wochen nach Stromapplikation) für mehrere Neglectphänomene (Aufgaben aus BIT und Alltagsleistungen (Barthel-Index)) nach, wobei sie ausschließlich rechts-kathodal stimulierten. Die aktuellste Studie stammt von Nakamura und Kollegen (2015), welche eine Reduktion des egozentrischen Neglects ("line-cancellation task") während links-kathodaler GVS messen konnten. Inwiefern sich die GVS spezifisch auf einzelne Neglectphänomene auswirkt, ist eine der Zielsetzungen dieser Arbeit und wurde an Schlaganfallpatienten in Anlehnung an den Artikel von Rorsman und Kollegen (1999) untersucht (siehe Publikation II). Die Ergebnisse dieser Studie werden in Abschnitt 5.2 kurz vorgestellt und diskutiert. Ein weiteres Anliegen dieser Dissertation ist es, den Effekt der GVS auf die Symptomreduktion von Störungen in der Vertikalenwahrnehmung (Kapitel 2) zu untersuchen. Neben Publikation III sind bisher dazu nur zwei weitere Arbeiten bekannt. Saj und Kollegen (2006) fanden eine temporäre Reduktion der kontraläsional verdrehten SVV bei Schlaganfallpatienten während rechts-kathodaler Stimulation. Und ein aktueller Artikel von Bonan und Kollegen (2015) berichtet vom positiven Effekt der links-kathodalen Stimulation auf die SPV (subjektive posturale Vertikale). Wir haben in einer Patientenstudie (Publikation III) in Anlehnung an die Arbeit von Saj und Kollegen (2006) überprüft, welche Auswirkungen die Methode auf die visuelle

(SVV) und taktile (STV) Vertikalenstörung hat. In Abschnitt 5.3 werden die Resultate dieser Studie kurz vorgestellt und diskutiert. Inwiefern sich die GVS als Therapiemethode bei Neglectphänomenen und Vertikalenstörungen nach einem Schlaganfall eignet, wird abschließend in Abschnitt 5.4 beleuchtet.

5 Fragestellungen und Diskussion der Ergebnisse

5.1 Fragestellungen

In der vorliegenden Dissertation wurden die folgenden Fragestellungen untersucht:

Eignet sich die GVS als Tool zur Neuromodulation kognitiv-sensorischer Defizite?

Kann die GVS als "Bottom-Up"-Stimulationsverfahren Neglectphänomene nach Schlaganfall reduzieren?

Ist die GVS in der Lage, Störungen der Vertikalenwahrnehmung (visuell, haptisch) nach Schlaganfall zu verringern??

Welche klinischen Implikationen ergeben sich für die GVS in Anbetracht des aktuellen Forschungsstandes und der Ergebnisse aus den beiden Patientenstudien?

5.2 Diskussion der Ergebnisse

5.2.1 Fragestellung 1: Eignet sich die GVS als Tool zur Neuromodulation kognitiv-sensorischer Defizite?

Publikation I

Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—a review of current data and future implications. *Neuropsychologia*, *48*(10), 2789-2810.

Wie in Abschnitt 4.2 und im Review von Utz, Dimova, Oppenländer & Kerkhoff (2010) (Publikation I) beschrieben handelt es sich bei der galvanisch vestibulären Stimulation (GVS) um eine Variante der transkranialen Gleichstromapplikation (tDCS), bei der das vestibuläre System mit Gleichstrom stimuliert wird. Besonders attraktiv an dieser Methode ist die einfache, kostengünstige und sichere Anwendung, bei welcher im Vergleich zur kalorisch vestibulären Stimulation (KVS) unangenehme Nebenwirkungen, wie Schwindel und Nystagmus, vernachlässigbar sind (Utz, Korluss, Schmidt, Rosenthal, Oppenländer, Keller, & Kerkhoff, 2011c, Abschnitt 4.2). Ein weiterer Vorteil der GVS ist, dass sie subliminal durchgeführt werden kann, weshalb sie vom Probanden bzw. Patienten gut angenommen wird und darüber hinaus Placeboeffekte verringert.

Seit Aufkommen der funktionellen Bildgebung ist es möglich, die über "Bottom-Up"-Prozesse ausgelösten Neuromodulationen in peripheren, subkortikalen und kortikalen vestibulären Arealen während GVS sichtbar zu machen (siehe Abschnitt 4.2, 4.3.1, Publikation I). Die Befunde zu kortikalen vestibulären Arealen aus Lokalisationsstudien sind teilweise heterogen (siehe Review von Lopez & Blanke 2011, Baier et al. 2012b). Erklärungen hierfür könnten sein, dass bedeutsame Unterschiede in der Methodenanwendung (exakte Studienprotokolle fehlen meist) vorlagen, die genauen Wirkmechanismen der GVS noch nicht vollständig geklärt sind und das komplizierte vestibuläre Netzwerk bis heute nicht ausreichend verstanden ist. Eine aktuelle Studie mit bildgebenden Verfahren von Kirsch und Kollegen (2015) (Abschnitt 3.1.2) lässt erahnen, wie komplex dieses multisensorische, vestibuläre System arbeitet. Es veranschaulicht auch die verschiedenen subkortikalen Bahnen, welche unterschiedliche Schaltzentralen passieren, um schließlich in verschiedene multisensorische kortikale Regionen zu projizieren, die sowohl intra- als auch interhemisphärisch miteinander kommunizieren (siehe Abb. 3.2b). Die galvanisch vestibuläre Stimulation könnte bei standardisierter Anwendung und genaueren Kenntnissen über deren Wirkprinzip in Zukunft eine vielversprechende Forschungsmethode darstellen, um über induzierte Neuromodulationen dieses komplexe Netzwerk mit seinen untereinander kommunizierenden kortikalen multisensorischen Integrationszentren sowie deren Austausch mit assoziierten Kortexarealen transparenter und dadurch verständlicher zu machen. Ebenso könnte die GVS einen wichtigen Beitrag leisten beim Aufdecken der Rolle vestibulärer Funktionen bei beispielsweise räumlichen Aufmerksamkeitsprozessen, Körper- und Emotionswahrnehmungen.

Neben den bisherigen spannenden Befunden bezüglich Neuro- und

Funktionsmodulationen (Abschnitt 4.3.1) wurde bereits temporär eine Symptomreduktion während GVS bei schlaganfallbedingtem Hemineglect und Vertikalenstörungen (Abschnitt 4.3.2) nachgewiesen. Im Folgenden werden die Ergebnisse aus den beiden Patientenstudien dieser Doktorarbeit zur Wirkung von GVS auf Neglectphänomene (Publikation I) und auf Störungen der Vertikalenwahrnehmungen (Publikationen III) vorgestellt sowie kurz diskutiert und abschließend mögliche klinische Implikationen der GVS für die Therapie diskutiert sowie ein Ausblick gegeben.

5.2.2 Fragestellung 2: Kann GVS als "Bottom-Up"-Stimulationsverfahren Neglectphänomene nach Schlaganfall reduzieren?

Publikation II
Oppenländer, K., Keller, I., Karbach, J., Schindler, I., Kerkhoff, G., & Reinhart, S. (2015a). Subliminal galvanic-vestibular stimulation influences ego-and object-centred components of visual neglect. *Neuropsychologia, 74*, 170-177.

Die häufigste neuropsychologische Störung infolge rechtsseitigem Schlaganfall ist der multimodale Hemineglect (visuell, taktil, sensomotorisch) (Kerkhoff, 2011). Der viel untersuchte visuelle Neglect lässt sich in eine egozentrische und objektzentrierte Komponente unterteilen (Abschnitt 1.2). Während das egozentrische Phänomen als gut verstanden gilt und mehrere therapeutische Interventionen bereits erfolgreich in der Praxis eingesetzt werden, wurde der objektzentrierte Neglect kaum berücksichtigt (Kerkhoff & Schenk, 2012). Insgesamt ist das Angebot an effektiven, speziell auf den *einzelnen* Patienten (z.B. Schweregrad der Störung, Wachheit, Aufmerksamkeitsdauer, weitere Beeinträchtigungen) angepassten Therapieverfahren für Schlaganfallpatienten mit multimodalem Neglect deutlich eingeschränkt (Kerkhoff & Schenk, 2012).

Ein Anliegen dieser Dissertation ist, die GVS als "Bottom-Up"-Stimulationsverfahren auf mögliche On-/Off- Modulationseffekte bei egozentrischen und objektzentrierten Neglectphänomenen hin zu prüfen und deren Potential als therapeutische Anwendung zu diskutieren. In Studie II (Oppenländer, Keller, Karbach, Schindler, Kerkhoff & Reinhart, 2015a) zeigten sich für alle untersuchten Phänomene (egozentrisch, objektzentriert sowie deren Kombination) und für die Alltagsleistung „Abschreiben“ eine transiente, signifikante Symptomreduktion während der GVS (wobei eine bedeutsame

Einschränkung der Validität aufgrund möglicher Lerneffekte zwar unwahrscheinlich, jedoch nicht ganz auszuschließen ist, siehe dazu Diskussion in Publikation II: 4.4 Limitation of the study).

Signifikante Effekte auf die Neglectphänomene bzw. Leistungen der verschiedenen Aufgaben zeigten sich abhängig von der jeweiligen Polarität (rechts- versus links-katodale Stimulation): links- und rechts-kathodale Stimulation reduzierte signifikant den egozentrischen Neglect in der Zahlendurchstreichaufgabe, wobei die rechts-kathodale GVS wie bei Rorsman und Kollegen (1999) einen stärkeren Effekt hatte, rechts-kathodale GVS verringerte zudem signifikant den objektzentrierten Neglect in der Aufgabe "Objekte abzeichnen", links-kathodale Stimulation hingegen reduzierte signifikant Linienhalbierungsfehler, der sowohl den egozentrischen als auch objektzentrierten Neglect abbildet, und die Auslassungen in der alltagsnahen Abschreibaufgabe.

Im Diskussionsteil der Publikation II wurden zur Erklärung der Polaritätseffekte die rechtsseitige Dominanz des vestibulären Systems (Bartenstein et al., 1998) und die von Fink und Kollegen (2003) gefundenen GVS-Polaritätseffekte (bilaterale Aktivierung in temporo-parietalen Kortexarealen bei links-kathodaler und rechtshemisphärische Aktivierung temporo-parietaler Regionen bei rechts-kathodaler Stimulation) herangezogen. Darüber hinaus könnte die rechts-kathodale GVS im Sinne des "integrated Space-Object map (ISO-map)" nach Niemeier & Karnath (2002) (siehe Abschnitt 1.3.1) zu einer Reduktion des in ipsiläsionaler Richtung um die vertikale Körperachse rotierten Aufmerksamkeitsvektor führen und somit sowohl ego- als auch objektzentrierte Neglectphänomene reduzieren. Dies erklärt jedoch nicht die signifikanten Effekte bei der Linienhalbierungsaufgabe (Kombination aus ego- und objektzentriertem Neglect) während Kathode links. Nakamura und Kollegen (2015) fanden einen Zusammenhang zwischen GVS-Effekten und Stimulationsparametern (Polarität, Intensität und Dauer) und konnten nachweisen, dass rechts-kathodale Anwendung bei kürzerer und links-kathodale bei längerer Stimulationsdauer bessere Wirkung zeigt. Da in unserer Arbeit der Zeitpunkt der jeweiligen Aufgabenbearbeitung nicht auf die Stimulationsdauer abgestimmt war, könnte diese einen Einfluss auf die Resultate gehabt haben. Möglich wäre auch, dass die aufgabenspezifischen Leistungen (Aufmerksamkeit, Kognition und Sensomotorik) durch die Polarität unterschiedlich beeinflusst worden sind. Sicher ließen sich noch weitere Einflussfaktoren und Erklärungsmöglichkeiten heranziehen, um die Ergebnisse zu diskutieren. Zukünftige Studien mit bildgebenden Verfahren könnten durch standardisierte Stimulationsparameter und detaillierte Studienprotokolle die genauen Wirkmechanismen der Polaritäten (links-kathodal vs. rechts-kathodal) auf Neglectphänomene sowie auf weitere aufgabenspezifische Leistungen aufdecken helfen.

Die positive Wirkung von GVS im Sinne einer Reduktion von Neglectphänomenen lässt sich anhand der Transformationstheorie (Jeannerod & Biguer, 1987) und des "integrativen Modells des räumlichen Neglects" (Karnath, 2015, siehe Abschnitt 1.3.2) erklären. Bei Neglectpatienten kommt es durch defizitäre Transformationsprozesse aufgrund fehlender kontraläsionaler sensorischer Informationen zu einer Störung im egozentrischen Referenzsystem und dadurch zu einer ipsiläsionalen Rotation des Raumes um die egozentrische Körpermittelachse. Mittels galvanischer Stimulation des vestibulären Systems könnte es über "Bottom-Up"-Prozesse zur Rekalibrierung des egozentrischen Referenzsystems und über anschließende top-down Steuerungen zu einer zuverlässigeren Zuwendung zu Reizen in der kontraläsionalen Raumhälfte kommen (Karnath, 2015, Abschnitt 1.3.2).

5.2.3 Fragestellung 3: Ist GVS in der Lage, Störungen der Vertikalenwahrnehmung (visuell, haptisch) nach Schlaganfall zu verringern?

Publikation III

Oppenländer, K., Utz, K. S., Reinhart, S., Keller, I., Kerkhoff, G., & Schaadt, A. K. (2015b). Subliminal galvanic-vestibular stimulation recalibrates the distorted visual and tactile subjective vertical in right-sided Schlaganfall. *Neuropsychologia, 74*, 170-177.

Störungen der Vertikalenwahrnehmung treten häufig (Inzidenzrate: 50 bis 70%, Jesshope et al. 1991) und oft in Kombination mit dem multimodalen Hemineglect infolge rechtsseitigem Schlaganfall auf. Trotz deren Häufigkeit, den mehrfach assoziierten weiteren räumlichen Störungen und den vielschichtigen Beeinträchtigungen im alltäglichen Leben, gibt es für die Vertikalenstörungen kaum Forschungsarbeiten, welche die Effektivität der sensorischen Stimulation auf die Symptomreduktion untersuchten, und bislang nur wenige Funktionstherapien (Funk et al. 2013, Abschnitt 1.4).

Eine weitere Zielsetzung dieser Arbeit ist, zu prüfen, ob die GVS einen Einfluss auf die meist multimodal vorliegende Vertikalenstörungen hat, also die konstanten Fehler und die pathologisch erhöhten variablen Fehler (bzw. perzeptuelle Unsicherheit) in der SVV (subjektive visuelle Vertikale) und STV (subjektive taktile Vertikale) reduziert und zu diskutieren, ob sich diese Methode auch für diese Störungen als repetitive Therapiemethode eignen könnte.

In Studie III konnten wir während GVS Verringerungen der Vertikalenstörungen nachweisen (wobei eine bedeutsame Einschränkung der Validität aufgrund möglicher Lerneffekte zwar unwahrscheinlich, jedoch nicht ganz auszuschließen ist, siehe dazu Diskussion in Publikation III: 4.4 Limitation of the study). Wie in der vielfach zitierten Studie von Saj und Kollegen (2006) fanden auch wir bei links-kathodaler Stimulation eine statistisch bedeutsame Verringerung der gestörten SVV. Bei der gleichen Polarität zeigte sich zudem eine signifikante Reduktion der pathologischen STV, was im Einklang zu den GVS-Effekten auf die STV steht, wie sie Mars und Kollegen (2001) und Volkening und Kollegen (2014) bei Gesunden gefunden haben. Die subliminal durchgeführte GVS reduzierte in unserer Untersuchung nicht nur die konstante Abweichung, sondern auch die sensorische Ungenauigkeit in der Beurteilung der Vertikalität, und zwar in beiden Modalitäten.

Im Hinblick auf die im Abschnitt 2.3 vorgestellten "multisensorischen Integrationssysteme", welche visuelle, vestibuläre und somatosensorische (propriozeptive) Informationen kombiniert und daraus multiple Raumrepräsentationen konstruiert, könnte die GVS durch Stimulation des vestibulären Systems Einfluss nehmen auf diese multisensorischen Integrationssysteme. Eine Störung innerhalb der räumlichen Repräsentationen aufgrund einer Schädigung könnte durch neuromodulative Prozesse reduziert werden und Beeinträchtigungen in diversen räumlichen Funktionen verringern (siehe Abbildung 2.2). Es konnte bereits in weiteren Studien eine Reduktion der pathologischen Kippung der folgenden subjektiven Vertikalenmaße beobachtet werden: SVV (Lopez et al., 2005) sowie STV (Funk et al., 2010) und SPV (Posturalen Asymmetrie, Bonan et al., 2015) (Abschnitt 2.3).

5.2.4 Fragestellung 4: Welche klinischen Implikationen ergeben sich für die GVS in Anbetracht des aktuellen Forschungsstandes und der Ergebnisse aus den beiden Patientenstudien?

Publikation I

Utz, K. S., Dimova, V., Oppenländer, K., & Kerkhoff, G. (2010). Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—a review of current data and future implications. *Neuropsychologia, 48*(10), 2789-2810.

Publikation II

Oppenländer, K., Keller, I., Karbach, J., Schindler, I., Kerkhoff, G., & Reinhart, S. (2015a). Subliminal galvanic-vestibular stimulation influences ego-and object-centred components of visual neglect. *Neuropsychologia, 74,* 170-177.

Publikation III

Oppenländer, K., Utz, K. S., Reinhart, S., Keller, I., Kerkhoff, G., & Schaadt, A. K. (2015b). Subliminal galvanic-vestibular stimulation recalibrates the distorted visual and tactile subjective vertical in right-sided stroke. *Neuropsychologia, 74,* 170-177.

Der Schlaganfall ist die häufigste Ursache von chronischen Einbußen in allen westlichen Ländern, was u.a. mit der dort kontinuierlich steigenden Lebenserwartung und demzufolge höheren Schlaganfallinzidenz im höheren Lebensalter zusammenhängt. Ein breiter Pool an Therapiemethoden, aus dem der Praktiker ein individuell angepasstes Therapieprogramm zusammenstellen kann, wäre für ein besseres individuelles "Outcome" in der verhältnismäßig kurzen stationären neurologischen Rehabilitationsphase dringend nötig. Vorläufer und damit Grundlage neuer Therapieverfahren für neurologische Störungen stellten in der Vergangenheit häufig experimentelle Ergebnisse zur kurzzeitigen Symptommodulation durch sensorische Stimulation dar.

Diese Arbeit möchte mit der Untersuchung der GVS als Methode zur Neuromodulation und Symptomreduktion einen Beitrag zur Evaluation einer potentiell neuen Therapiemethode leisten. Publikation I gibt einen Überblick über die bis dato aktuelle Forschungslage zur GVS als vielversprechendes Werkzeug zur Neuro- und Verhaltensmodulation und darüber hinaus erste Hinweise auf das Potential der GVS als therapeutisches Instrument. Die von uns gefundenen positiven Effekte der GVS auf den Neglect (Publikation II) und die Störungen der Vertikalenwahrnehmung (Publikation III) legen nahe, dass es sich bei der galvanisch vestibulären Stimulation um eine attraktive Therapiemethode in der Rehabilitation von Schlaganfallpatienten handeln könnte. In aktuellen Untersuchungen konnten Nacheffekte (Schmidt et al., 2013a), aber auch Langzeiteffekte (Kerkhoff et al., 2011; Schmidt et al., 2013b; Wilkinson et al. 2014) gemessen werden, was für neuroplastische Prozesse spricht und die Grundlage für einen therapeutischen Lerneffekt darstellt. Darüber hinaus konnte eine aktuelle Untersuchung von Harvey & Kerkhoff (2015) zeigen, dass GVS kombinierbar ist mit einem weiteren visuellen Stimulationsverfahren, das in der Neglectherapie oft eingesetzt wird: der optokinetischen Stimulation (OKS). Wie bereits erwähnt, treten Störungen der Vertikalität und Neglectphänomene häufig zusammen und in Kombination mit weiteren Störungen auf und verursachen vielfältige Beeinträchtigungen im Alltag. Die Portabilität des kleinen Stimulationsgerätes und die Mobilität des Trägers stellen einen weiteren gewinnbringenden Vorteil der GVS-Technik dar, da dies den Einsatz in Kombination mit anderen Therapieverfahren begünstigt und eventuell zu stärkeren therapeutischen Effekten führen könnte. Neben einer Kombination mit weiteren Stimulationsmethoden wäre der Einsatz der GVS auch bei kognitiven Kompensationstherapien, sowie bei physiotherapeutischen und ergotherapeutischen Interventionen im Alltag möglich. Darüber hinaus lässt die multimodale Verschaltung des komplexen vestibulären Systems vermuten, dass die GVS auch auf weitere neurologisch bedingte Störungen der Aufmerksamkeit (Harvey & Kerkhoff, 2015), Emotionen (Franke et al. 2012) und der Körper-Kognitionen sowie auf die konstruktive Apraxie (Publikation I) haben könnte. Positive GVS-Effekte auf Symptomreduktion konnten bereits für die Extinktion (Kerkhoff et al., 2011, Schmidt et al., 2013b), die Wahrnehmung der Armposition bei Neglectpatienten (Schmidt et al. 2013a) und die Störung der aufrechten Körperhaltung (SPV, Bonan et al. 2015) nachgewiesen werden. Darüber hinaus zeigte die GVS bei Haltungsstörungen von Patienten mit Morbus Parkinson einen modulierenden Effekt (Okada et al., 2015).

Bis zum Routineeinsatz der GVS im therapeutischen Kontext sind jedoch weitere Forschungsarbeiten mit exakt erstellten Studienprotokollen, insbesondere über verwendete Stimulationsparameter, idealerweise unter Verwendung von bildgebenden Verfahren und Verhaltensbeobachtungen bei Gesunden und Patienten nötig, um die genauen Wirkmechanismen der Methode auf neuronaler und behavioraler Ebene besser zu verstehen. Dies könnte helfen, das jeweilig günstigste GVS-Protokoll individuell für jeden einzelnen Patienten und in Kombination mit anderen Therapieangeboten zu konfigurieren. Gelingt dies, so könnte die GVS ähnlich wie andere Methoden wie etwa die optokinetische Stimulationstherapie beim Neglect bald zu einer Routine-Therapie-Methode in der Neurorehabilitation werden.

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7 Vollständige Publikationsliste

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10 Anhang: Originalarbeiten

Anhang A:

Utz, K. S., Dimova, V., **Oppenländer, K.**, & Kerkhoff, G. (2010). Electrified minds: transcranial direct current stimulation (tDCS) and galvanic vestibular stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—a review of current data and future implications. *Neuropsychologia*, *48*(10), 2789-2810.

Anhang B:

Oppenländer, K., Keller, I., Karbach, J., Schindler, I., Kerkhoff, G., & Reinhart, S. (2015a). Subliminal galvanic-vestibular stimulation influences ego-and object-centred components of visual neglect. *Neuropsychologia*, *74*, 170-177.

Anhang C:

Oppenländer, K., Utz, K. S., Reinhart, S., Keller, I., Kerkhoff, G., & Schaadt, A. K. (2015b). Subliminal galvanic-vestibular stimulation recalibrates the distorted visual and tactile subjective vertical in right-sided stroke. *Neuropsychologia*, 74, 178–183.

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Reviews and perspectives

Electrified minds: Transcranial direct current stimulation (tDCS) and Galvanic Vestibular Stimulation (GVS) as methods of non-invasive brain stimulation in neuropsychology—A review of current data and future implications

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ABSTRACT

Transcranial direct current stimulation (tDCS) is a noninvasive, low-cost and easy-to-use technique that can be applied to modify cerebral excitability. This is achieved by weak direct currents to shift the resting potential of cortical neurons. These currents are applied by attaching two electrodes (usually one anode and one cathode) to distinct areas of the skull. Galvanic Vestibular Stimulation (GVS) is a variant of tDCS where the electrodes are attached to the mastoids behind the ears in order to stimulate the vestibular system. tDCS and GVS are safe when standard procedures are used. We describe the basic physiological mechanisms and application of these procedures. We also review current data on the effects of tDCS and GVS in healthy subjects as well as clinical populations. Significant effects of such stimulation have been reported for motor, visual, somatosensory, attentional, vestibular and cognitive/emotional function as well as for a range of neurological and psychiatric disorders. Moreover, both techniques may induce neuroplastic changes which make them promising techniques in the field of neurorehabilitation. A number of open research questions that could be addressed with tDCS or GVS are formulated in the domains of sensory and motor processing, spatial and nonspatial attention including neglect, spatial cognition and body cognition disorders, as well as novel treatments for various neuropsychological disorders. We conclude that the literature suggests that tDCS and GVS are exciting and easily applicable research tools for neuropsychological as well as clinical-therapeutic investigations.

Contents

Abbreviations: tDCS, transcranial direct current stimulation; GVS, Galvanic Vestibular Stimulation; DC, direct current; TMS, transcranial magnetic stimulation; fMRI, functional magnetic resonance imaging; PET, Positron Emission Tomography; CVS, caloric vestibular stimulation; MEP, motor evoked potentials; EMG, electromyogram; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; mA, milliAmpere; SEPs, somatosensory evoked potentials.

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1. Introduction

Neuropsychology has enormously benefited from the advent of modern neuroimaging techniques such as functional magnetic reasonance imaging (fMRI), recording of event-related potentials (ERPs) and brain stimulation techniques such as transcranial magnetic stimulation (TMS; Wasserman, Epstein, & Ziemann, 2008). Recently, a number of novel brain stimulation techniques have become increasingly popular, including deep brain stimulation, magnetic seizure therapy and vagus nerve stimulation (Been, Ngo, Miller, & Fitzgerald, 2007; Eitan & Lerer, 2006). A serious drawback of these methods is the fact that all except TMS are invasive and expensive to administer. TMS has been used to study the excitability of the cortex, cortical regional connectivity, the plasticity of brain responses and cognitive processes in healthy subjects and the functional deficits underlying psychiatric disorders such as depression (Been et al., 2007). As a result of advances in brain imaging our knowledge of relevant brain regions which should be targeted to induce changes in motor, sensory, cognitive or emotional functions has greatly increased in the last two decades. Consequently, techniques of neurostimulation that are easier to use and less expensive than TMS might further broaden our understanding of neuropsychological functions both in normal and clinical subjects. A very promising method is transcranial direct current stimulation (tDCS). tDCS offers the possibility of changing cortical excitability and this can be achieved by the application of electrodes with different polarity to different locations on the surface of the skull to excite the underlying neural tissue. A variant of this method is Galvanic Vestibular Stimulation (GVS) where the vestibular system is stimulated by attaching two electrodes to the mastoids behind the ears. GVS does not only induce electrical activation in peripheral vestibular afferents but also affects different cortical-vestibular areas and neighbouring cortical regions. Both techniques are non-invasive, safe, inexpensive and without serious adverse effects when certain standards are maintained. Moreover, tDCS does not only produce *online-effects during* the application but can induce significant *aftereffects* (Nitsche & Paulus, 2001) depending on the duration of stimulation. This makes tDCS an attractive tool for researchers interested in learning, neuroplasticity and neurorehabilitation. Finally, in comparison with TMS both tDCS and GVS are less expensive, easy to administer and without serious adverse effects.

This review describes the basic physiological principles of tDCS and GVS, addresses issues of safety and usability, and then assesses the state of the art of these techniques when used in different neuropsychological domains. Additionally, we will suggest novel and potentially fruitful applications of both techniques in a number of research fields, including spatial neglect, spatial and non-spatial attentional processing as well as spatial-cognitive and body-cognition disorders. Finally, we will conclude with a brief discussion of the findings, a description of the main conclusions and an outlook on future directions of these exciting methods in neuropsychology. Although covering a great deal of relevant literature the current review is not intended as an exhaustive and systematic review of *all* available studies in the field. In selecting the studies we searched international journals and the PubMed database. Our main intention in this review is to present particularly illustrative examples of the potential applications of tDCS and GVS in a broad range of topics including perception, sensory, motor, cognitive and emotional processes as well as a limited range of clinical disturbances relevant for researchers and clinicians in the field of neuropsychology. We hope that the variety of applications and findings presented here in so diverse fields of neuropsychology attracts researchers and alerts them about the considerable potential of tDCS and GVS to answer important research questions in the fields of neuropsychology, neuroplasticity and neurotechnology. We did not consider single cases and non-English studies.

2. Procedure for tDCS

2.1. History

tDCS is a non-invasive method for modulating cortical excitability that has a long history. The first records of electrical therapy date back to 43–48 AD when the roman physician, Scribonius Largus, reported on the treatment of pain by electric fish. Other milestones were Galvani's[1] (1791) and Volta's (1792) experiments on animal and human electricity which initiated the clinical application of direct current stimulation in 1804, when Aldini successfully treated melancholic patients with this technique. The discovery of electroconvulsive therapy by Bini and Cerletti in the 1930s, however, led to an abrupt loss of interest in the technique of tDCS. In the 1960s this method had a brief comeback and its effects were systematically investigated. During that time it could already been shown that tDCS is able to affect brain functions *via* modulation of cortical excitability (Albert, 1966a, 1966b). In two papers that appeared 1966 in the fourth issue of NEUROPSYCHOLOGIA D.J. Albert showed that electrical (cathodal) stimulation of the rat's medial cortex abolished retention (Albert, 1966a) and anodal stimulation speeded

[1] Galvani lent his name for the later coined term Galvanic stimulation, see Section 3.

up memory consolidation (Albert, 1966b). Despite this temporary interest, the technique of tDCS was abandoned once again because of the progress made in the treatment of psychiatric disorders by drugs (for a detailed historical review see Priori, 2003).

Perhaps, a deeper insight into the basic mechanisms of tDCS was fundamental for the increased popularity of this method during recent years. This improved understanding was most likely facilitated by the study of brain mechanisms *via* new techniques such as TMS (Wasserman et al., 2008), and functional brain imaging (fMRI) and resulted in the development of clinical applications. Another important milestone was the development of safety standards, together with evidence of a lack of serious adverse effects. This makes tDCS a promising method to study the effects of local brain stimulation on cognitive functions – both in healthy subjects and patients with central nervous system lesions. In the following, a detailed description of tDCS is given including aspects of safety.

2.2. Method

tDCS consists of applying direct current over the scalp – usually delivered by a small battery-driven constant current stimulator – by attaching electrodes of different polarities to the skin (Iyer et al., 2005; Nitsche & Paulus, 2000, 2001). The electrodes should be made of conductive rubber and be put in saline-soaked synthetic sponges to prevent chemical reactions at the contact point between electrode and skin (Nitsche, Liebetanz, 2003). Concerning the ideal size of the electrodes there is no consensus. Most of the electrodes used in human studies have a size of 25–35 cm^2, which results in a current density of 0.03–0.08 milliAmpere (mA)/cm^2 when used with a current of 1–2 mA. In order to focus the effects of the electrode over the stimulation area some authors recommend a smaller electrode size. Alternatively, an enlargement of the other electrode makes this electrode functionally less active and enhances the selectivity of the other electrode (Nitsche et al., 2007).

2.3. Positioning of the electrodes

The position of the electrodes is of crucial significance for the spatial distribution *and* direction of the flow of current which together determine the effectiveness of the stimulation. In most of the tDCS studies one anode and one cathode is placed in different positions on the scalp skin, depending on the brain function under study. But other montages such as one anode and two cathodes (Miranda, Lomarev, & Hallett, 2006) or two anodes and two cathodes (Ferrucci, Mameli, et al., 2008) have also been used. For some research questions it may be more advisable to place one electrode on an extra-cephalic position (e.g. the right upper arm; Cogiamanian, Marceglia, Ardolino, Barbieri, & Priori, 2007). This may resolve the ambiguity in the interpretation of the tDCS effects with two cephalic electrodes. On the other hand, increasing the distance between the electrodes leads to an enhancement of current flow into the brain and of the depth of current density (Miranda et al., 2006). Fig. 1 illustrates these principles and shows four standard stimulation sites of tDCS in neuropsychology for different sensory, motor or cognitive research questions.

In a study using a computer-based model Wagner et al. (2007) found that the strength of the current density in the cortex depends on the following factors: size, polarity and position of the electrodes, the applied current intensity and the properties of the tissue in the stimulated area. Approximately 45% of the current delivered to the skull reaches the surface of the cortex (Rush & Driscoll, 1968). Once the electrodes are placed the current intensity has to be raised in a ramp-like fashion until the desired level is reached. During the flow of the current subjects usually feel a mild tingling sensation which disappears after a few seconds when current intensity is below 1.5 mA (Hummel & Cohen, 2005). For *subliminal* stimulation the individual sensory threshold has to be determined as follows. The current intensity is increased in small steps of 0.1 mA until the subject perceives a mild tingling beneath the electrodes. Then the current is decreased by 0.3 mA and gradually increased again until the tingling recurs. This procedure yields an estimate of the current intensity which induces a just perceptible tingling. The sensory threshold is set at 90% of this value (Wilkinson, Ko, Kilduff, McGlinchey, & Milberg, 2005).

For *sham* stimulation the electrodes are placed in the same way as for real (verum) stimulation and the current intensity is increased in both conditions in a ramp-like fashion. However, in the case of sham stimulation the current is gradually turned off after a few seconds. Subjects are not able to distinguish between verum and placebo stimulation, which makes the method an attractive research tool in the field of neurorehabilitation and cognitive neuroscience. It is more difficult to achieve a convincing sham condition for other stimulation methods. For example in the case of TMS a specific pattern of noise, constant tap sensation and in some cases muscle twitches are produced. Sham stimulation typically involves discharging a TMS coil which is not held to the skull. This reproduces the noise, but not the tap sensation or muscle twitches (Gandiga, Hummel, & Cohen, 2006). In contrast, subsensory or sham-stimulation in neuroscientific research with tDCS is convincing and easy to realize.

In summary, the application of tDCS is easy to handle. However there are limitations both in its low focality, because of the large electrode sizes (Nitsche et al., 2007), and its low temporal resolution (Schlaug, Renga, & Nair, 2008).

2.4. Safety

Concerning the safety of tDCS, a stimulation intensity of up to 2 mA and a duration of about 20 min is considered to be safe (Iyer et al., 2005; Nitsche, Liebetanz, et al., 2003). The observed adverse effects are minor and consist of light itching beneath the electrodes or mild headache during sham and verum stimulation (Fregni, Boggio, Lima, et al., 2006). Such effects have been observed for different cortical areas in healthy subjects as well as in patients with different neurological disorders (Poreisz, Boros, Antal, & Paulus, 2007).

Repeated sessions of tDCS did not result in different frequencies of adverse effects (headache, itching) in groups receiving verum stimulation compared with placebo stimulation groups. In addition, there were no adverse cognitive effects in these studies as indicated by a neuropsychological test battery. This battery included tests of global cognitive functions, attention and working memory capacity, processing speed, focused and sustained attention and design fluency (Fregni, Boggio, Lima, et al., 2006; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006; Fregni, Gimenes, et al., 2006).

During MRI no changes of the blood-brain barrier or cerebral tissue appeared while stimulating the frontal cortex (Nitsche, Niehaus, et al., 2004). Furthermore, 13 min of tDCS did not result in alterations of the serumneuron-specific enolase concentration (Nitsche & Paulus, 2001), which is a sensitive indicator of neuronal damage.

Although not directly transferable to humans, a recent animal study by Liebetanz et al. (2009) determined the safety limits of cathodal tDCS. Rats received cathodal stimulation *via* an epicranial electrode and brain tissue damage was assessed. More than 10 min stimulation with a current density of 142.9 A/m^2 resulted in brain lesion. Lesion size rose linearly with charge density for current densities between 142.9 and 285.7 A/m^2 and was zero if a charge density was below 52400 Coloumb/m^2. Hence, brain damage will result if threshold for current and the charge density are exceeded. The charge density of 171–480 Coloumb/m^2 that is currently used in human participants falls far below this quantified threshold and suggests that stimulation protocols of increased intensity would remain within safe limits but this would need to be confirmed by further animal research.

Human subjects who had undergone recent brain neurosurgery or who have metallic implants within their brain should be

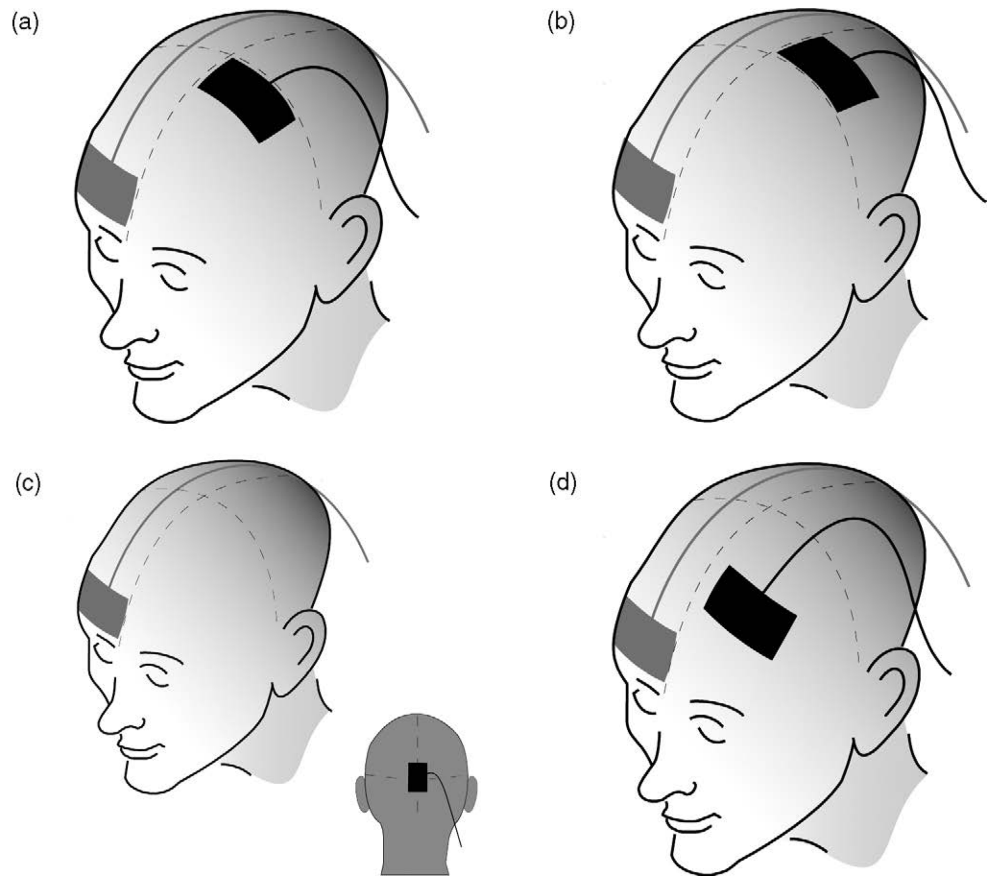

Fig. 1. Demonstration of 4 typical electrode locations on the skull surface when using tDCS. The four figures illustrate the typical placement of anode and cathode during stimulation of the primary motor cortex (A), somatosensory cortex (B), primary visual cortex (C), anterior language cortex (D). Note that in Fig. 1(C) one electrode is placed at the back of the head (see small image of the head), while the other electrode is placed at the right supra-orbital area. One electrode is placed on the area of the skull covering the target structure and the other electrode is typically placed either over the supraorbital area of the other hemisphere or over the corresponding area of the contralateral hemisphere. Note, that other stimulation positions have been used as well (see text for details).

excluded from stimulation for safety reasons. Further exclusion criteria are a sensitive skin on the scalp and signs of epilepsy. Furthermore it should be noted that certain medications modulate the effects of tDCS, such as neuroleptic and antiepileptic drugs, antidepressants, benzodiazepines and L-Dopa (Hesse et al., 2007). When these safety criteria are adhered to, approximately 80% of neurological patients with chronic cerebrovascular disorders (i.e. stroke, intracerebral bleeding) are eligible for tDCS studies according to our experience. In order to monitor possible adverse effects of tDCS a questionnaire (Poreisz et al., 2007) or visual analog scales (Gandiga et al., 2006), containing questions about headache, mood changes, attention, fatigue or discomfort are recommended.

In sum tDCS is a safe stimulation method when certain standard procedures are followed. Nonetheless, further safety studies concerning longer stimulation intervals and higher stimulation intensities are necessary, especially when brain-lesioned subjects are to receive repetitive tDCS or single-session tDCS with higher current intensities (>1.5 mA), or when repeated applications are performed for therapeutic purposes.

2.5. Physiological mechanisms of action

The mechanisms of action of tDCS have yet to be elucidated. It has been frequently found that anodal (surface-positive) stimulation increases the spontaneous firing rate and the excitability of cortical neurons by depolarizing the membranes, whereas cathodal (surface-negative) stimulation leads to hyperpolarization of the neurons membranes and thus invokes a decrease of the neuronal firing rate and excitability (see Fig. 2). This pattern of activity was first shown in animals receiving stimulation *via* epidural or intracerebral electrodes (Bindman, Lippold, & Redfearn, 1962; Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965). The direction of cortical modulation is however not solely polarity-dependent, but also determined by the type and the spatial orientation of neurons as well as the stimulation intensity: Creutzfeldt et al. (1962) demonstrated that neurons in deeper layers of the cat motor cortex are activated by cathodal and inhibited by anodal stimulation,

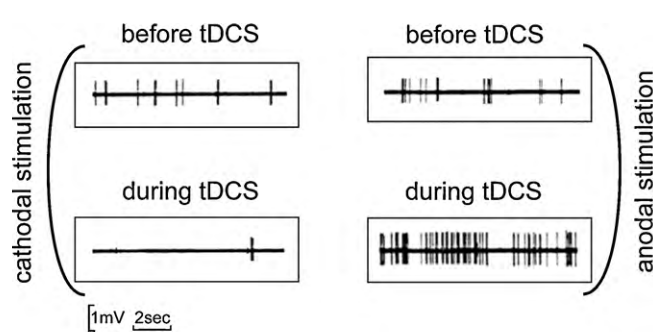

Fig. 2. Illustration of the physiological mechanisms of anodal (right side of figure) and cathodal (left side of figure) transcranial direct current stimulation on spike activity in animals (adapted and modified after Bindman et al., 1964). Anodal stimulation increased subsequent spike activity by lowering the membrane potential whereas cathodal stimulation reduced subsequent spike activity in the stimulated area by increasing the membrane potential.

probably as a result of the inversion of current flow associated with the neuron's spatial orientation. Furthermore, high current intensities are required to activate pyramidal cells, whereas non-pyramidal neurons are activated by weak stimulation strength (Purpura & McMurtry, 1965). Sustained excitability elevations have also been demonstrated in these early animal studies. Bindman et al. (1962) and Bindman, Lippold, and Redfearn (1964) showed aftereffects lasting for hours, induced by anodal cortical stimulation of 5–10 min in the rat (Bindman et al., 1962, 1964) which seem to be protein synthesis-dependent (Gartside, 1968).

Effects of tDCS in humans are quite consistent with the physiological mechanisms found in animals. Anodal stimulation increases cortical excitability, whereas cathodal stimulation has the reverse effect (Nitsche & Paulus, 2000). Nitsche and Paulus (2001) demonstrated prolonged aftereffects of tDCS up to 90 min in human motor cortex. The duration of these effects depend on stimulation duration and current intensity.

Pharmacological studies have shown that voltage-dependent ion channel blockers like carbamazepine and flunarizine diminish or even eliminate the effects during tDCS as well as the aftereffects of anodal stimulation (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche, Fricke, et al., 2003). On the other hand, the NMDA-receptor-antagonist dextromethorphane impedes the long-term effects of tDCS, irrespective of polarity (Nitsche, Fricke, et al., 2003). The authors conclude, that polarization effects of the neuronal membrane are responsible for the short-term effects of tDCS, whereas the long-lasting effects are caused by the modulation of NMDA receptor strength. Further evidence concerning the importance of NMDA receptors for the generation of aftereffects of tDCS comes from the observation that the partial NMDA agonist D-Cycloserine prolongs anodal tDCS-induced excitability enhancements (Nitsche, Jaussi, et al., 2004). The same is true for amphetamine, a catecholaminergic re-uptake-blocker, whose effects are prevented by additional application of an NMDA receptor antagonist (Nitsche, Grundey, et al., 2004). The shortening of anodal tDCS-induced aftereffects by application of the β-adrenergic antagonist proanolol indicates that the consolidation of the NMDA receptor-modulated cortical excitability modifications depends on adrenergic receptors (Nitsche, Grundey, et al., 2004). Cathodal tDCS-generated excitability reductions for up to 24 h after the end of stimulation were induced by dopaminergic receptor (D2) activation (Nitsche et al., 2006).

On the basis of these observations Liebetanz et al. (2002) and Nitsche, Fricke, et al. (2003) suggested NMDA receptor-dependent long-term potentiation (LTP) and long-term depression (LTD) as possible candidates for the explanation of the tDCS aftereffects. Both LTP and LTD are well-known phenomena of neuroplasticity. In contrast, Ardolino, Bossi, Barbieri, and Priori (2005) postulate a non-synaptic mechanism underlying the long-term effects of cathodal tDCS. They suggest that these long-term effects are caused by alterations in neuronal membrane function, possibly arising from changes in pH and in transmembrane proteins.

Nitsche et al. (2005) examined the excitability modulation generated by tDCS of the motor cortex *via* alterations of TMS parameters by tDCS. Global measures of cortico-spinal excitability such as motor thresholds and input–output curves were assessed as well as indirect wave (I-wave) interactions, intracortical facilitation and inhibition. I-waves are cortico-spinal waves, emerging after the first cortico-spinal burst and are presumably controlled by intracortical neuronal circuits. Nitsche et al. (2005) conclude that short-term stimulation depends on the alteration of subthreshold resting membrane potentials. In contrast, aftereffects are induced by changes of intracortical facilitation and inhibition.

3. Procedure for GVS

3.1. History

The history of GVS is like the history of tDCS based on Galvani's (1791) and Volta's (1792) experiments on animal and human electricity (see Section 2.1). Volta was the first who reported on the perceptual effects of electric stimulation in 1790, when putting electrodes in his ears. He felt a twitch and spinning in his head and heard a noise, which is unsurprising with a current strength of approximately 30 V. Breuer and Hitzig reported illusory body movement during stimulation with the electrodes placed on the mastdoids.

In 1820 Johann Purkyne systematically investigated the dizziness and disturbance of balance induced by galvanic stimulation. The first report on nystagmus resulting from galvanic stimulation stems from Hitzig who experimented on dogs and humans. By the combination of labyrinthectomy and galvanic stimulation in animals, Josef Breuer showed the vestibular origin of the induced nystagmus and balance distortions. Since that time GVS has been used for the investigation of the vestibular system in animals and humans (for a review see Fitzpatrick & Day, 2004).

3.2. Method

Stimulation of the vestibular system can be induced when the anode and cathode are applied to the left and right mastoids (or *vice versa*) behind the ears. This form of direct current stimulation is termed Galvanic Vestibular Stimulation (GVS). Underneath the mastoids the vestibular nerve runs from the inner ear towards vestibular brain stem nuclei, which in turn are interconnected with thalamic relay stations (nucleus ventroposterolateralis). From there, ascending vestibular fiber pathways reach a number of cortical vestibular areas including area 2cv near the central sulcus, area 3a,b in the somatosensory cortex, parietal area 7a, and the parieto-insular-vestibular-cortex (PIVC; Guldin & Grusser, 1998). Although there is no primary vestibular cortex as in the visual, auditory or tactile modality, the above-mentioned array of multiple, interconnected vestibular cortical areas is thought to be under the control of the PIVC. Fig. 3 illustrates schematically the mechanisms of GVS *via* stimulation of the mastoids behind the ears as well as the main anatomical pathways including subcortical and cortical relay stations.

3.3. Positioning of the electrodes

Stimulation with two electrodes of different polarity placed behind the mastoids is more precisely termed *bilateral bipolar GVS*. There are other electrode montages such as unilateral monopolar GVS, at which only one electrode is placed behind one ear or bilateral monopolar stimulation with two electrodes of the same polarity on both mastoids and a remote electrode of the other polarity (Fitzpatrick & Day, 2004). The application of the electrodes is identical to that of tDCS to the skull, as are most of the other features. Note however, that the physiological mechanism of action is different in GVS as tDCS as the current runs from the periphery to the cortex in GVS, whereas it runs directly from the skull into the underlying cortex in tDCS. Like tDCS, GVS is well suited for subliminal stimulation so that the subject is unaware of verum or placebo (sham) stimulation. This is an important advantage in neuroscientific research as the placebo or sham stimulation conditions can be more efficiently realized than with TMS.

3.4. Physiological mechanisms of action

GVS acts on the entire vestibular nerve *via* polarization effects, hence on otoliths *and* the semicircular canal, but not on the vestibular end organ (Stephan et al., 2005). This activation pattern is different from other vestibular stimulation techniques, for instance caloric vestibular stimulation which activates only the horizontal semicircular canal (Bottini et al., 1994; Dieterich et al., 2003), which in turn causes nystagmus.

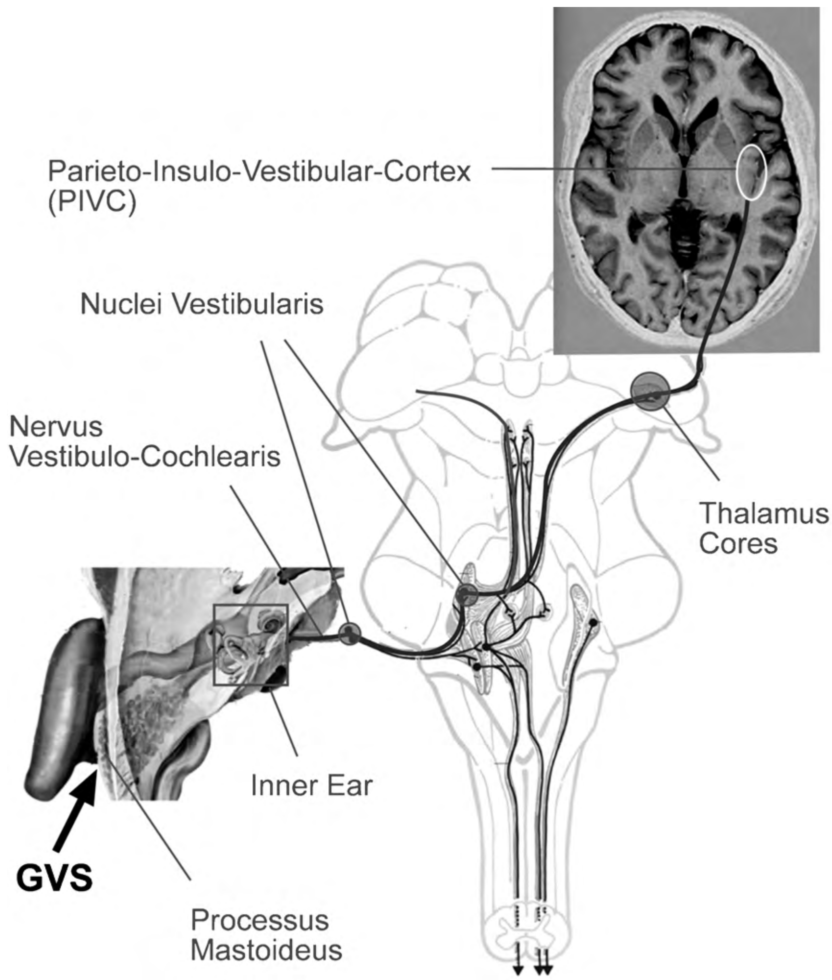

Fig. 3. Schematic illustration of the mechanisms of Galvanic Vestibular Stimulation (GVS). Stimulation at the mastoids (see arrow) activates the vestibular nerve, and subsequently all vestibular relay stations located upstream including nervus vestibulo-cochlearis, vestibular nuclei in the brainstem, thalamic nuclei and finally the parieto-insular vestibular cortex (PIVC), as well as adjacent areas such as the temporoparietal junction and the parietal cortex (not indicated).

Functional imaging studies of GVS using direct current stimulation (Bense, Stephan, Yousry, Brandt, & Dieterich, 2001; Bucher et al., 1998) have revealed a network of activated multisensory cortical areas including the insular and retroinsular regions, the superior temporal gyrus, temporo-parietal cortex, the basal ganglia and the anterior cingulate gyrus. Moreover, Fink et al. (2003) showed activations of the PIVC and the temporoparietal junction area during GVS in healthy subjects. Notably, left-anodal/right-cathodal GVS led to a *unilateral* activation of the right-hemispheric vestibular system, while left-cathodal/right-anodal GVS led to a *bilateral* activation of both vestibular cortices.

3.5. Safety

Until now, no formalized safety studies of GVS have been published to our knowledge. However, from our own experience with more than 50 patients with right-hemispheric stroke and 20 healthy subjects we know that subliminal (below the sensory threshold) GVS with approximately 0.6–0.8 mA current intensity for a maximum of 20 min is safe and does not produce any adverse effects in any of these 70 subjects (Utz, Kerkhoff, Oppenländer, unpublished observations).

In the following sections we will review studies that have used either tDCS or GVS in different fields of neuropsychology.

4. tDCS of the motor cortex

Most of the pioneering studies investigating the effects of tDCS on the modulation of cortical function were done on motor cortex (Nitsche & Paulus, 2000). The anatomy and physiology of motor cortex is comparatively well understood and previous TMS work on motor cortex has provided further information about how cortical stimulation affects the response of the motor system. This offers the opportunity to use motor-response parameters to quantify the effects of cortical stimulation. Two main groups of tDCS studies on motor cortex can be distinguished: (1) studies which use the motor cortex to investigate the physiological mechanisms underlying tDCS and (2) studies which use tDCS to study the function of the motor cortex and how its modulation affects motor behaviour. This section chiefly considers the second group (see Table 1 for a summary of the reviewed studies).

In a study with 24 healthy subjects (Cogiamanian et al., 2007) the effect of anodal stimulation of the right motor cortex on neuromuscular fatigue was investigated. Neuromuscular fatigue is the exercise-dependent decrease in muscle force which results from peripheral and cortical factors. This is relevant for many motor functions in daily life (Cogiamanian et al., 2007). Ten minutes of anodal tDCS (1.5 mA current intensity, motor cortex stimulation) produced a significant (15%) reduction in fatigue while cathodal tDCS and sham tDCS at the same site were ineffective. Hence, anodal tDCS may increase muscle endurance – a finding which may be of

Table 1
Selection of studies using tDCS of the motor cortex.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Boggio, Castro, et al. (2006)	Sham-controlled modulation study	One electrode over the right/left M1 at C3/C4[a] and the other electrode over the contralateral supraorbital area	1 mA for 20 min, 2 sessions, anodal vs. sham	8 healthy subjects	Enhancement of motor performance of the non-dominant hand after anodal stimulation of right M1
Boggio et al. (2007)	Sham-controlled-treatment study	M1 at C3/C4[a] (for anodal stimulation: anode over the M1 of the affected hemisphere; for cathodal stimulation: cathode over the M1 of the unaffected hemisphere); the other electrode over the contralateral supraorbital area	1 mA for 20 min/day, 4 sessions, anodal vs. cathodal vs. sham; 1 mA for 20 min/day, 5 sessions cathodal tDCS	9 stroke patients	Improvement of hand motor functions after anodal stimulation of M1 of the affected hemisphere and as well after cathodal stimulation of the unaffected hemisphere; similar improvement magnitude from both stimulation conditions; lasting effects after 5 sessions of cathodal tDCS of the unaffected hemisphere at 2-week-follow-up
Boros et al. (2008)	Modulation study	One electrode over the left premotor cortex (2.5 cm anterior to the left M1), the left DLPFC at F3[a] and the other electrode above the contralateral orbita	For anodal stimulation: 1 mA for 13 min, for cathodal stimulation: 1 mA for 9 min, 2 sessions anodal vs. cathodal	17 healthy subjects	Increased excitability of the ipsilateral motor cortex after anodal stimulation of the left premotor cortex in comparison to cathodal tDCS and anodal tDCS of the DLPFC; duration of effects: 30 min
Cogiamanian et al. (2007)	Modulation study	One electrode over the right motor cortex and the other electrode above the right shoulder	1.5 mA for 10 min, 2 sessions, anodal vs. cathodal	24 healthy subjects	Amelioration of neuromuscular fatigue after anodal stimulation of the right motor cortex; increase in endurance time of elbow flexor muscles in a submaximal isometric task 1 h after baseline fatigue task
Fregni, Boggio, Mansur, et al. (2005)	Double-blind, sham-controlled modulation study	M1 at C3/C4 (for anodal stimulation: anode over the M1 of the affected hemisphere; for cathodal stimulation: cathode over the M1 of the unaffected hemisphere); the other electrode over the contralateral supraorbital area	1 mA for 20 min, 3 sessions, anodal vs. cathodal vs. sham	6 stroke patients	Improvement of hand motor functions after anodal stimulation of M1 of the affected hemisphere and as well during and immediately after cathodal stimulation of the unaffected hemisphere
Hummel et al. (2006)	Pseudo-randomized, double-blind, sham-controlled, cross-over modulation study	Anode over M1 of the affected hemisphere and the cathode over the contralateral supraorbital area	1 mA for 20 min, anodal vs. sham	11 stroke patients	Improvement of hand motor functions measured as pinch force and reaction times of the paretic hand after anodal stimulation of the affected hemisphere
Jeffery et al. (2007)	Sham-controlled modulation study	One electrode over the left M1 (leg area) and the other electrode above the contralateral orbita	2 mA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	8 healthy subjects	Increase in the excitability of the leg corticospinal tract after anodal stimulation; duration of effects: 60 min

Table 1 (*Continued*)

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Lang et al. (2004)	Modulation study	One electrode over the left M1 and the other electrode over the contralateral orbita	1 mA for 10 min, 2 sessions, anodal vs. cathodal	8 healthy subjects	Increase after anodal and decrease after cathodal stimulation of the left M1 in MEPs evoked from the same hemisphere; duration of effects: <40 min; no changes in MEPs from right M1; effect on transcallosal inhibition only from right M1 (prolonged effect after anodal and shortened after cathodal tDCS)
Lang et al. (2005)	Sham-controlled modulation study; (PET)	One electrode over the left M1 and the other over the contralateral frontopolar cortex	1 mA for 10 min, 2 sessions, anodal vs. cathodal vs. sham	10 healthy subjects	Widespread increase and decrease in regional cerebral blood flow in cortical and subcortical areas of both hemispheres by anodal as well as cathodal stimulation; increase of rCBF after real tDCS (irrespective of polarity) in left M1, right frontal pole, right sensorimotor cortex, posterior brain regions; duration of effects: 50 min (during the PET scan).
Power et al. (2006)	Sham-controlled modulation study	One electrode over the left motor cortex and the other electrode over the contralateral orbita	1 mA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	10 healthy subjects	Increase in MEP size and in β-band intermuscular coherence after anodal stimulation; decrease in the same parameter after cathodal stimulation; duration of effects: 5–10 min, partially significant
Quartarone et al. (2004)	Sham-controlled modulation study	One electrode over the left M1 (motor cortical representation field of the right first dorsal interosseous muscle)[b] and the other electrode above the contralateral orbita	1 mA for 5 min, 3 sessions, anodal vs. cathodal	21 healthy subjects	Effects on cortical excitability (reduction of MEP size) during motor imagery by cathodal stimulation; duration of effects: 30 min; no effects after anodal stimulation
Reis et al. (2009)	Sham-controlled treatment study	Left M1 and above the contralateral supraorbital area	1 mA for 20 min, 5 sessions anodal vs. cathodal vs. sham	36 healthy subjects	Facilitation of motor learning after repetitive anodal stimulation; duration of effects: 3 months

M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; left/right: stimulation was conducted over the same cortical area in the left and the right hemisphere separately; MEP: motor evoked potentials.

[a] According to the international 10/20 EEG System.

[b] Revealed by TMS.

relevance to sports science but also of potential clinical interest for patients with pathologically altered muscle endurance. The data are in line with recent data showing that anodal tDCS of the motor cortex improves hand function in healthy subjects or patients with stroke (see below).

Lang, Nitsche, Paulus, Rothwell, and Lemon (2004) tested the influences of 10 min of anodal or cathodal tDCS applied to the left primary motor cortex (M1) on the following two parameters: (1) corticospinal excitability of the left and right motor cortex as measured by motor evoked potentials, and (2) transcallosal excitability between the motor cortices as measured by the onset latency and duration of transcallosal inhibition, in both cases assessed by TMS. Anodal tDCS over the left primary motor hand area (M1) increased the MEPs (+32%), whereas cathodal stimulation of the same location decreased MEPs (−27%). The duration of the aftereffect (40 min post-test) was longer in the cathodal condition. MEPs evoked from the right M1 were not affected, but the duration of inhibition from M1 was reduced after cathodal tDCS, and prolonged after anodal tDCS (Lang et al., 2004). The results indicate that the effects of tDCS were restricted to the hemisphere that was stimulated (but see the different results of the PET study by Lang et al., 2005). Power et al. (2006) also showed modulating effects of tDCS on motor evoked potentials. In this study, increased MEPs after anodal tDCS were accompanied by increased intramuscular coherence, and a decrease after cathodal tCDS. Sham stimulation influenced none of the parameters. Furthermore, tDCS seemed to also affect deeper seated parts of the motor cortex such as the leg area. Anodal tDCS of 2 mA intensity for 10 min increased the excitability of corticospinal tract projection to the tibialis anterior muscle of the lower leg as assessed by TMS-evoked MEPs (Jeffery, Norton, Roy, & Gorassini, 2007). On the contrary, cathodal tDCS under the same stimulation conditions seemed to produce only small changes in MEPs assessed at rest or during contraction of the tibialis anterior muscle.

A recent study by Boros, Poreisz, Munchau, Paulus, and Nitsche (2008) provided evidence that tDCS activates not only the directly stimulated area (the area under the location of the current application) but also interconnected brain areas within the same hemisphere. Anodal tDCS of the premotor cortex increased the excitability of the ipsilateral motor cortex compared with cathodal tDCS of the premotor cortex and anodal tDCS of the dorsolateral prefrontal cortex (DLPFC). These results may be taken as an indication that cortical activity can be modulated indirectly *via* tDCS of remote but interconnected brain areas. This indirect brain stimulation technique may be useful in certain pathological conditions, such as pain (see Section 8.2).

In a PET study (Lang et al., 2005) the aftereffects of 10 min of anodal and cathodal tDCS over the left M1 on regional cerebral blood flow were investigated. When compared with sham tDCS, anodal and cathodal tCDS induced widespread increases and decreases in regional cerebral blood flow in cortical *and* subcortical areas of *both* cerebral hemispheres. Interestingly, these changes in regional cerebral blood flow were of the same magnitude as task-related changes observed during finger movements. Both real tDCS conditions induced increased blood-flow in the left motor hand cortex, the right frontal pole, right primary sensorimotor cortex and posterior brain regions. Apart from some exceptions, anodal stimulation resulted in a widespread activation of dorsal brain areas (post-central sulcus, premotor cortex, SMA, prefrontal cortex, parietal cortex, precuneus, superior temporal gyrus, superior occipital sulcus) whereas cathodal stimulation mainly activated more ventral cortical areas (superior temporal sulcus and gyrus, insula, posterior cingulate gyrus, inferior occipital lobe). The effects were sustained for the duration of the PET scanning period (50 min). In sum, this important study shows long-lasting and widespread effects of 10 min tDCS on cortical blood flow. Although the complex activation patterns observed may in part depend on the precise location of the electrodes, it is obvious that tDCS not only induces activations or deactivations close to the electrodes, but also remote effects in *both* cerebral hemispheres, the latter indicating transcallosal interactions.

Boggio, Castro, et al. (2006) showed that anodal tDCS (20 min, 1 mA) compared with sham stimulation of the non-dominant M1 improved motor function as assessed by the Jebson Taylor Hand Function Test. This was not found for anodal and sham stimulation of the dominant M1. The authors assume that these results reflect cortical plasticity associated with the under-used non-dominant hand (Boggio, Castro, et al., 2006). Quartarone et al. (2004) investigated motor imagery, namely the effects of tDCS on imagined movements of one's own index finger. Subjects were required to imagine the abduction of their right index finger. Muscular relaxation in the course of the task was controlled by audio-visual EMG monitoring. Only cathodal tDCS over the left M1 reduced the size of the MEP amplitudes by 50% in the mental motor imagery paradigm while anodal tDCS had no effect. The aftereffects of cathodal tDCS lasted for up to 30 min.

DC stimulation also influences *long-term* skill motor learning. Reis et al. (2009) used a computerized motor skill task to evaluate the effects of anodal tDCS on the course of learning. They measured speed and accuracy in this task as online effects (within one training day), offline effects (between training days), short-term training effects (within 5 days of motor training) and long-term effects (at 3-month follow-up). The experimental training group received 5 sessions of 20 min anodal tDCS (1 mA, left M1 stimulation) whereas the two control groups received either sham stimulation or cathodal tDCS under the same study conditions. Anodal tDCS showed greater effects on the total learning effect (online + offline effects for the whole training period of 5 days) as cathodal or sham stimulation. These beneficial effects were maintained at follow-up, when the anodal group still performed better than the two other groups (Reis et al., 2009). These results demonstrate a facilitation of motor learning induced by multi-session, anodal tDCS of the motor cortex.

Another research field that has been opened by tDCS research is the induction of neuroplastic changes in stroke patients with contralateral hemiparesis. Fregni, Boggio, Mansur, et al. (2005), addressed the issues of stimulation condition (anodal vs. cathodal) and hemisphere (lesioned vs. intact) in 6 chronic (lesion age: 27 months), hemiparetic stroke patients. The patients received, in a counterbalanced design, either anodal tDCS over M1 of the affected hemisphere, or cathodal tDCS over M1 of the unaffected hemisphere or sham tDCS. The two verum stimulations (1 mA for 20 min, the other electrode at supraorbital area) showed significant improvements in the Jebsen-Taylor hand function test as assessed *after* tDCS. In contrast, only the cathodal tDCS over M1 of the unaffected hemisphere produced an *online* effect during stimulation, although the difference to the effect obtained with anodal tDCS was not statistically significant. A recent study by Boggio et al. (2007) replicated these findings in a new patient sample. Hummel et al. (2006) investigated the impact of anodal, cathodal and sham tDCS (1 mA for 20 min. over M1 of the motor cortex) of the affected hemisphere on performance in daily motor activities as assessed by the Jebsen-Taylor hand function test. All 6 patients showed contralateral hand pareses after ischemic brain infarctions sparing the primary motor cortex. Remarkably, every patient benefited from anodal tDCS but not sham or cathodal tDCS. These benefits outlasted the stimulation and correlated with parameters of motor cortical excitability as measured by TMS. Brain stimulation *via* tDCS may have an important adjuvant role in the treatment of motor impairments after stroke (see also Section 9.1).

To summarize, the studies reported here reveal that tDCS changes cortical excitability in the motor system and improves performance in daily motor tasks as well as motor learning and motor cognition, both in healthy subjects and clinical populations. Whilst the first clinical studies show very promising results of tDCS in motor rehabilitation they need to be replicated in larger, randomized controlled patient studies.

5. tDCS of the visual cortex

A number of studies have addressed the effects of tDCS on vision both in behavioural and electrophysiological paradigms (summarized in Table 2). Antal, Nitsche, and Paulus (2001) showed a reduction in contrast sensitivity during cathodal stimulation, but no improvement with anodal visual cortex stimulation. Cathodal tDCS of area V5 impaired visual motion discrimination while anodal stimulation improved it (Antal, Nitsche, et al., 2004). Other studies measured visual evoked potentials to study the effects of tDCS on visual-cortex activity. When stimulating over the occipital cortex (presumably V1) for at least 10 min, and using low-contrast stimuli, an increase in the N70 component was found with anodal stimulation and a decrease of this component with cathodal stimulation (Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004). Significant aftereffects were also shown in this study. In a related study, Accornero, Li Voti, La Riccia, and Gregori (2007) found slightly different results: they reported a decreased P100 component with anodal occipital stimulation and an increased P100 amplitude with cathodal stimulation. The differences are probably related to differences in the placement of the second electrode in the two studies. Finally, Antal, Varga, Kincses, Nitsche, and Paulus (2004) showed a decrease of the normalized gamma-band frequencies with cathodal occipital stimulation and a slight increase with anodal stimulation of the same site. This finding indicates that occipital DCS can alter neural networks involved in higher order cognitive functions (Herrmann, Munk, & Engel, 2004).

In clinical populations, tDCS over the visual cortex might be a promising technique to modulate residual visual capacities (Ro & Rafal, 2006), investigate blindsight (Stoerig & Cowey, 1997), or enhance treatments for patients with postchiasmatic visual field defects, for whom currently a number of successful *compensatory* treatment techniques have been developed (i.e. scanning: Roth et al., 2009; reading: Spitzyna et al., 2007; for a review see: Lane, Smith, & Schenk, 2008). However, no effective treatment for the visual field loss itself is currently available (Glisson, 2006). The upgrading of dysfunctional, perilesional remnants of the visual cortex or unmasking of subcortical visual areas important for visuomotor capacities might be achieved by anodal, occipital tDCS and assist compensatory treatment methods or even lead to novel visual treatments (Kerkhoff, 2000; Ro & Rafal, 2006).

In sum, until now, few studies have addressed the potential effects of tDCS of the visual cortex, especially of cortical visual areas beyond V1. The available evidence – mostly derived from stimulation of the primary visual cortex (V1, Oz electrode location) in healthy subjects – suggests modulatory effects in visual sensitivity or motion discrimination (after V5-stimulation) as well as significant aftereffects following 10–20 min of stimulation. In light of the known cortical architecture of the visual system and its multiple pathways and processing stages from V1 to more than 32 cortical and subcortical visual areas (Felleman & Van Essen, 1991) many interesting hypotheses remain to be tested: Does tDCS of the right occipito-temporal cortex modulate face perception or categorization, or that of the left occipito-temporal cortex shape or object perception and categorization (or *vice versa*)? What effects are obtained with tDCS of the superior temporal sulcus on the perception of social cues from the face (analogous to the effects of electrical stimulation with intracranial electrodes, cf. Allison, Puce, & McCarthy, 2000)? Can tDCS of the left or right lingual gyrus influence colour perception, categorization or colour imagery? Technically, it is easier to reach such ventral brain structures *via* tDCS than with TMS without inducing often painful activation of nearby nerves. Finally, future studies could investigate the effect of tDCS over different dorsal visual stream areas, such as the left or right parieto-occipital cortex to test its influence on visuospatial cognition, such as the judgment of spatial positions, orientation discrimination and the subjective visual vertical or constructional apraxia.

6. tDCS of the parietal cortex

6.1. Somatosensory cortex

Rogalewski, Breitenstein, Nitsche, Paulus, and Knecht (2004) tested the influence of stimulation of the somatosensory cortex on tactile discrimination of vibratory stimuli delivered to the left ring finger. They found that 7 min of cathodal but not anodal or sham stimulation disrupts tactile perception. Likewise, Dieckhofer et al. (2006) showed that cathodal stimulation decreased low-frequency components of somatosensory evoked potentials (SEPs) after contralateral median nerve stimulation. In another study, Ragert, Vandermeeren, Camus, and Cohen (2008) established that 20 min of anodal tDCS over the primary somatosensory cortex improves spatial tactile acuity in the contralateral index-finger. Furthermore, anodal tDCS of the primary somatosensory cortex led to long-lasting increases of SEPs recorded from the contralateral median nerve at the wrist. In contrast, no effects on SEPs were obtained after stimulation of the left median nerve or cathodal tDCS (Matsunaga, Nitsche, Tsuji, & Rothwell, 2004). Differences in stimulation duration and in size (Ragert et al., 2008) or location of the electrodes could have led to the diverging results (Dieckhofer et al., 2006).

In clinical populations (i.e. stroke, hemorrhage) somatosensory disturbances are a frequent (>50%, cf. Groh-Bordin & Kerkhoff, 2009) and disturbing occurrence which not only impaires touch and tactile object recognition but also motor performance. tDCS of the somatosensory cortex might be a promising add-on-technique that could augment the effects of behavioural trainings known to improve somatosensory capacities (Groh-Bordin & Kerkhoff, 2009; Wang, Merzenich, Sameshima, & Jenkins, 1995; Yekutiel & Guttman, 1993). Table 3 summarizes the reviewed studies concerning tDCS of the parietal cortex.

6.2. Posterior parietal cortex

So far, only a few studies have investigated the effects of tDCS of the posterior parietal cortex. Stone and Tesche (2009) investigated the effects of anodal and cathodal stimulation of the left posterior parietal cortex (P3 electrode location according to the 10–20 EEG reference system) on attentional shifts from global to local features and *vice versa* in 14 healthy subjects using single vs. compound letter stimuli. Their results indicate that cathodal stimulation acutely degraded attentional switches during stimulation, and anodal stimulation persistently degraded local-to-global attentional switching for at least 20 min after stimulation. These results support the involvement of the left parietal cortex in attentional switching. Another recent study by Sparing et al. (2009) addressed the question of interhemispheric parietal (im)balance in 20 healthy subjects and 10 patients with left spatial neglect using anodal and cathodal parietal stimulation (P3 and P4 electrode location). Sparing et al. (2009) found in their healthy subjects, that anodal stimulation enhanced visual target detection in the contralateral visual field in a demanding detection task, whereas cathodal stimulation depressed detection performance in the same task in the contralateral hemifield. Furthermore, the effects of anodal and cathodal tDCS were complementary: left parietal anodal stimulation had similar effects on target detection in the right visual field as right parietal cathodal stimulation and *vice versa*.

Table 2
Selection of studies using tDCS of the visual cortex in healthy subjects.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Accornero et al. (2007)	Modulation study	One electrode at Oz[a], the other electrode at the base of the posterior neck	1 mA for 3–10 min	20 healthy subjects	Increase of P100 amplitude during anodal stimulation and decrease during cathodal stimulation
Antal et al. (2001)	Modulation study	One electrode at Oz[a], the other electrode at Cz[a]	1 mA for 9 min, 2 sessions, anodal vs. cathodal	15 healthy subjects	No effect of anodal stimulation on static and dynamic contrast sensitivity. Cathodal stimulation impaired both dynamic and static contrast sensitivity during and up to 10 min post-stimulation
Antal, Nitsche, et al. (2004)	Modulation study	One electrode at left V5, the other at Cz[a]	1 mA for 10 min, 2 sessions, anodal vs. cathodal	8 healthy subjects	Modified motion perception threshold during anodal and cathodal stimulation
Antal, Kincses, et al. (2004)	Modulation study	One electrode at Oz[a], the other at Cz[a]	1 mA for 20 min, 2 sessions, anodal vs. cathodal	20 healthy subjects	Increase in the N70 amplitude of the visual evoked potential during and up to 10 min after anodal stimulation. Cathodal stimulation without effect
Antal, Varga, et al. (2004)	Modulation study	One electrode at Oz[a], the other at Cz	1 mA for 10 min, 2 sessions, anodal vs. cathodal	12 healthy subjects	Cathodal stimulation decreased normalized gamma and beta oscillatory frequencies in the evoked potential while anodal stimulation slightly increased it

[a] According to the international 10/20 EEG System.

Hence, the activation of the left parietal cortex and the deactivation of the right parietal cortex resulted in a similar performance increase in the right hemifield. Moreover, Sparing et al. (2009) found that *deactivating* the left (anatomically intact) parietal cortex with cathodal tDCS in patients with left visual hemineglect after right-hemisphere stroke led to an improvement in leftsided visual target detection, while *activation* of the right (lesioned) parietal cortex via anodal tDCS also improved leftsided target detection. Finally, lesion size correlated negatively with the beneficial effect of tDCS on neglect, indicating the strongest effects in patients with smaller lesions. This study elegantly demonstrates the concept of interhemispheric competition, originally formulated by Kinsbourne (1977) for spatial attentional processes by using the method of biparietal tDCS.

Although this idea of interhemispheric (im)balance or rivalry is well established in motor research (cf. Nowak, Grefkes, Ameli, & Fink, 2009) it has only rarely been investigated in attentional and neglect research. This is surprising, given the early description of this concept by Kinsbourne (1977) and abundant animal research on neglect in cats favouring such an interhemispheric account of neglect. Rushmore, Valero-Cabre, Lomber, Hilgetag, and Payne (2006) have shown in a series of experiments, that unilateral cooling deactivation of the cat's (i.e. right) perisylvian cortex results in leftsided visual neglect. However, subsequent cooling of the contralateral (i.e. left) mirror-symmetric cortex to the same temperature restores normal orienting behaviour. Further cooling of the left perisylvian cortex to an even lower temperature induces then *rightsided* visual neglect, which can again be cancelled by subsequent cooling of the right perisylvian cortex to the same temperature, and so on. These results – as exciting as they are – have so far had only little impact on human neglect models. Most of the models of human neglect assume some intrahemispheric (mostly right-hemispheric) deficient mechanism that is related to certain (parieto-temporal, subcortical) brain areas or disrupted fibre pathways such as the superior longitudinal fasciculus (Bartolomeo, Thiebaut de Schotten, & Doricchi, 2007) of the damaged hemisphere. Treatment approaches derived from such models therefore strive to activate this damaged hemisphere with different stimulation techniques, i.e. prism adaptation, optokinetic stimulation, attentional training, neck-muscle-vibration or related approaches (for review see Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Kerkhoff, 2003). Treatment approaches derived from a model of dysfunctional interhemispheric competition in unilateral (i.e. leftsided) neglect would suggest that the intact (left) hemisphere is hyperactive and the lesioned (right) hemisphere hypoactive. Consequently, three potential ways of intervention could reduce this leftsided neglect: (a) deactivation of the hyperactive left hemisphere; (b) activation of the hypoactive right hemisphere, and (c) a combination of both. A recent study by Nyffeler, Cazzoli, Hess, and Muri (2009) impressively illustrates the potential of this different treatment approach. The authors tested whether a deactivation of the intact (left) parietal cortex *via* repetitive TMS (theta-burst-stimulation) induces long-lasting recovery from spatial neglect. In their study they found that two stimulation sessions over the intact parietal cortex led to a reduction of left spatial neglect for 8 h, while 4 stimulation sessions prolonged this therapeutic effect up to 32 h. This encouraging result could possibly be also achieved by the technically much less demanding technique of repetitive parietal tDCS or GVS (see below).

Another interesting avenue for further research in this field is to assess the effect of *combined* parietal tDCS and sensory stimulation techniques known to alleviate neglect such as optokinetic stimulation, prism adaptation or attentional training. As tDCS (and probably also GVS) produce clear aftereffects (see Section 3 of this review) it could significantly augment and prolong the therapeutic effects of such neglect treatments, without requiring additional time, which by themselves are still too ineffective to enable full independence or even return to work in neglect patients (Bowen & Lincoln, 2007).

7. Effects of Galvanic Vestibular Stimulation

So far, very few studies have dealt with GVS in the field of neuropsychology (summarized in Table 4). The *behavioural* effects of

Table 3
Selection of studies using tDCS of the parietal cortex in healthy subjects or patients.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
(a) Somatosensory cortex					
Dieckhofer et al. (2006)	Modulation study	16 electrodes over the somatosensory cortex and 16 electrodes over the contralateral forehead	1 mA for 9 min, 2 sessions, anodal vs. cathodal	10 healthy subjects	Decrease of low-frequency components of SEPs by cathodal stimulation lasting for 60 min after the end of stimulation
Matsunaga et al. (2004)	Modulation study	Left motor cortex: over the central field of the right abductor pollicis brevis muscle and above the contralateral orbita	1 mA for 10 min, 2 sessions, anodal vs. cathodal	8 healthy subjects	Increase of SEPs by anodal stimulation lasting for 60 min after the end of stimulation
Ragert et al. (2008)	Sham-controlled modulation study	Over C3′, 2 cm posterior to C3[a] and above the contralateral orbita	1 mA for 20 min, 2 sessions, anodal vs. sham	10 healthy subjects	Improvement of spatial tactile acuity by anodal stimulation lasting for 40 min after the end of stimulation
Rogalewski et al. (2004)	Sham-controlled modulation study	Over C4[a] and above the contralateral orbita	1 mA for 7 min, 3 sessions, anodal vs. cathodal vs. sham	13 healthy subjects	Disruption of tactile discrimination of vibratory stimuli by cathodal stimulation lasting for 7 min after the end of stimulation
(b) Posterior parietal cortex					
Sparing et al. (2009)	Sham-controlled modulation study	Left parietal cortex (P3[a]) vs. right parietal cortex (P4[a])	57 μA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	20 healthy subjects; 10 patients with leftsided visual neglect	Healthy subjects: anodal stimulation enhanced visual target detection in contralateral visual hemifield, cathodal stimulation depressed it. Neglect patients: anodal stimulation of right parietal cortex improved target detection in left visual hemifield; cathodal stimulation of left parietal cortex improved target detection in left visual hemifield.
Stone and Tesche (2009)	Sham-controlled modulation study	Left parietal cortex (P3[a])	2 mA for 20 min, 3 sessions: anodal vs. cathodal vs. sham	14 healthy subjects	Cathodal stimulation impaired attention switches from local to global visual processing; Anodal stimulation impaired local-to-global switching for at least 20 min post-stimulation

SEPs: somatosensory evoked potentials.
[a] According to the international 10/20 EEG System.

anodal GVS in healthy subjects include a slight ipsiversive ocular tilt reaction of 0.5–3.7° (Zink, Steddin, Weiss, Brandt, & Dieterich, 1997), a modest perceptual tilt of the subjective visual and tactile vertical in the roll plane (Mars, Popov, & Vercher, 2001) and a sensation of lateral or rotational self-motion (with higher current intensities) which is often viewed as a core sign of vestibular stimulation induced by GVS (Stephan et al., 2005).

Two recent studies have investigated the influence of GVS on cognitive functions in healthy subjects. Wilkinson and colleagues (Wilkinson, Nicholls, Pattenden, Kilduff, & Milberg, 2008) showed that subsensory anodal stimulation over the left mastoid speeds visual memory recall of faces. Lenggenhager, Lopez, and Blanke (2008) showed in healthy subjects increased response times in a mental transformation task during anodal right-mastoid, but not during anodal left-mastoid GVS. Interestingly, this disrupting effect was only evident in subjects using an egocentric transformation strategy (that is, they imagined turning themselves) to solve the task, and not in those subjects using an allocentric strategy (imagining that the environment is rotated; Lenggenhager et al., 2008). This study therefore suggests that GVS seems to act more on ego- rather than allocentric spatial cognition, and neatly illustrates the interaction of the physiological stimulation with individual processing strategies.

Fink et al. (2003) showed in healthy subjects the effect of GVS on horizontal line bisection and related it to significant activations in the right parietal and frontal cortex during cathodal GVS of the right mastoid.

Clinical studies with parietally lesioned patients show a strong influence of GVS on a variety of multimodal spatial cognition tasks, including neglect, which is in agreement with the multisensory properties of the activated vestibular cortical areas outlined above. Rorsman, Magnusson, and Johansson (1999) showed in an early pioneering study the effects of subliminal GVS on the line cancellation task in 14 patients suffering from visual-spatial neglect. With the anode on the left and the cathode on the right mastoid, the authors showed an improvement of target detection in the left hemifield of the line crossing task during GVS. Saj, Honore, and Rousseaux (2006) showed that left-cathodal GVS improved the contraversive tilt of the subjective visual vertical in patients with a right hemispheric lesion, whereas right-cathodal stimula-

Table 4
Selection of studies using Galvanic Vestibular Stimulation (GVS) in healthy subjects or neurological patients.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Fink et al. (2003)	Modulation study	One electrode on the left and the other on the right mastoid	2–3 mA for periods of 24 s (rise time of 2 mA/s), left-anodal/right-cathodal vs. right-anodal/left-cathodal	12 healthy subjects	Activations (as indicated by fMRI) in the right posterior parietal and ventral premotor cortex when performing a horizontal line bisection task during left-anodal/right-cathodal GVS
Lenggenhager et al. (2008)	Sham-controlled modulation study	Two electrodes at both mastoids (one anode, one cathode) + 2 reference electrodes 5 cm below at the neck	1.0 mA (±0.2 mA) for epochs of 10 or 15 s during task performance	11 healthy subjects	A: slight tilt of visual vertical towards the anode B: Increase of response times in a mental transformation task during right-anodal/left-cathodal stimulation → impairment of mental transformation by GVS but only in subjects using an ego-centric vs. object-centric processing strategy
Mars et al. (2001)	Modulation study	One electrode on the left and the other on the right mastoid	1.25 mA, 2.5 mA left-anodal/right cathodal vs. right-anodal/left-cathodal vs. no stimulation	14 healthy subjects	Tilt of the visual and haptic vertical in the frontal plane towards anode; larger tilts with higher current intensity
Rorsman et al. (1999)	Sham-controlled modulation study	Anode on the left and cathode on the right mastoid	Subsensory stimulation (median 1.15 mA); left-anodal/right-cathodal vs. sham	14 stroke patients with left-sided neglect	Improvement of target detection in the left hemifield of the line-crossing task during left-anodal/right-cathodal stimulation
Saj et al. (2006)	Sham-controlled modulation study	One eletrode on the left and the other on the right mastoid	1.5 mA; left-anodal/right-cathodal vs. right-anodal/left-cathodal vs. sham	12 patients with right-hemispheric lesions and 8 healthy individuals	Reduction of the contraversive tilt of the subjective visuo-haptic vertical in patients with right-hemispheric lesions, especially when neglect was present
Wilkinson et al. (2008)	Sham-controlled modulation study	One eletrode on the left and the other on the right mastoid	Subsensory, noise-enhanced stimulation; Subsensory, constant stimulation (mean: 0.8 mA)	Exp. 1: 12 healthy subjects Exp. 2: 12 healthy subjects	Speeding up of visual memory recall of faces during left-anodal/right-cathodal stimulation (reaction-time decrease by 0.5 s)
Zink et al. (1997)	Modulation study	One eletrode on the left and the other on the right mastoid	1.5–3 mA seven times at 10 s intervals, unipolar stimulation	12 healthy individuals	Ipsiversive ocular torsion (0.5–3.7°), a contralateral tilt of the peripheral visual field (1–9°) and of a foveal vertical line (0.5–6.2°) during anodal stimulation of the right mastoid

tion aggravated the tilt, but to a lesser extent. These modulatory effects were larger in patients with neglect compared with right-brain damaged patients without neglect.

Fig. 4 shows the effects of GVS on horizontal line bisection in patients with leftsided visual neglect following right cerebral brain lesions. Left cathodal GVS leads to a nearly full normalization of the initial rightward deviation in line bisection (Oppenländer et al., unpublished observations) typically observed in these patients (Fink et al., 2003). A similar effect was seen on cancellation performance in the same patient group (see Fig. 4B) as well as in the perception of the subjective visuo-haptic vertical in right brain damaged patients (Fig. 4C; Oppenländer et al., unpublished observations). Although this online-effect is temporary it would be interesting to evaluate repetitive, multi-session GVS in such patients. In accordance with other sensory stimulation techniques (Kerkhoff, 2003) such as optokinetic stimulation (Kerkhoff, Keller, Ritter, & Marquardt, 2006), transcutaneous electric stimulation (Pizzamiglio, Vallar, & Magnotti, 1996; Schroder, Wist, & Homberg, 2008), or head-on-trunk rotation (Schindler & Kerkhoff, 1997) the prediction would be that repetitive GVS could induce a permanent, though perhaps partial, recovery of line bisection or cancellation deficits in neglect patients.

A phenomenon which is often associated with the neglect syndrome and occurs quite often after unilateral right- or leftsided cortical damage is extinction. In extinction, the patient is unimpaired in the processing of a stimulus presented *unilaterally* to the right or left side but shows a contralateral processing deficit when stimuli are presented simultaneously on both sides (Bender, 1977). This phenomenon can be significantly modulated by peripheral repetitive magnetic stimulation of the hand (Heldmann, Kerkhoff, Struppler, Havel, & Jahn, 2000). Fig. 4D shows findings from a patient with chronic leftsided tactile extinction caused by an intracerebral bleeding into the superior parietal region of the right hemisphere (lesion age: 5 years). Left cathodal GVS but not sham or right cathodal stimulation reduced leftsided tactile extinction by 40% as compared with baseline (Kerkhoff, Dimova, & Utz, unpublished observations).

Other disorders of spatial cognition frequently observed in patients with brain damage are constructional apraxia (Grossi & Trojano, 2001) and impaired spatial navigation (de Renzi, 1982). Patients with neglect and spatial cognition deficits are also often unaware of their neurological impairments such as a contralesional hemiparesis (Karnath, Baier, & Nagele, 2005). Given the knowledge of GVS-induced activations in brain areas such as the supramarginal

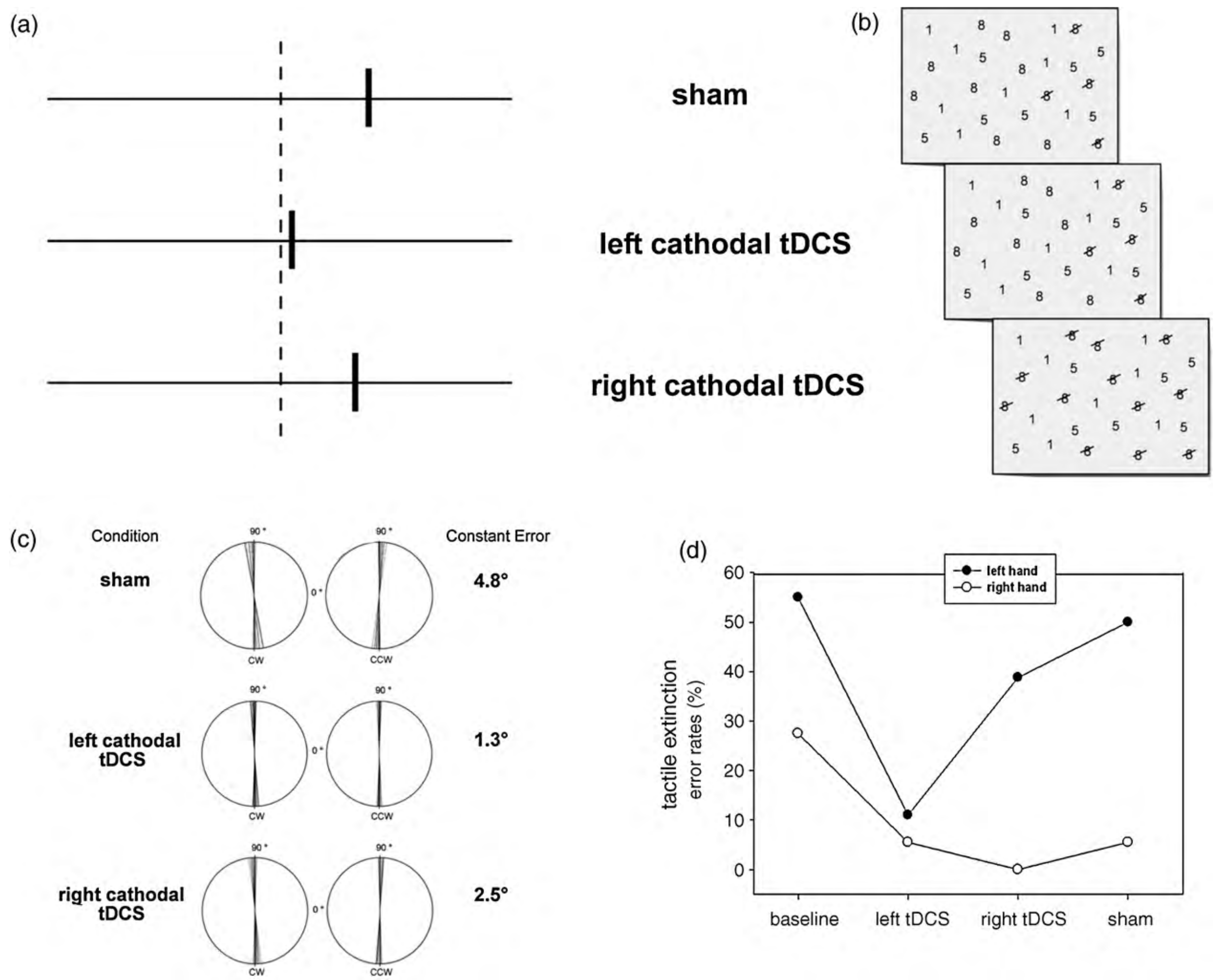

Fig. 4. Illustration of the effects of Galvanic Vestibular Stimulation (tDCS of the mastoids behind the ears) on different aspects of spatial cognition. (A) Effect of tDCS on horizontal line bisection. Left-cathodal stimulation normalizes the typical rightward bias of patients with leftsided visual neglect, while right-cathodal stimulation has no effect when compared with the baseline. (B) Effects of tDCS on cancellation performance in a patient with leftsided visual neglect. Right-cathodal stimulation improved cancellation performance, while left-cathodal stimulation had no significant effect when compared with sham-stimulation (electrodes mounted, but no current delivered). (C) Effect of tDCS on the judgment of the subjective visual vertical in patients with unilateral right-hemispheric brain lesions. During left cathodal stimulation the contralesional tilt of the visual vertical typically observed in these patients (Kerkhoff, 1999) is transiently normalized (data presented in A, B, C: Oppenländer et al., unpublished observations). (D) Improvement of leftsided tactile extinction in a chronic patient with a right parietal lesion and severe leftsided tactile extinction. Note the significant reduction of leftsided tactile extinction errors (see arrow) during left-cathodal stimulation at the mastoid, while sham tDCS or right cathodal tDCS had no effect (data from Kerkhoff, Dimova, & Utz, unpublished observations).

gyrus and the posterior insula it might be promising to evaluate modulatory effects of GVS on neuropsychological deficits, such as neglect, extinction, spatial cognition deficits and unawareness. Future studies addressing these research questions could not only help to uncover a possible "vestibular" influence on these neuropsychological disorders but also identify novel and more effective treatment techniques for affected patients.

8. Effects of tDCS on mood, pain and cognitive functions

8.1. Mood

The idea of treating mood disorders with tDCS is not new since Aldini, as stated before, used this technique in 1804 to treat melancholic patients successfully. When tDCS had its comeback in the 1960s, Costain, Redfearn, and Lippold (1964) conducted a controlled double-blind trial with 24 depressed patients (see summary in Table 5a). The anode was placed over each eyebrow and the cathode on the leg and a current of 0.25 mA was delivered on several days, each session lasting for 8 h. The authors reported an antidepressant effect of the stimulation as indicated by psychiatrists' and nurses' ratings as well as self-ratings. Recently, Koenigs, Ukueberuwa, Campion, Grafman, and Wassermann (2009) reexamined this technique of bilateral frontal tDCS with an extra-cephalic electrode in 21 healthy individuals and concluded that it had no effect on affect, arousal, emotional state, emotional decision-making or psychomotor functions. In another study, stimulation with bilaterally attached electrodes at fronto-cortical sites and on the mastoids led to an improvement of mood after stimulation during wake intervals and during sleep (Marshall, Molle, Hallschmid, & Born, 2004).

Fregni, Boggio, Nitsche, Marcolin, et al. (2006) investigated the effects of repeated stimulation on major depression. In a controlled, randomized double-blind trial, they treated 10 patients with anodal stimulation of the left DLPFC. A total of 5 sessions distributed over 9 days were provided. The scores in the Beck Depression Inventory and the Hamilton Depression Rating Scale in the treatment group decreased significantly as compared with their baseline scores. Boggio, Rigonatti, et al. (2008) reported effects lasting for 4 weeks after 10 sessions (during 2 weeks) of anodal stimulation over the left DLPFC in 40 medication-free patients suffering from major depression.

Table 5
Selection of studies investigating the effects of tDCS on mood (a), pain (b) and cognitive functions (c) in healthy subjects or patients.

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
(a) Mood					
Boggio et al. (2007)	Randomized, double-blind, sham-controlled	Left DLPFC: anode over F3[a]; occipital cortex: anode placed on the midline and 2 cm above the inion; cathode over the left supraorbital area in each case	2 mA for 20 min/day on 10 days, anodal vs. sham	26 patients with major depression	Improvement in an affective go-no-go task after 1 session anodal stimulation of the left DLPFC; no correlation with mood changes after 10 stimulation sessions
Boggio, Rigonatti, et al. (2008)	Randomized, double-blind, sham-controlled	Left DLPFC: anode over F3[a]; occipital cortex: anode placed on the midline and 2 cm above the inion; cathode over the left supraorbital area in each case	2 mA for 20 min/day on 10 days, anodal left prefrontal vs. anodal occipital vs. sham	40 patients with major depression	Reduction of Scores in the Beck Depression Inventory and Hamilton Depression Rating Scale after anodal prefrontal stimulation; stable for 4 weeks after end of intervention
Boggio et al. (2009)	Randomized, double-blind, sham-controlled, cross-over	M1: anode over C3[a], DLPFC: anode over F3[a], occipital cortex: anode over Cz[a], cathode over the contralateral suborbital area in each case	2 mA for 5 min, 4 sessions, anodal motor cortex vs. anodal DLPFC vs. anodal occipital cortex vs. sham	23 healthy subjects	Reduction of discomfort and unpleasantness ratings of aversive pictures during DLPFC stimulation
Costain et al. (1964)	Randomized, double-blind, sham-controlled, cross-over	Anodes placed over each eyebrow and cathode on one leg	0.25 mA for 8 h/day over 12 days, anodal vs. sham	24 depressed patients	Antidepressant effect psychiatrists' and nurses' ratings and self-ratings
Fregni, Boggio, Nitsche, Marcolin, et al. (2006)	Randomized, double-blind, sham-controlled	Left DLPFC, anode placed over F3[a], cathode over the contralateral supraorbital area	1 mA for 20 min/day on 5 days, anodal vs. sham	10 patients with major depression	Decrease of Scores in the Beck Depression Inventory and Hamilton Depression Rating Scale after anodal stimulation
Koenigs et al. (2009)	Double-blind, sham-controlled, cross-over	Two electrodes placed on the forehead over F_{p1}[a] and F_{p2}[a] and one on the non-dominant arm	2.5 mA for 35 min, 3 sessions, anodal vs. cathodal vs. sham	21 healthy subjects	No effect on affect, arousal, emotional state, emotional decision-making and psychomotor functions
Marshall et al. (2004)	Double-blind, sham-controlled, cross-over	Bilateral fronto-lateral, anodes over F3[a] and F4[a] and cathodes at the mastoids	0.26 mA/cm^2 intermittently stimulation (15 s on, 15 s off) for 30 min during sleep and wakefullness, 2 sessions, anodal vs. sham (double-blind, cross-over)	30 healthy men	Improvement of mood after stimulation during wake intervals and during sleep
(b) Pain					
Antal et al. (2008)	Sham-controlled modulation study	One electrode over the left S1[b] and the other electrode over the right eyebrow	1 mA for 15 min, 3 sessions, anodal vs. cathodal vs. sham	10 healthy subjects	Decrease in perceived pain intensity and in the amplitude of N2 component under laser stimulation of the contralateral hand to the side of tDCS after cathodal stimulation
Boggio, Zaghi, et al. (2008)	Double-blind, randomized, sham-controlled modulation study	M1: anode over C3[a], DLPFC: anode over F3[a], V1: anode over Oz[a]; cathode over the contralateral supraorbital area in each case	2 mA for 5 min, 2 sessions, anodal vs. sham	20 healthy subjects	Increase in perception and pain thresholds during anodal stimulation of M1; increase in pain threshold during anodal stimulation of DLPFC; no effect for occipital anodal or sham stimulation
Chadaide et al. (2007)	Sham-controlled modulation study	One electrode over occipital cortex at Oz[a] and other electrode at Cz[a]	1 mA for 10 min, 3 sessions, anodal vs. cathodal vs. sham	16 migraine patients with and without aura; 9 healthy subjects	Decrease in phosphene thresholds in migraine patients as in the healthy subjects after anodal stimulation; larger effect in migraine patients with aura

Table 5 (*Continued*)

Reference	Type of study	Position of electrodes	Stimulation parameters	Population	Effects
Fregni, Boggio, Lima, et al. (2006)	Double-blind, randomized, sham-controlled, parallel-group treatment study	M1: anode over C3/C4[a] (for patients with asymmetric pain contralateral M1; for patients with symmetric pain the dominant left M1); cathode over the contralateral supraorbital area; sham stimulation of M1	2 mA for 20 min/day on 5 consecutive days	17 patients with central pain after traumatic spinal cord injury	Improvement in pain intensity ratings after treatment with anodal stimulation over M1; no adverse effects on cognitive functions; duration of effects: no significant effects at 16 days-follow-up
Fregni, Gimenes, et al. (2006)	Double-blind, randomized, sham-controlled, parallel-group treatment study	M1: anode over C3[a] (for patients with asymmetric pain contralateral M1; for patients with symmetric pain the dominant left M1), left DLPFC: anode over F3[a]; cathode over the contralateral supraorbital area; sham stimulation of M1	2 mA for 20 min/day on 5 consecutive days	32 female patients with fibromyalgia	Improvement in pain ratings after treatment with anodal stimulation over M1; mild adverse effects after both active stimulation as well as after sham stimulation; duration of effects: lasting effects at 3-week-follow-up
Roizenblatt et al. (2007)	Double-blind, randomized, sham-controlled, parallel-group treatment study	M1: anode over C3[a] (for patients with asymmetric pain contralateral M1; for patients with symmetric pain the dominant left M1), left DLPFC: anode over F3[a]; cathode over the contralateral supraorbital area; sham stimulation of M1	2 mA for 20 min/day on 5 consecutive days	32 female patients with fibromyalgia	Increase in sleep efficacy and delta activity in non-REM sleep after M1 anodal stimulation; decrease in sleep efficacy, and increase in REM and sleep latency after DLPFC anodal stimulation; improvement in clinical parameters associated with increase in sleep efficacy after M1 stimulation
(c) Cognitive functions					
Beeli et al. (2008)	Modulation study	Left and right DLPFC: over F3[a] or F4[a] and on the ipsilateral mastoid	1 mA for 15 min, 2 sessions, anodal vs. cathodal	24 male subjects	More cautious driving behaviour in a driving simulator after anodal stimulation
Boggio, Ferrucci, et al. (2006)	Single-blind, sham-controlled modulation study	Left DLPFC: anode over F3[a]; Motor Cortex: anode over M1; cathode over the contralateral right orbit in each case	1 mA (study 1) and 2 mA (study 2) for 20 min, 3 sessions, anodal DLPFC vs. anodal M1 vs. sham	18 patients with Parkinson's disease	Improved accuracy in performance during a three back working memory task by anodal tDCS of the left DLPFC with 2 mA
Boggio, Khoury, et al. (2008)	Single-blind, sham-controlled modulation study	Left DLPFC: anode over F3[a]; left temporal cortex: anode over T7[a]; cathode over the right supraorbital area in each case	2 mA for 30 min, 3 sessions, anodal left DLPFC vs. anodal left temporal cortex vs. sham	10 patients with Alzheimer's disease	Improved performance in an visual recognition memory task during anodal stimulation over the left DLPFC and the left temporal cortex
Fecteau et al. (2007)	Randomized, single-blind, sham-controlled modulation study	Left and right DLPFC: anode over F3[a] and cathode over F4[a] and vice versa (study 1); anode over F3[a] or over F4[a] and cathode over the contralateral orbita (study2)	2 mA < 20 min, 1 session, anodal vs. cathodal vs. sham	35 healhty subjects	Reduction in risk-taking behaviour during bilateral stimulation of the left or right DLPFC (with the cathode over the contralateral DLPFC)

Ferrucci, Mameli, et al. (2008)	Blinded subjects and observer, sham-controlled modulation study	Bilateral temporoparietal: over P3[a]–T5[a] (left side), P6[a]–T4[a] (right side) and over the right deltoid muscle	1.5 mA for 15 min, 3 sessions, anodal vs. cathodal vs. sham	10 patients with probable Alzheimer's disease	Anodal stimulation improved the accuracy in a word recognition memory task 30 min post-stimulation, whereas cathodal stimulation decreased performance
Ferrucci, Marceglia, et al. (2008)	Single-blind, sham-controlled modulation study	Cerebellum: 2 cm under the inion, 2 cm posterior to the mastoid process and over the right deltoid muscle; prefrontal corex: between F_{p1}[a] and F3[a] (left side) and between F_{p2}[a] and F4[a] (right side) and over the right deltoid muscle	2 mA for 15 min, 3 sessions, anodal vs. cathodal vs. sham	13 healthy subjects	Disruption of the practice-dependent improvement in reaction times during a modified Sternberg verbal memory task 35 min after anodal and cathodal cerebellar tDCS
Fregni, Boggio, Nitsche, et al. (2005)	Single-blind, sham-controlled modulation study	Left DLPFC: anode over F3[a], cotor cortex: anode over M1, cathode over the contralateral suborbital area in each case	1 mA for 10 min, 2 sessions, anodal vs. cathodal	15 healthy individuals	Improved accuracy of performance during a sequential-letter working memory task during anodal stimulation over the left DLPFC
Fregni, Boggio, Nitsche, Riganotti, et al. (2006)	Blinded subjects and observer, randomized, sham-controlled treatment study	Left DLPFC: anode over F3[a], cathode over the contralateral suborbital area	1 mA for 20 min/day on 5 alternate days, anodal vs. sham	18 patients with major depression	Improvement in a digit-span (forward and backward) task
Kincses et al. (2004)	Randomized modulation study	Occipital cortex: over Oz[a] and Cz[a]; left prefrontal cortex: over F_{p3}[a] and Cz[a]	1 mA for 10 min, 3 sessions, anodal vs. cathodal	22 healthy individuals	Improvement of implicit classification learning during anodal stimulation of the left prefrontal cortex
Marshall et al. (2004)	Double-blind, sham-controlled cross-over modulation study	Bilateral fronto-lateral, anodes over F3[a] and F4[a] and cathodes at the mastoids	0.26 mA/cm^2 intermittently stimulation (15 s on, 15 s off) for 30 min during sleep and wakefullness, 2 sessions, anodal vs. sham	30 healthy men	Improved retention of word pairs after anodal stimulation during periods rich in slow-wave sleep
Marshall et al. (2005)	Double-blind, sham-controlled cross-over modulation study	Bilateral fronto-lateral, anodes over F3[a] and F4[a] and cathodes at the mastoids	0.26 mA intermittently stimulation (15 s on, 15 s off) for 15 min, 3 sessions, anodal vs. cathodal vs. sham	12 healthy individuals	Impaired response selection and preparation in a modified Sternberg task during anodal and cathodal stimulation

S1: primary somatosensory cortex; M1: primary motor cortex; DLPFC: dorsolateral prefrontal cortex; V1: primary visual cortex.

[a] According to the international 10/20 EEG System.

[b] According to Talairach coordinates.

Furthermore, a single session of anodal tDCS of the left DLPFC combined with cathodal stimulation of the frontopolar cortex improved the performance in an affective go-no-go task in 26 patients with major depression, but only for pictures containing positive emotions. No significant correlation with mood changes that were assessed after 10 treatments with tDCS was obtained. The authors conclude that the left DLPFC plays a role in the processing of *positive* emotions but that the effects of tDCS on cognition and mood in major depression are independent of each other (Boggio et al., 2007).

A study investigating the effects of tDCS on emotions associated with pain revealed a reduction of discomfort and unpleasantness ratings of aversive pictures during tDCS over the DLPFC. These results suggest that the DLPFC is involved in emotional pain processing and that different pathways are critical in tDCS-evoked modulation of pain-related emotions and somatosensory pain perception (Boggio, Zaghi, & Fregni, 2009). Table 5 summarizes the studies concerning the effects of tDCS on mood, pain and cognitive functions.

8.2. Pain

Antal et al. (2008) demonstrated beneficial effects on acute pain perception after DC stimulation applied over the somatosensory cortex in 10 healthy subjects (see Table 5b). The effects on pain perception were assessed in terms of pain intensity ratings and EEG components that were related to the induction of pain by laser stimulation (N1, N2 and P2 components). Only cathodal tDCS showed significant effects (behavioural and EEG) while anodal and sham tDCS were ineffective. Moreover, differential effects on nociception in healthy subjects arising from different stimulation sites were reported by Boggio, Zaghi, et al. (2008). Three different application conditions with anodal and cathodal tDCS were investigated: over the primary M1, DLPFC and over the occipital cortex (V1). The perception threshold and the pain threshold evoked by peripheral electrical stimulation of the right index finger were measured as outcome parameters. The greatest effects were found after anodal stimulation of M1 (the motor cortex in the hemisphere related to the stimulated finger), a marginal significant effect for the pain threshold after anodal tDCS over DLPFC, but no effect of V1 stimulation.

Chadaide et al. (2007) investigated the effects of tDCS on migraine. Migraine may be – at least in some forms – because of an overexcitability of the visual cortex. This can be assessed by measuring the threshold of TMS stimulation intensity necessary to produce phosphenes (light sensations after TMS). Using tDCS (1 mA for 10 min over the visual cortex at Oz, other electrode at Cz) Chadaide et al. (2007) revealed changes in such phosphene thresholds. Anodal tDCS had the highest impact in migraine patients with aura: they showed a *decrease* in the phosphene threshold due to the increase in cortical excitability as measured by TMS. In contrast, cathodal tDCS showed no effect in migraine patients with or without aura. In healthy subjects cathodal tDCS increased the phosphene threshold, which indicates a reduction in cortical excitability as measured by TMS.

In another clinical population, Fregni, Boggio, Lima, et al. (2006) studied patients with central pain after traumatic spinal cord injury. They demonstrated therapeutic effects of anodal tDCS over M1. The treatment procedure included 20 min of 2 mA tDCS for 5 consecutive days. For patients with symmetric pain on both body sides, the anode was placed over the dominant left M1, for those with asymmetric pain it was placed over the contralateral M1. Significant reductions were obtained in ratings of pain intensity after 5 sessions. This beneficial effect did not covary with changes in anxiety or depression during the treatment. Effects did not reached significance at 16-days-follow-up as compared to baseline.

Fregni, Gimenes, et al. (2006) used the same stimulation setup in patients with fibromyalgia. Fibromyalgia is a chronic disease with the following symptoms: pain in all areas of the body, generalized weakness, neurological symptoms, attention and sleep deficits, chronic fatigue and a general reduction of physical and mental capacities. Two different real tDCS conditions were compared: anodal tDCS of the primary motor cortex (same application procedure as Fregni, Boggio, Lima, et al., 2006) and anodal tDCS of the left DLPFC, as well as sham stimulation over M1. The greatest effects were seen for anodal tDCS of M1, which is in accordance with the findings reviewed above. Finally, Roizenblatt et al. (2007) studied the same sample as Fregni, Gimenes, et al. (2006) and investigated the effects of anodal tDCS of M1 and anodal tDCS of the DLPFC on sleep and pain parameter in patients with fibromyalgia. Increase in sleep efficacy associated with improvement in clinical parameters was assessed after anodal stimulation of M1. Here again, the greatest reduction in pain intensity was found after anodal stimulation of M1.

The findings reviewed above may suggest a variety of different mechanisms related to the modulation of pain. So far, beneficial effects of tDCS are mostly associated with anodal stimulation of the primary motor cortex, suggesting not a strong focal but rather a connectivity-based mechanism of action of tDCS on pain syndromes. Other relevant pain syndromes might be interesting for tDCS research such as thalamic pain syndrome or low back pain.

In conclusion, tDCS provides an interesting technique for pain research – both from an experimental and a clinical perspective. Furthermore, the different components of pain (physiological, emotional, attentional, pain-memory) could suggest different directions for future research in this relevant area.

8.3. Cognitive functions

The results of studies investigating the influence of tDCS on cognitive functions show facilitating as well as inhibitory effects (see Table 5c). For instance, anodal stimulation of the DLPFC improved the accuracy of performance during a sequential-letter working-memory task in healthy subjects (Fregni, Boggio, Nitsche, et al., 2005), in a three-back working memory task in patients with Parkinson's disease (Boggio, Ferrucci, et al., 2006) and in a digit-span (forward and backward) task in patients with major depression after five daily stimulation sessions (Fregni, Boggio, Nitsche, Rigonatti, et al., 2006). In another study, Ferrucci, Marceglia, et al. (2008) showed that anodal and cathodal tDCS over the cerebellum disrupted the practice-dependent improvement in the reaction times during a modified Sternberg verbal working-memory task. Furthermore intermittent bilateral tDCS at frontocortical electrode sites during a modified Sternberg task impaired response selection and preparation in this task (Marshall, Molle, Siebner, & Born, 2005).

Further effects of tDCS on cognitive functions were shown by Kincses, Antal, Nitsche, Bartfai, and Paulus (2004) who demonstrated that anodal, but not cathodal stimulation over the left prefrontal cortex improved implicit classification learning. Moreover, bilateral tDCS over the left or the right DLPFC (with the cathode over the contralateral DLPFC) reduced risk-taking behaviour (Fecteau et al., 2007). In a related study, Beeli and colleagues (Beeli, Koeneke, Gasser, & Jancke, 2008) recently found that anodal tDCS over the left and the right DLPFC (with the cathode over the ipsilateral mastoid) evoked more cautious driving in normal subjects placed in a driving simulator.

Marshall et al. (2004) investigated the effects of tDCS, delivered during sleep, on verbal memory. They showed that bilateral anodal tDCS at frontocortical electrode sites during sleep periods rich in slow wave sleep improved the retention of word pairs. This was not observed during wakefulness.

In a clinical study with patients suffering from Alzheimer's disease Ferrucci, Mameli, et al. (2008) tested the effects of tDCS on a word recognition memory task. Current was delivered bilaterally by two direct current stimulation devices, whereby one electrode of each device was placed over the temporoparietal areas and the other electrodes over the right deltoid muscle. Anodal stimulation improved, whereas cathodal stimulation decreased, memory performance in the patients.

Boggio, Khoury, et al. (2008) also showed effects of tDCS on a memory task in patients with Alzheimer's disease. Anodal stimulation over the left DLPFC as well as over the left temporal cortex improved the performance in a visual recognition memory task, which was not because of an enhancement in attention. However, since the second electrode was placed over the right supraorbital area, the improvements might also be the result of the stimulation of this area.

In summary tDCS modulates many aspects of cognition, both in healthy subjects and clinical populations. Surprisingly few studies have so far been conducted to evaluate the effects of tDCS on different aspects of attention (selective, sustained, divided). This might be an interesting field for future research.

9. Discussion, conclusions and future directions

The reviewed studies show that tDCS and GVS are attractive, easy-to-use and relatively safe methods for neuroscientific research. In comparison with TMS, tDCS is technically less demanding, induces similar aftereffects, but is less focal in its mechanism of action. tDCS induces online-effects and in some cases also longer lasting aftereffects in a great variety of sensory, motor, cognitive and emotional domains, both in healthy subjects and in different clinical populations. Both facilitation and inhibition of function is possible and has been shown. What are the most promising directions for future research in the next 5–10 years?

9.1. Sensory and motor processing

Many applications of tDCS in the visual, auditory and haptic modality, or even in olfaction and taste are conceivable, both in healthy subjects and patients. In vision research and vision rehabilitation the "old" idea of a visual prosthesis (Brindley & Lewin, 1968) or a vision-substitution system (Bach-y-Rita, 1983) for blind subjects or patients with cortical visual field defects may be revitalized with tDCS. In fact, visual prostheses are currently investigated as retinal implants or as brain–computer interfaces (Andersen, Burdick, Musallam, Pesaran, & Cham, 2004). In a similar vein, occipital or parietal tDCS might be employed as a permanent stimulation prosthesis for patients with visual field defects or spatial neglect, respectively. Similar ideas might be applicable in the haptic and auditory modality where only few studies regarding the effects of tDCS are currently available.

In motor research, motor cognition and motor rehabilitation tDCS has already shown its usefulness. Studies in healthy subjects show a significant effect of anodal stimulation on isometric force endurance and a smaller muscular fatigue effect. This may be an interesting starting point for applications in sports medicine, ageing subjects and neurological patients suffering from rapid fatigue. Anodal tDCS improves motor capacities in stroke patients with hemiparesis (Hummel & Cohen, 2005), and may also be helpful for patients with postural disorders which occur frequently after right-hemisphere stroke (Perennou et al., 2008). Furthermore, tDCS might be a useful technique for the adjuvant treatment of disorders such as apraxia, optic ataxia and non-visual ataxia, for which only few or no effective treatments (in the case of optic ataxia) are currently available.

9.2. Spatial-attentional and nonspatial attentional processing

In the domain of multimodal spatial cognition and spatial neglect tDCS or GVS, both may constitute easily applicable tools suitable to modulate vestibular-cortical functions and related spatial-attentional capacities without inducing significant nystagmus and vertigo as typically observed during caloric-vestibular stimulation (CVS). In the same vein, subliminal ("unconscious") or sham stimulation is much easier to realize than with TMS or CVS. As already suggested in Section 7, GVS might also be used to investigate the potential "vestibular" contributions to a variety of neuropsychological disorders that include a spatial component. These might include constructional apraxia, where early studies suggest a vestibular contribution based on lesion localization and clinical signs (Hecaen, Penfield, Bertrand, & Malmo, 1956). Another such topic may be the multifaceted disorders of body cognition (Frederiks, 1969; Goldenberg, 2001; Groh-Bordin et al., 2009) where the same idea might be pursued.

However, another interesting focus of research is nonspatial attentional functions. Recent studies have found that the right inferior parietal lobe is also involved in nonspatial attentional functions, and this in a multimodal way (for review see Husain & Rorden, 2003). GVS could be tested for its effects on such nonspatial attentional functions, i.e. alertness or sustained attention. This would help to identify the relationship between the various vestibular cortical areas (Guldin & Grusser, 1998) and attentional functions organized in close vicinity to each other within the inferior and superior parietal lobe (Husain & Rorden, 2003) and the temporoparietal junction area (Friedrich, Egly, Rafal, & Beck, 1998).

9.3. Neuroplasticity and neurorehabilitation

Stroke is a major cause of chronic disability in all western societies. This problem is set to increase as the proportion of the elderly in these societies further increases. More effective treatments for stroke and its consequences are therefore urgently needed (Clarke, Black, Badley, Lawrence, & Williams, 1999). Here, tCDS may offer a valuable tool to study the online-effects, immediate aftereffects and the long-term-effects of single and repetitive applications (Schlaug et al., 2008). On their own many behavioural interventions for neuropsychological disorders (e.g. neglect therapy, cognitive training, physiotherapy) are not sufficient to promote full independence of the patient, such treatments might be enhanced by brain stimulation using the safe, portable, noninvasive and inexpensive technique of tDCS. As tDCS produces clear aftereffects after stimulation it may prolong the therapeutic effects of established behavioural treatments. To further augment the effects, tDCS could be combined with other *technical* (i.e. robotic arm training, grip force training, optokinetic neglect training) or behavioural treatments.

To conclude, tDCS holds promise as an important add-on-therapy in neurological and neuropsychological rehabilitation. But first it needs to be established that the effects observed in the above reviewed studies can be replicated and transformed into longer-lasting effects by using for example multi-session tDCS.

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Subliminal galvanic-vestibular stimulation influences ego- and object-centred components of visual neglect

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ABSTRACT

Neglect patients show contralesional deficits in egocentric and object-centred visuospatial tasks. The extent to which these different phenomena are modulated by sensory stimulation remains to be clarified. Subliminal galvanic vestibular stimulation (GVS) induces imperceptible, polarity-specific changes in the cortical vestibular systems without the unpleasant side effects (nystagmus, vertigo) induced by caloric vestibular stimulation. While previous studies showed vestibular stimulation effects on egocentric spatial neglect phenomena, such effects were rarely demonstrated in object-centred neglect. Here, we applied bipolar subsensory GVS over the mastoids (mean intensity: 0.7 mA) to investigate its influence on egocentric (digit cancellation, text copying), object-centred (copy of symmetrical figures), or both (line bisection) components of visual neglect in 24 patients with unilateral right hemisphere stroke. Patients were assigned to two patient groups (impaired vs. normal in the respective task) on the basis of cut-off scores derived from the literature or from normal controls. Both groups performed all tasks under three experimental conditions carried out on three separate days: (a) sham/baseline GVS where no electric current was applied, (b) left cathodal/right anodal (CL/AR) GVS and (c) left anodal/right cathodal (AL/CR) GVS, for a period of 20 min per session. CL/AR GVS significantly improved line bisection and text copying whereas AL/CR GVS significantly ameliorated figure copying and digit cancellation. These GVS effects were selectively observed in the impaired- but not in the unimpaired patient group. In conclusion, subliminal GVS modulates ego- and object-centred components of visual neglect rapidly. Implications for neurorehabilitation are discussed.

1. Introduction

Neglect is a multicomponent syndrome where patients typically fail to explore sensory stimuli in the contralesional hemispace or body side. Neglect most often follows after right-hemispheric lesions (Kerkhoff, 2001) and entails several different components (Grimsen et al., 2008). For example, neglect patients may show severe impairments in a wide range of egocentric tests of neglect including cancellation, visual and tactile exploration as well as writing. These egocentric neglect phenomena can be defined as a failure to attend to contralateral stimuli in space in relation to the body's midsaggital plane. Hence, the body serves as the egocentric anchor or reference (Ventre and Flandrin, 1984) for the patient's performance in space. Another component of neglect is termed object-centred neglect. Here, the contralateral side of a single perceptual object is neglected irrespective of its location relative to the viewer. In contrast to egocentric neglect phenomena, the midline of the object and not the patient's body serves as a reference for tasks like copying a flower or a clock face (Halligan et al., 2003). Finally, some tests may require a combination of both reference frames. In those tests, the contralateral side of a single perceptual object is neglected but the spatial location of the stimulus relative to the viewer determines the severity of neglect. Horizontal line bisection, for example, may be considered an object-centred task given that the bisection error (LBE) correlates with the extent of the neglected letter string of single words in neglect dyslexia (Reinhart et al., 2013), and covaries with line length (Halligan and Marshall, 1991). On the other hand, LBE has also been found to vary relative to the viewer (Utz et al., 2011a, i.e. in the Schenkenberg test) and to correlate positively with search

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and reading biases in cancellation tasks as well as paragraph reading (Reinhart et al., 2013).

On a neural level, ego- and object-centred visual processing seem to recruit different brain structures (Olson and Gettner, 1996): Single-cell recordings in monkeys have identified neurons in the frontal cortex (Olson and Gettner, 1995) that discharge selectively when the allocation of attention to the contralateral part of a perceptual object is required. This contrasts with the properties of neurons in the monkey parietal cortex, where neurons discharge when the allocation of attention to regions in contralateral space is required (Gottlieb, 2002). In a recent study, Benwell et al. (2014) found an association between the leftward line bisection error in healthy participants (pseudo neglect; Jewell and McCourt, 2000) and the right hemisphere ventral attention network, in particular areas of the right parietal cortex around the temporo-parietal junction. Functional imaging studies in healthy humans yielded similar findings of differential activations associated with ego- and object-centred space processing (Honda et al., 1999; Vallar et al., 1999): object-centred visual processing was found to be mostly related to activations in the temporal and – to a smaller extent – in the frontal cortex. Egocentric visual processing, on the other hand, has been associated with activations in the parietal and – to a lesser degree – in the frontal cortex (Vallar et al., 1999). Finally, studies in neuropsychological patients show a similar picture: Hillis et al. (2005) observed object-centred visual neglect phenomena in a cancellation task in patients with lesions of the right superior temporal gyrus, but egocentric errors (omissions) in the same task in patients with damage of the right angular gyrus. Put differently, egocentric visual neglect phenomena are mostly linked to the dorsal visual stream (parieto-frontal cortices) while object-centred visual neglect phenomena are more associated with ventral stream lesions, in particular the temporal lobe (Grimsen et al., 2008; Ptak and Valenza, 2005).

Electrical stimulation of the vestibular system can be induced by placing one electrode behind each ear over the left and right mastoid respectively (termed galvanic vestibular stimulation or GVS, for review see Utz et al., 2010). Underneath the mastoids the vestibular nerve projects from the inner ear to the vestibular brain stem nuclei, which in turn are interconnected with the nucleus ventroposterolateralis of the thalamus. From there, ascending vestibular fibre pathways reach a number of cortical vestibular areas including area 2cv near the central sulcus, area 3a,b in the somatosensory cortex, parietal area 7a, and the parieto-insular-vestibular-cortex (PIVC). Although there is no primary vestibular cortex as for the visual-, auditory- or tactile modality, the above mentioned array of multiple, interconnected vestibular cortical areas is thought to be under the control of the PIVC (Guldin and Grusser, 1998). Practically, GVS consists of applying direct current to the mastoids – usually delivered by a small battery-driven constant current stimulator (Wilkinson et al., 2008). Subliminal GVS can be administered by adjusting the current intensity below an individual's sensory threshold. This has the methodological advantage that different GVS protocols and polarities can be manipulated elegantly without the patient's knowledge that might otherwise influence his performance due to “spatial cueing” effects induced by a tingling sensation under one electrode. Furthermore, GVS is painless, easily applicable, safe, and induces minimal side effects when used in accordance with standard safety guidelines (Utz et al., 2011b).

GVS has significant effects on a wide variety of cognitive and perceptual tasks, both in healthy persons and neurological patients (for review see Utz et al., 2010). For example, Wilkinson and co-workers found that GVS facilitated visual memory recall in healthy participants (Wilkinson et al., 2008) and improved visuoconstructive deficits in a right-hemisphere lesioned patient (Wilkinson et al., 2010). A recent study by Wilkinson et al. (2012) found significant effects of GVS on an electrophysiological component (N170) in a face processing task. This underlines the physiological effects of GVS in modulating neuronal activity in visual areas of the ventral stream. Moreover, a few sessions of GVS were shown to induce a lasting treatment effect in visuospatial neglect (Wilkinson et al., 2014). Furthermore, Saj et al. (2006) demonstrated a positive effect of CL/AR GVS on the perceptual tilt of the subjective vertical in right-hemisphere lesioned patients with left neglect. In addition, Kerkhoff et al. (2011) and Schmidt et al. (2013b) found a long-lasting beneficial effect after 3 verum sessions of CL/AR and AL/CR GVS in tactile extinction. Finally, Utz et al. (2011a) showed a significant improvement in line bisection (Schenkenberg test) after AL/CR and partially also after CL/AR GVS in 6 patients with left visuospatial neglect, but no effect in 11 right-hemisphere stroke patients without neglect.

In summary, there is increasing evidence that GVS can significantly modulate a range of cognitive capacities or impairments in both healthy persons and neurological patients (partially with neglect). So far, it is not known whether the modulatory effect of GVS on neglect is restricted to egocentric space processing such as observed in cancellation tasks (Rorsman et al., 1999) or whether it has also the capacity to influence additional components of impaired space processing such as object-centred neglect. As the brain areas associated with object-centred visual attention (Honda et al., 1999) are remote from those typically activated by GVS (Bense et al., 2001) it is unclear whether their activity can be modulated by GVS. From both, a theoretical and a clinical viewpoint, it would be important to know whether galvanic vestibular stimulation modulates not only egocentric but also object-centred components of visual neglect. Clinically, this is clearly relevant as neglect patients are typically impaired in both spatial components of visual neglect and therefore require specific rehabilitation techniques for intervention. Moreover, while egocentric neglect phenomena can be treated by a variety of novel therapies (for review see Kerkhoff and Schenk, 2012) no treatment is currently available for object-centred neglect, to the best of our knowledge. Theoretically, a potential vestibular influence on these different components is also interesting, as it may clarify the relationship between mechanisms of visual attention operating in ego- vs. object centred coordinate systems and the cortical vestibular system (Grimsen et al., 2008; Olson and Gettner, 1996). Hence, the aim of the present study was to investigate whether subliminal GVS modulates ego- and object-centred spatial processing components of visual neglect significantly.

2. Patients and methods

2.1. Patients and healthy controls

The study – which was approved by the local ethics committee (Ärztekammer des Saarlandes, Nr. 147/08, 16.9.2008) – included 24 patients with unilateral right-sided stroke (Table 1). Inclusion criteria were right-handedness and a single right hemisphere infarction or haemorrhage. Exclusion criteria were other neurological or psychiatric diseases, epilepsy, sensitive skin on the scalp, metallic brain implants and medications altering the level of cortical excitability (Iyer et al., 2005). The participants were 10 women and 14 men with a median age of 63.6 years (range 42–84 years), and a median time since lesion of 2 months (range: 1–84 months). For each of the four neglect tasks described below the patients were – depending on their performance in the sham-baseline condition – allocated to a patient group *with neglect* (RBD+) in a specific task or a patient group *without neglect* (RBD−) in that task.

In addition, 28 healthy, age-matched controls (11 male, 17 female, median age: 56 years (range: 44–75 years) were tested to collect normative data for these tasks. This was achieved by establishing cut-off criteria for assigning patients to the RBD− or RBD+ groups. The healthy controls did not participate in the experimental (stimulation) sessions.

2.2. Experimental procedures

In the first session all participants performed the four tasks while the electrodes of the stimulation device were fixed over the mastoids but not active

Table 1
Patient characteristics of 24 patients with unilateral right-hemispheric stroke (RBD).

Patient	Age/sex	Etiology	Lesion	TSL (months)	Hemi-paresis	Field defect	NC	CSF	HLB	TC
RBD-1	55/m	I	F, T	4	p	a	+	×	+	+
RBD-2	76/m	I	F, T, P	84	p	HH	+	+	+	+
RBD-3	65/m	I	F, T, P, BG	3	p	Q	−	+	+	+
RBD-4	65/m	I	T	15	p	a	+	+	−	+
RBD-5	70/f	H	BG	2	p	a	+	+	+	+
RBD-6	62/m	I	T	1	p	a	+	+	+	+
RBD-7	59/m	I	P, O	1	a	a	+	+	+	+
RBD-8	72/f	I	T	2	p	HH	−	+	+	×
RBD-9	50/m	I	T	2	p	a	−	+	−	×
RBD-10	51/m	I	BG	1	p	a	−	−	−	−
RBD-11	70/m	I	T	1	p	a	−	−	−	−
RBD-12	67/m	I	T, F	1	p	a	+	+	−	+
RBD-13	79/f	I	T, F	2	p	a	+	×	+	×
RBD-14	84/f	I	F, T	12	p	a	−	−	−	−
RBD-15	72/m	I	T, P	1	p	Q	−	−	+	−
RBD-16	70/m	I	T	2	p	a	−	−	−	+
RBD-17	70/m	I	F	35	p	a	+	+	+	+
RBD-18	42/f	I	T, BG	1	a	a	−	+	−	−
RBD-19	76/f	I	F, T, P, O	1	p	HH	+	×	×	+
RBD-20	53/f	I	O	3	a	HH	−	−	−	−
RBD-21	51/m	H	P	1	a	Q	−	−	−	−
RBD-22	57/f	H	T, P	3	p	a	+	+	−	−
RBD-23	67/f	I	F	1	p	a	+	+	+	+
RBD-24	44/m	H	F, T, P	3	p	a	+	+	+	−
	Mean: 63.3 yrs	20 I, 4H		Median: 2 month	17/24 impaired	7/24 impaired	13RBD+/11 RBD− N=24	14 RBD+/ 7 RBD− N=21	12 RBD+/ 11 RBD− N=23	12 RBD+/ 9 RBD− N=21

Abbreviations: I/H: ischaemic/haemorrhagic stroke; P/T/F/O/BG: parietal/temporal/frontal/occipital/basal ganglia; TSL: time since lesion; HH: homonymous hemianopia, Q: quadrantanopia; p/a: present/absent; NC/CSF/HLB/TC: number cancellation/copy of symmetrical figures/ horizontal line bisection/text copying, +/−/×: with neglect in this task/without neglect in this task/not tested in this task.

(Sham=Baseline condition). To this purpose, after fixing the electrodes, the current was initially turned on until the participant perceived a tingling sensation, after which the current was smoothly turned off within 30 s, without the patient being aware of this (due to the subthreshold stimulation, see below). The stimulator was always invisible for the participant. This created an effective sham-stimulation since the individuals were not able to discriminate between the conditions where real current was applied and those where the current was turned off due to the imperceptible, sub-threshold intensity of the stimulus. In sessions 2 and 3, the patients repeated all experimental tasks, but received subliminal GVS (CL/AR or AL/CR GVS). The sequence of these 2 experimental conditions was counterbalanced within each group, with one half of the participants receiving CL/AR GVS in session 2 and AL/CR GVS in session 3, and the other half receiving the opposite sequence. The three sessions were performed on three separate days. The total experiment was completed within 5 days. Session 1 was always on day 1, session 2 on day 3 and session 3 on day 5, to control for carry-over effects. Each session lasted approximately one hour. GVS-stimulation started a few seconds before the task instruction by the experimenter and terminated immediately after completion of the four tests.

Galvanic bipolar stimulation was delivered by a constant direct current (DC) stimulator (9 voltage battery, Type: ED 2011, manufacturer: DKI GmbH, DE-01277 Dresden). The carbon-rubber electrodes (50 mm × 35 mm) were mounted on the skin over each mastoid (binaural stimulation), in order to activate the peripheral vestibular organs. Similar to Rorsman et al. (1999) we stimulated below the sensation threshold (subliminal) in order to prevent awareness of any electrical stimulation in the 3 experimental conditions. A switch on the stimulation device delivered current at individually adjusted levels for each patient. This threshold was individually determined in the Sham/Baseline condition by slowly increasing current intensity in steps of 0.1 mA until the participant indicated a tingling sensation. The current was subsequently reduced until the participant reported that the sensation had disappeared. This procedure was repeated a second time and the median of these 4 threshold values was defined as the sensory threshold. This value of current intensity was then used for the CL/AR and AL/CR sessions. The thresholding procedure was always performed in the beginning of session 1 and lasted 30–60 s. The mean threshold level across all patients was 0.7 mA (range: 0.4–1.5 mA). This strategy of subliminal GVS eliminates any “spatial cueing” effects as a consequence of the tingling sensation typically felt by the participant when *above-threshold* electrical current is delivered to the anode on the mastoid. As a possible limitation, the threshold determination could have influenced the results in the sham-GVS session, but time constraints in the clinical setting prevented us from running a sham session independently from the threshold procedure (see also Section 4.4., for discussion).

2.3. Experimental neglect tests

2.3.1. Number cancellation

Cancellation tasks are classic tools for assessing egocentric visual neglect and considered most sensitive for its diagnosis (Machner et al., 2012). Here, patients were presented with a $29.7 \times 21\ cm^2$ white sheet of paper containing 200 randomly distributed single digit numbers ranging from 0 to 9 (cf. Reinhart et al., 2011). Every number was present 20 times on the display, 10 times on the left side and 10 times on the right side (Fig. 1A). Following a demonstration in which the examiner crossed out one of these digits on the right side of the paper on a sample sheet (which was not scored), the patients were asked to cross out all target digits (i.e. all “7”) on a separate test sheet. Patients were required to search for different target digits (with different spatial positions of the target stimuli in each subtest) in each experimental session to eliminate memory or practice effects. None of the test sheets was given twice to the same patient and the order of target type was randomised across participants.

The mere number of neglected targets in a cancellation task might not be a sensitive measure for the severity of egocentric neglect as it provides no information about the degree of contralesional bias in the distribution of omissions. Therefore, the centre of cancellation (CoC) was calculated as a measure of spatial bias based on the procedure described in Binder et al. (1992) and Rorden and Karnath (2010). The CoC accounts for the spatial position of every omitted target which has the advantage of measuring neglect severity as a function of the search bias on a continuous scale (Rorden and Karnath, 2010). CoC scores can vary between −1 and +1 with values close to +1 indicating a severe rightward neglect in a patient who only cancelled the rightmost targets (and vice versa for a score of −1). Accordingly, search performances that show a large number of *evenly* distributed omissions result in CoC values close to zero. A patient was assigned to the RBD− group when the CoC was smaller than 0.10- (including negative scores). The available norms (from the 28 healthy controls) for the number cancellation test show detection rates of 100% for left-sided target stimuli in healthy controls and even in RBD patients without spatial neglect (Reinhart et al., 2011). The suggested cut-offs for the spatial cancellation biases (CoC) derived from the Bells Test and the Letter Cancellation Test in Rorden and Karnath's (2010) study were 0.081 and 0.083. Therefore, our criteria can be considered as conservative. We chose these

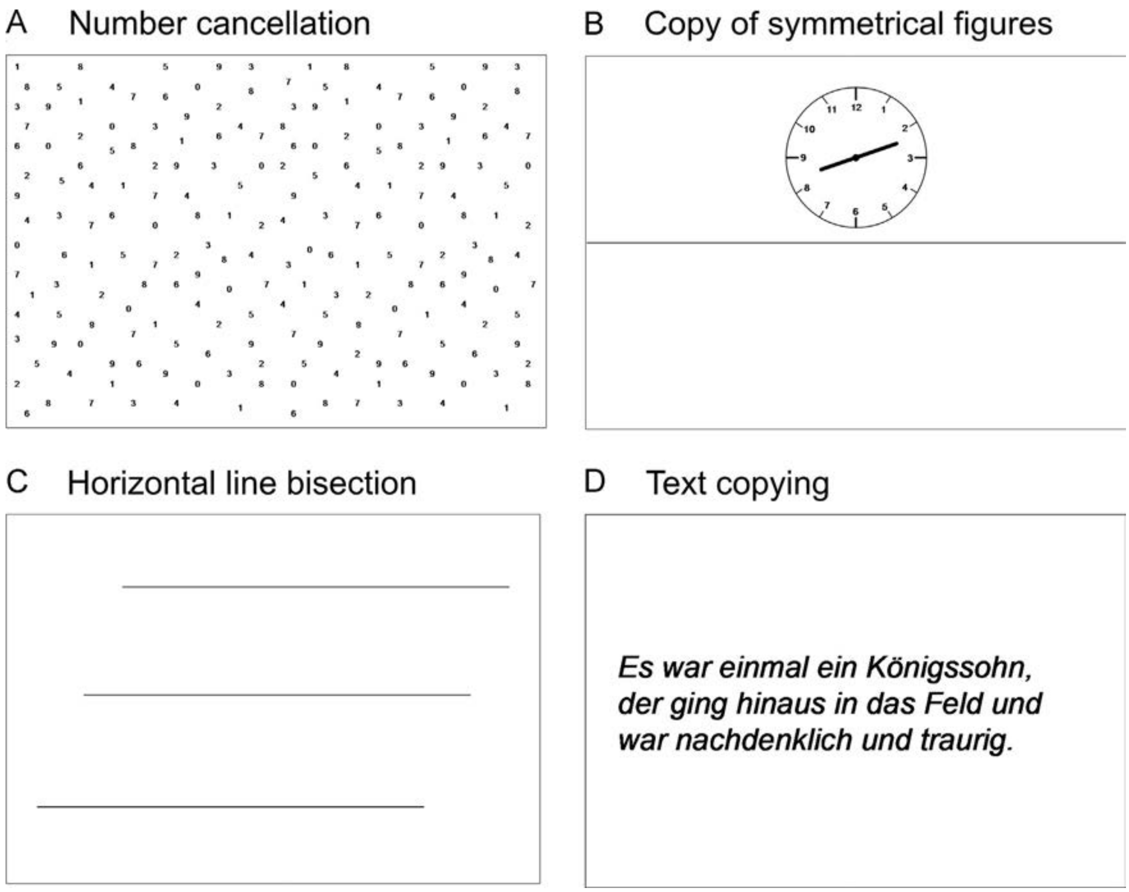

Fig. 1. Schematic display of the four experimental neglect tests (see text for further details).

conservative criteria to avoid ceiling effects in the RBD− group. The assignments to the RBD+ group compliant with both criteria were identical ($r=1.0$, $p<0.001$).

2.3.2. *Copy of symmetrical figures*

Object-centred visual neglect was assessed by copying symmetrical figures. Six different figures (two for each session) were drawn by the patients using their ipsilesional, right hand. None of the drawings was given twice to the same patient to rule out practice or memory effects. The drawing was placed in the centre of an A4 (29.7×21.0 cm^2) sheet of paper and the patient was asked to copy the figure below the template under a horizontal line (see Fig. 1B). For each of the three conditions (Sham, CL/AR, AL/CR) omissions (missing details of the reproduced figure) were counted. As the available norms from the 28 healthy controls showed no left- or right-sided omissions in figure copying, the cut-off value for the assignment to the RBD+ versus RBD− group was set at 0 omissions. Patients who showed at least 1 omission on the left side in the Baseline/Sham condition were assigned to the RBD+ group, all others were assigned to the RBD− group.

2.3.3. *Horizontal line bisection*

We used the horizontal line-bisection subtest from the German version of the Behavioural Inattention Test (BIT; Wilson et al., 1987) in order to detect the degree and direction of the combination of egocentric and object centred aspects of visual neglect. Three horizontal lines (length: 200×1 mm^2) were presented on a 29.4×21 cm^2 paper sheet in landscape format (see also Fig. 1C). Participants were instructed to mark the middle of each line using their right hand and a pencil. For each of the three conditions (Sham, CL/AR, AL/CR) the mean deviation from the objective centre of the three lines was measured and averaged in mm. Studies in healthy participants have shown a maximum deviation of +4.51 mm to the right side in this line bisection test, which was taken as the cut-off value for spatial neglect (Fels and Geissner, 1997). Thus, patients with a mean rightward deviation beyond +4.51 mm in the Sham condition were assigned to the RBD+ group whereas all others were assigned to the RBD− group.

2.3.4. *Text copying*

Text copying was assessed by asking patients to copy a short text (presented in Arial, 44 pt, right-aligned). Interestingly, writing has received little attention in neglect research while reading and neglect dyslexia have been studied quite often in the last years (Reinhart et al., 2010). Undoubtedly, both are relevant for daily life. Analogous to paragraph reading tasks where omissions of whole words on the contralesional side indicate egocentric deficits while substitutions or misreading of contralesional parts of single words reflect a word- or object-centred neglect deficit (Reinhart et al., 2011, 2010) we defined two types of errors in text copying: Space-related omissions of whole words on the left side were classified as egocentric deficits while omissions or miswritings of left-sided parts (syllables, letters) of single words were considered manifestations of object- (word) centred neglect. Thus, the text copy task entailed both egocentric and object-centred components which were analysed separately.

Six different sentences (two for each experimental session), arranged centrally in three lines on a 29.7×21 cm^2 white sheet of paper, were taken from a German fairy tale book (Fig. 1D). None of the sentences were given twice to the same patient to rule out repetition or memory effects. This stimulus sheet was presented in front of the patient and aligned with the body midsaggital plane. The patient was instructed to write down the text on an empty sheet of paper as correctly as possible. Omissions of letters and words were counted separately for each session. As available norms showed no omissions in this task, the cut-off value for assignment of patients into the two groups (RBD+, RBD−) was 0. Patients who showed at least 1 omission in the Sham condition were assigned to the RBD+ group, all others were assigned to the RBD− group.

2.4. *Statistics*

ANOVAs were carried out for the parametric data of the cancellation (CoC) and the line bisection tasks (LBE in mm). The results of the ANOVAs were Greenhouse-Geisser corrected when sphericity was violated according to significant Mauchley-Tests. As the visual extent of the words used in the text copying tasks as well as the visual extent of details of the figures used in the figure copy tasks was highly variable, we classified the number of omitted words and of omitted figure details as nonparametric, not interval scaled variables. Therefore, nonparametric statistics (Friedman-Tests, Wilcoxon-Tests) were computed for these two tests. The alpha-level of subsequent analyses was Bonferroni-adjusted according to Holm's method (Holm, 1979).

3. Results

3.1. *Spatial bias in number cancellation*

All 24 patients performed this task. Eleven patients were assigned to the RBD+ group and 13 to the RBD− group according to the criteria described above (Section 2.3). A 2 × 3 ANOVA with the factors group (RBD+ and RBD−) and stimulation condition (sham, CL/AR GVS, and AL/CR GVS) revealed significant main effects of stimulation condition [$F(1.35, 29.71)=5.99$, $p=0.013$] and group [$F(1, 22)=47.88$, $p<0.001$] and a significant stimulation condition × group interaction [$F(1.35, 27.71)=6.73$, $p=0.009$]. Subsequent *t*-tests revealed a significant reduction of the CoC during AL/CR compared to sham stimulation [mean difference=0.164, $t(10)=3.61$, $p=0.005$, $r=0.75$] in the RBD+ group. There were no significant differences between CL/AR and sham stimulation [mean difference=0.095, $t(10)=1.46$, $p=0.176$, $r=0.42$] or CL/AR and AL/CR stimulation [mean difference=0.068, $t(10)=2.00$, $p=0.073$, $r=0.53$]. For the RBD− group, subsequent *t*-tests were significant for the comparisons between Sham and CL/AR [$t(12)=-2.87$, $p=0.014$, $r=0.62$] and CL/AR vs. AL/CR stimulation [$t(12)=-2.75$, $p=0.017$, $r=0.61$], both indicating an increased CoC in the CL/AR condition. However, it should be noted that the mean CoC during CL/AR (CoC=0.041) was below the cut-off of 0.10. There was no significant difference between sham and AL/CR stimulation [$t(12)=-0.05$, $p=0.96$, $r=0.00$]. The results are shown in Fig. 2A.

3.2. Copy of symmetrical figures

21 out of 24 patients completed this task. Three patients were unable to complete this task due to fatigue. In the RBD+ group ($N=14$) Friedman analyses of variance showed a significant GVS effect across the experimental sessions ($X^2=11.65$, df=2, $p=0.003$). Subsequent Wilcoxon tests revealed neither significant differences between CL/AR and Sham ($Z=-1.84$, $p=0.070$, $r=0.49$) nor between CL/AR and AL/CR ($Z=-1.31$, $p=0.190$, $r=0.35$). There was, however, a significant decrease of omissions in the AL/CR condition as compared to Sham ($Z=-2.46$, $p=0.014$, $r=0.65$). No significant effects were found in the RBD− group across the experimental sessions ($N=7$; Friedman-test, $X^2=2.00$, df=2, $p=0.368$; Fig. 2B).

3.3. Horizontal line bisection

23 out of 24 patients completed this task. One patient misunderstood the instruction and was therefore excluded. Twelve patients were assigned to the RBD+ group and 11 to the RBD− group according to the criteria described above (Section 2.3). A 2 × 3 ANOVA with the factors group (RBD+ and RBD−) and stimulation condition (Sham, CL/AR GVS, and AL/CR GVS) revealed significant effects of stimulation condition [$F(2, 42)=4.52$ $p=0.017$] and group [$F(1, 21)=19.14$, $p<0.001$] and a significant stimulation condition × group interaction [$F(2, 42)=5.81$, $p=0.006$]. Subsequent *t*-tests yielded a significant reduction of the LBE during CL/AR compared to sham stimulation [mean difference=14.4 mm, $t(11)=4.00$, $p=0.002$, $r=0.76$] in the RBD+ group. There were no significant differences between AL/CR and sham [mean difference=6.2 mm, $t(11)=1.43$, $p=0.179$, $r=0.39$] or CL/AR and AL/CR stimulation [mean difference=−8.2 mm, $t(11)=-1.92$, $p=0.080$, $r=0.50$]. Furthermore, there were no significant differences in the RBD− group (all ps > 0.29; Fig. 3A).

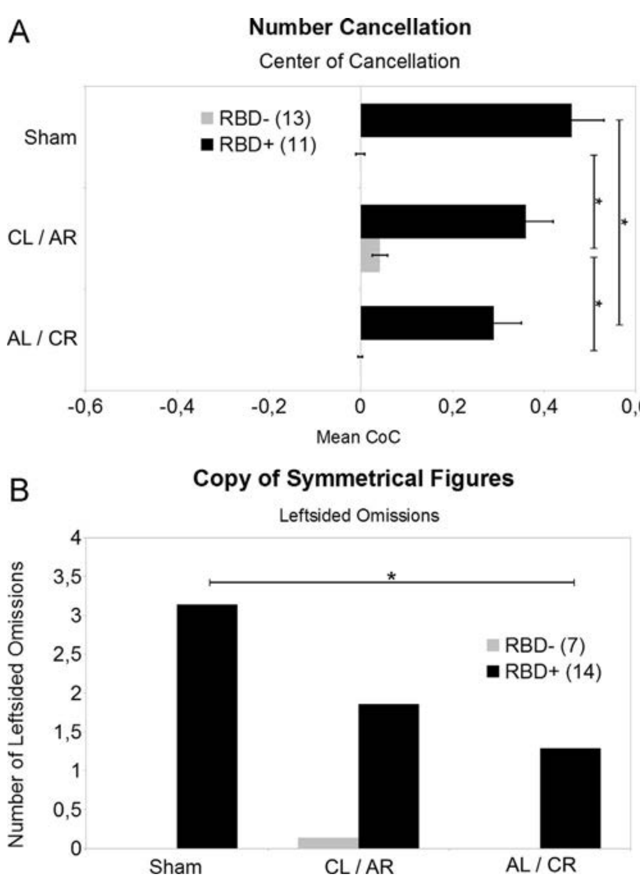

Fig. 2. Results of galvanic vestibular stimulation (GVS) on number cancellation (A) and copying of symmetrical figures (B) across the three experimental conditions (Sham, CL/AR, AL/CR). *$p<0.05$. Error bars (A) indicate 1 SEM. CoC values close to +1 indicate a severe rightward neglect in a patient who only cancelled the rightmost targets (and vice versa for a score of −1). Error bars in (B) are not shown due to non-parametrical analyses. See text for details.

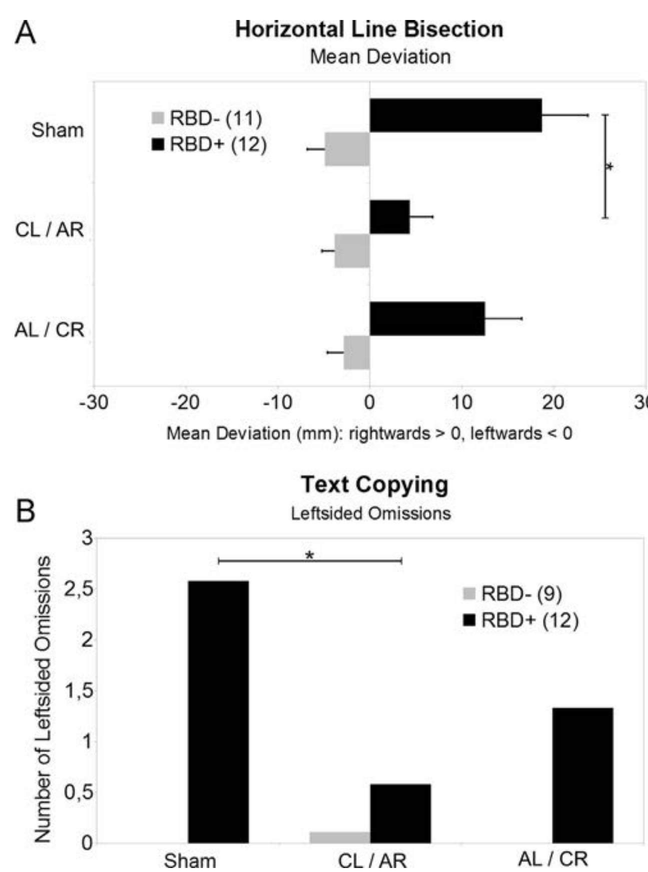

Fig. 3. Results of galvanic vestibular stimulation (GVS) on horizontal line bisection (A) and text copying (B) across the three experimental conditions (Sham, CL/AR, AL/CR). *$p<0.05$. Error bars in (A) indicate 1 SEM. Error bars in (B) are not shown due to non-parametrical analyses. See text for details.

3.4. Text copying

21 out of 24 patients completed this task. Omissions of whole words on the left side in copying accounted for 99% of errors while word-centred copying errors were very rare (1% of all errors). Therefore, only left-sided omission errors were analysed. In the RBD+ group ($N=12$) Friedman analyses of variance showed a significant effect of GVS ($X^2=9.39$, df=2, $p=0.009$). Significant differences were found neither between AL/CR and Sham ($Z=-1.50$, $p=0.133$, $r=-0.43$) nor between AL/CR and CL/AR ($Z=-1.71$, $p=0.088$, $r=0.49$). There was a significant decrease of omissions in the patients' copies in the CL/AR condition as compared to Sham ($Z=-2.84$, $p=0.004$, $r=0.82$). In contrast, no significant effect of GVS was seen in the RBD− group ($N=9$, $X^2=2.00$, df=2, $p=0.368$, Fig. 3B).

4. Discussion

Several findings are apparent from our study: First, GVS modulated all components of visual neglect in the RBD+ but not the RBD− group: egocentric, object-centred, and the combination of both aspects. This shows, that GVS affects not only egocentric attentional mechanisms – which could be expected because the vestibular system codes spatial information mainly in an egocentric way (Fitzpatrick and Day, 2004), as well as pure object-centred (symmetrical figure copy) attentional mechanisms but also attention processes that rely on a combination of egocentric and object centred reference systems (line bisection). Moreover, we found a significant effect of GVS on neglect dysgraphia (text copying), a task that has received little attention in the modulation and rehabilitation of neglect.

Second, the effects of GVS were polarity-specific for the different tasks: CL/AR stimulation significantly improved horizontal line bisection and text copying, while AL/CR stimulation improved figure copying and number cancellation. We will discuss these aspects below.

4.1. Effects of GVS on different components of visual neglect

Rorsman et al. (1999) were the first to explore the effects of subliminal, galvanic GVS on visual neglect using a cancellation test. In line with their pioneering results we found improved contralesional target detection as indicated by a decreased rightward bias (CoC) in the number cancellation task in the RBD+ group. The significant although modest shift of line bisection performance in the RBD− group during AL/CR parallels similar performance deteriorations of the position sense during AL/CR GVS in healthy participants (Schmidt et al., 2013a). This may be explained by an overexcitation of the vestibular system normally involved in this task in unimpaired (control) patients or in healthy controls. Put differently: only patients with a spatial deficit in the task under study may benefit from GVS induced activation.

Also similar to Rorsman et al. (1999) we found a strong effect of CL/AR GVS on horizontal line bisection. CL/AR GVS transiently completely normalised the pathological right-sided bias during line bisection in our neglect group (Fig. 3A). In contrast, GVS had no modulating effect in patients showing a leftward line bisection bias due to left-sided visual field defects (contralesional hemianopic line bisection error; Kuhn et al., 2012a, 2012b). Our results are largely in line with the findings of a recent study by Utz et al. (2011b), who found *both* AL/CR and CL/AR GVS effective in reducing the rightward bisection bias, with AL/CR stimulation being slightly but not significantly more potent than CL/AR stimulation. The bisection task in that study (a modified Schenkenberg test with 27 lines to be bisected; Schenkenberg et al., 1980), however differed from ours (the German version of the BIT with only 3 horizontal lines to be bisected, cf Fig. 1A; Wilson et al., 1987). Moreover, GVS was applied at 1.5 mA by Utz et al. (2011a) instead of subliminal GVS (0.7 mA) in the present study. These task- and stimulation differences may explain the slightly different polarity effects of GVS on line bisection. One plausible hypothesis that could account for the modulating effect of GVS on horizontal line bisection is that GVS decreases the rightward line bisection error selectively in neglect patients by activating preserved structures of the right posterior parietal cortex, which are usually involved in horizontal line bisection performance (Benwell et al., 2014; Mort et al., 2003; Verdon et al., 2010). Interestingly, 6 of our RBD+ patients that were impaired in the line bisection task showed sparing of the right parietal cortex (Table 1). Imaging studies of GVS in healthy participants show widespread cortical activations in the following brain regions: the temporo-parietal junction, the central sulcus, the intraparietal sulcus (Lobel et al., 1998), anterior parts of the insula, the thalamus, the putamen, the inferior parietal lobule [Brodmann area (BA) 40], the precentral gyrus (frontal eye field, BA 6), the middle frontal gyrus (prefrontal cortex, BA 46/9), the middle temporal gyrus (BA 37), the superior temporal gyrus (BA 22), and the anterior cingulate gyrus (BA 32) as well as in both cerebellar hemispheres (Bense et al., 2001). This widely activated network related to GVS surrounds and includes the critical lesion locus for impaired line bisection in neglect patients, namely the right angular gyrus (Mort et al., 2003; Verdon et al., 2010). It is therefore conceivable that such activations in neglect patients may have led to the improvement observed here. Finally, Fink et al. (2003) found an effect of suprathreshold GVS on horizontal line bisection in healthy persons mediated by right parietal activations as assessed with fMRI.

With respect to impaired text copying (neglect dysgraphia) we found a significant reduction of left-sided omissions under CL/AR GVS as well as a numerical, but non-significant reduction of such errors after AL/CR GVS (Fig. 3B). From a behavioural perspective, it is tempting to argue that CL/AR GVS shifted attention further to the neglected side (as in line bisection, Fig. 3A) thereby leading to a reduction of omissions in text copying. On the neural level, CL/AR GVS is known to induce bilateral activations of the cortical vestibular system (Fink et al., 2003). These rather symmetrical activations in both cerebral hemispheres might act on two mechanisms related to text copying: exploring further toward the left side of the display and moving the right arm further to the left during copying of the sentences.

Finally, we found – to our knowledge for the first time – a clear effect of vestibular stimulation (GVS) on object-centred neglect in the symmetrical figure copy tasks. In our view, this type of task represents a rather pure object-centred task. According to Olson and Gettner (1996) spatial attention is important for the processing of visuospatial information *within* a perceptual object. Here, both GVS conditions reduced the number of contralesional (left) omissions, but only the AL/CR condition reached significance (Fig. 2B). One plausible explanation is that AL/CR GVS increased activations in brain areas related to object-centred visual attention, i.e. in the frontal cortex and the ventral visual stream. In fact, imaging studies in healthy participants showed activations in the precentral gyrus (frontal eye field, BA 6), the middle frontal gyrus (prefrontal cortex, BA 46/9), the middle temporal gyrus (BA 37) and the superior temporal gyrus (BA 22), among others (Bense et al., 2001). GVS, therefore, might lead to an up-regulation of these frontal and ventral stream areas to symmetrical object features as required by the symmetrical figures task in our study. An alternative but not necessarily exclusive hypothesis is that AL/CR GVS – which mainly activates the right-hemispheric vestibular system, and temporo-parietal cortex in particular (Fink et al., 2003), leads to a general facilitation of spatially non-lateralized attentional mechanisms within the right fronto-parietal cortex

(Husain and Rorden, 2003). This in turn could improve alertness which might result in a more symmetrical performance in copying symmetrical figures. Future studies might investigate the influence of GVS on alertness and object-centred attention in greater detail. Independently of the precise underlying mechanism, our findings may have clinical implications as there is currently no effective treatment available for object-centred visual neglect (Kerkhoff and Schenk, 2012). Our results suggest that GVS might be an interesting candidate for the modulation and even treatment of such deficits in drawing, reading (word-based errors) or related visual pattern tasks which require allocation of attention *within* a structured visual display (Grimsen et al., 2008).

4.2. Polarity-specific effects of GVS

Functional imaging studies have established an unexpected hemispheric asymmetry in the human vestibular system: the right-hemispheric vestibular system is dominantly organised as compared to the left-hemispheric vestibular system (Bartenstein et al., 1998). As a consequence, vestibular stimulation of the right hemisphere via CL/AR may lead to a stronger and bi-hemispheric activation of the vestibular cortices as well as regions within the adjacent temporo-parietal cortex (Fink et al., 2003). In contrast, AL/CR is likely to produce weaker activations restricted to the left vestibular cortex and adjacent temporo-parietal regions. In accordance with these findings, it is interesting to note that we often found that one specific stimulation condition (CL/AR or AL/CR) produced significant reductions in a particular task, while the other condition led to a similar, though weaker, more variable and therefore often non-significant performance improvements in the same task (cf. Figs. 2 and 3). While we already referred to the asymmetry of cortical vestibular activations after CL/AR versus AL/CR GVS in the preceding paragraph as a potential explanation of these polarity effects, other explanations might be plausible as well. For example, the efficacy of CL/AR or AL/CR GVS in modulating performance in a cognitive task might also depend on a certain "activation threshold" that has to be exceeded in order to induce behaviourally observable effects in such a task. This "threshold" might be different for different tasks and may differ depending on the polarity of GVS. A parametric manipulation of CL/AR and AL/CR GVS of different current intensities in relation to behavioural tasks as assessed via fMRI might shed more light on these issues which were beyond the aims of the current study.

4.3. Implications for neglect rehabilitation

In accordance with previous studies and a recent treatment study (Wilkinson et al., 2014) our results show that GVS is a promising technique for non-invasive, bottom-up stimulation of brain damaged patients with neuropsychological impairments. The technique is easy to administer, low-cost, safe, and has been shown to modulate a wide range of neuropsychological functions transiently (Utz et al., 2010). A recent study showed *lasting* effects of a small number of repetitive GVS sessions on tactile extinction (cf. Schmidt et al., 2013b), thus showing its feasibility and efficacy as a treatment. It is likely that GVS could significantly modulate many other spatial and attentional dysfunctions seen in right-hemisphere lesioned patients, analogous to similar applications in the rehabilitation of motor deficits using transcranial direct current stimulation of the motor cortex (Schlaug et al., 2008). Future studies should evaluate the role of critical treatment factors, i.e. the stability of GVS effects, repeated stimulation sessions, polarity, and lesion chronicity. With respect to the latter, a recent study from our lab, however, did not show any influence of lesion chronicity on the beneficial effect of GVS on the impaired arm position sense in patients with left spatial neglect (Schmidt et al., 2013b). Another critical issue may be the potential combination of GVS with other treatments for neglect to obtain greater effects. It might be promising to test the combined effects of GVS with other techniques such as optokinetic smooth pursuit eye movement training (Kerkhoff et al., 2013, 2014), visuomotor feedback training (Harvey et al., 2010, 2003) or theta burst stimulation (Cazzoli et al., 2012), since all these techniques rely on different mechanisms. In fact, a recent study (cf. Hopfner et al., 2015), showed greater treatment effects of optokinetic smooth pursuit eye movement training when patients received additional theta burst stimulation. Such successful treatment combinations may further enhance the therapeutic outcome in neurologically disabled patients compared to single stimulation approaches.

4.4. Limitations of the study

As a limitation of our study, we cannot completely rule out practice effects as sham stimulation was always administered first. However, some of our findings argue against that possibility: First, our analysis of the spatial bias in number cancellation (CoC) shows a significant *deteriorating* effect of CL/AR GVS in the RBD− group which is not indicative of practice effects. Second, the RBD− group showed no effect in any condition in the line bisection task. Instead, there was a constant *leftward* line bisection error above 0 that should have been reduced if test repetition would have had an effect. In addition, except for line bisection, none of the tasks was given twice to the same patient to limit order effects. Taken together, even if we cannot completely rule out the contributing effects of test practice, these appear unlikely. Moreover, the thresholding procedure for GVS in the beginning of session 1 could have influenced the results, although it lasted only 30–60 s. This could have been circumwented by adding another (fourth) session devoted only to the threshold determination 1 or 2 days before starting with the Sham-session. This was not possible due to time constraints in the neurorehabilitation setting. Nevertheless, Sham GVS was less effective or completely ineffective as compared to *real* GVS thus highlighting the specificity of the latter. Moreover, the subliminal stimulation excluded any subtle attentional cueing effects arising from the tingling of the active electrode that are inevitable with suprathreshold GVS.

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Subliminal galvanic-vestibular stimulation recalibrates the distorted visual and tactile subjective vertical in right-sided stroke

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ABSTRACT

Stroke of the right cerebral hemisphere often causes deficits in the judgement of the subjective visual vertical (SVV) and subjective tactile vertical (STV) which are related to central vestibular functioning. Clinically, deficits in the SVV/STV are linked to balance problems and poor functional outcome. Galvanic Vestibular Stimulation (GVS) is a non-invasive, save stimulation technique that induces polarity-specific changes in the cortical vestibular systems. Subliminal GVS induces imperceptible vestibular stimulation without unpleasant side effects. Here, we applied bipolar subliminal GVS over the mastoids (mean intensity: 0.7 mA, 20 min duration per session) to investigate its online-influence on constant errors, difference thresholds and range values in the SVV and STV. 24 patients with subacute, single, unilateral right hemisphere stroke were studied and assigned to two patient groups (impaired vs. normal in the SVV and STV) on the basis of cut-off scores from healthy controls. Both groups performed these tasks under three experimental conditions on three different days: a) sham GVS where electric current was applied only for 30 s and then turned off, b) left-cathodal GVS and c) right-cathodal GVS, for a period of 20 min per session. Left-cathodal GVS, but not right-cathodal GVS significantly reduced all parameters in the SVV. Concerning STV GVS also reduced constant error and range numerically, though not significantly. These effects occurred selectively in the impaired patient group. In conclusion, we found that GVS rapidly influences poststroke verticality deficits in the visual and tactile modality, thus highlighting the importance of the vestibular system in the multimodal elaboration of the subjective vertical.

1. Introduction

The human brain constructs verticality perception by integrating vestibular, somatosensory and visual information. The correct perception of verticality is an important requirement for efficiently moving and acting in the world. An impairment of this ability frequently follows stroke as indicated by deviations of the patients' subjective visual vertical (SVV) larger than $\pm 2°$ from the earth vertical (Bender and Jung, 1948; Kerkhoff, 1999; Yelnik et al., 2002; Utz et al., 2011b). In this task patients have to judge when a rod, that is rotated mostly in the frontal (roll) plane, is aligned with the earth vertical. In addition to the visual domain, disturbed perception of verticality after stroke has been observed in the haptic modality. In the haptic variant of the task a rod has to be adepted with one hand (typically the nonparetic, ipsilesional hand) to the earth vertical (subjective tactile vertical = STV) while blindfolded. Tilts in these two sensory verticals are significantly associated with impairments in other perceptual tasks (i.e. line orientation judgments, constructional apraxia, visual neglect (Funk et al., 2013; Kerkhoff, 1999), balance problems (Bonan et al., 2007), a tilted subjective postural vertical (Perennou et al., 2008), and a poor functional outcome of the individuals with stroke (Funk et al., 2013). Those results have been interpreted in favor of a multimodal, graviceptive–vestibular pathway proceeding from the brainstem via the thalamus to temporoparietal multisensory cortical areas, and in case of a lesion leading to perturbations of the visual vertical (Brandt et al., 1994; Baier et al., 2012) or the tactile vertical (Funk et al., 2010a, 2010b). Moreover, some researchers postulate, that the right cerebral hemisphere elaborates an *integrated* verticality representation across different modalities (Perennou et al., 2008). As a consequence, lesions of the right hemisphere, i.e. due to stroke, might compromise perception of the vertical in a multimodal way.

Abbreviations: GVS, galvanic-vestibular stimulation; SVV, subjective visual vertical; STV, subjective tactile vertical

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As the vestibular system plays a significant role in the computation of the subjective vertical, its activation may modulate the verticality perception. For this purpose electrical stimulation of the vestibular system can be induced by placing one electrode behind each ear over the left and right mastoid respectively (termed galvanic vestibular stimulation or GVS, for review see Utz et al., 2010). Underneath the mastoids the vestibular nerve projects from the inner ear to the vestibular brain stem nuclei, over thalamic nuclei to a number of distributed cortical vestibular areas including area 2cv near the central sulcus, area 3a, b in the somatosensory cortex, parietal area 7a, and the parieto-insular-vestibular-cortex (PIVC). Although there is no primary vestibular cortex as in the visual, auditory or tactile modality, the above mentioned array of multiple, interconnected vestibular cortical areas is thought to be under the control of the PIVC (Guldin and Grüsser, 1998). Practically, GVS consists of applying direct current to the mastoids – usually delivered by a small battery-driven constant current stimulator. The positive electrode is termed the anode, the negative the cathode. Consequently, the two following electrode combinations are typically used for GVS: left-cathodal/right-anodal (CL) and right-cathodal/left-anodal (CR) GVS. Subliminal GVS can be administered by adjusting the current intensity below an individual's sensory threshold. This has the methodological advantage that different GVS protocols and polarities can be manipulated elegantly without the patient's knowledge (whether real current is flowing or not) that might otherwise influence his/her performance due to "spatial cueing" effects induced by a tingling sensation under one electrode. Furthermore, GVS is painless, easily applicable, safe, and induces minimal side effects when used in accordance with standard safety guidelines (Utz et al., 2011c).

GVS as a stimulation method has significant effects on a wide variety of cognitive and perceptual tasks, both in healthy persons and neurological patients (for review see Utz et al., 2010). For example, Wilkinson and co-workers found that GVS facilitated visual memory recall in healthy persons (Wilkinson et al., 2008) and improved visuo-constructive deficits in a right-hemisphere lesioned patient (Wilkinson et al., 2010, 2014). Similar studies showed modulatory effects of GVS on somatosensory deficits (Schmidt et al., 2013a) and different components of visual neglect (Utz et al., 2011a, 2011b; Oppenländer et al., 2014) thus demonstrating multifaceted effects on neuropsychological functions or deficits.

The first study that assessed the influence of GVS on verticality perception in healthy subjects found a shift of the visual and tactile vertical towards the anode (Mars et al., 2001). In a recent study (Volkening et al., 2014) the SVV and STV shifted towards the anode during GVS, whereas this shift was reversed towards the cathode in both modalities once stimulation was turned off. Overall, the effects were strongest for the haptic modality. Evidence from a recent clinical study (Saj et al., 2006) in right-hemisphere lesioned patients with vs. without visual neglect showed that left-cathodal GVS reduced the constant error in the SVV. Whether GVS also affects performance in the STV is unknown, to the best of our knowledge. Moreover, performance of impaired persons in both sensory verticals (visual, tactile) is most often characterized by two features: a frequently observed directional error (= the counterclockwise or clockwise tilt in the frontal or roll plane) and/or a reduced precision or pathologically increased variability as indicated by raised difference thresholds or huge ranges in these tasks (Kerkhoff, 1999; Utz et al., 2011a). These latter types of errors are frequently observed in patients with a tilted SVV or STV (Funk et al., 2010b, 2013) and are significantly related to disturbed spatial behavior as well (i.e. line orientation judgments, Funk et al., 2013) or balance problems (Bonan et al., 2007). Hence, both from a theoretical and a clinical viewpoint, it would be important to know whether GVS modulates not only the constant (directional) errors but also those parameters that indicate a reduced precision and higher variability in the SVV and STV. Finally, we sought to analyze whether modulatory GVS effects occur *selectively* in patients with disturbed SVV/STV or are also found in those patients without a deficit in these sensory axes.

Our research questions for this study were hence threefold: 1) Does GVS modulate constant/directional errors in the SVV and STV? 2) Does GVS modulate the precision in the SVV/STV as expressed by difference thresholds and range of performance? 3) Are the modulatory effects induced by GVS specific for patients with an impaired SVV/STV or do significant effects also occur in patients who are unimpaired in these tasks?

2. Methods

2.1. Patients

The study was approved by the local ethics committee (Ärztekammer des Saarlandes, Nr. 147/08, 16.9.2008) and included 24 patients with unilateral right-sided stroke (Table 1). Inclusion criteria were right-handedness and a single right hemisphere infarction or hemorrhage. Exclusion criteria were other neurological or psychiatric diseases, epilepsy, a sensitive scalp skin and metallic brain implants (Iyer et al., 2005). The participants were 9 women and 15 men with a median age of 63.6 years (range 42–84 years), and a median time since lesion of 2 months (range: 1–84 months). Patients were allocated into an "impaired" or "unimpaired" group depending on their performance in the SVV or the STV tasks (described below) separately. Normative data for both tasks had already been collected in a previous study (Kerkhoff, 1999). The cut-off-score for the constant error was 2.0° for the SVV and 2.5° for the STV. Healthy controls did not participate in the present study (see Table 1).

For both the SVV and STV the patients were allocated to a patient group *with or without a spatial deficit in the SVV or STV* (termed impaired or unimpaired) depending on their performance in the sham condition in both tasks. Further information about the patient sample and additional clinical assessments (i.e. visual neglect, visual field, motor status) can be found in the companion paper in this special issue on "Brain stimulation and Attention" (see Oppenländer et al., 2014). The sample studied in the present study was identical to that in the companion paper. All patients had a corrected visual acuity for the near distance (0.4 m) of at least 0.7 (=70%, 7/10).

2.2. Experimental procedures

In the first session the stimulation threshold for GVS was determined in all subjects. After fixing the electrodes, galvanic bipolar stimulation was delivered by a constant direct current (DC) stimulator (9 voltage battery, Type: ED 2011, manufacturer: DKI GmbH, DE-01277 Dresden). The carbon-rubber electrodes (50 mm × 35 mm) were fastened on the skin over each mastoid (binaural stimulation), in order to activate the peripheral vestibular organs. The conditions were termed Cathode Left (CL) when the cathode was placed over the left mastoid and the anode on the right, and Cathode Right (CR) when polarization was inversed. Similar to others (Rorsman et al., 1999) we stimulated below the sensation threshold (subliminal) in order to prevent awareness of any electrical stimulation in the 3 experimental conditions. A switch on the stimulation device delivered current at individually adjusted levels for each patient. This threshold was individually determined in this first session by slowly increasing current intensity in steps of 0.1 mA until the participant indicated a tingling sensation (first threshold). The current was subsequently reduced

Table 1
Patient characteristics of 24 patients with unilateral right-hemispheric stroke. See text for details.

Patient	Age/ sex	Etiology	Lesion	TSL (months)	Hemi-paresis	Field defect	Subjective visual vertical[a]	Subjective tactile vertical[b]
1	55/m	I	F, T	4	Left	No	Impaired	Unimpaired
2	76/m	I	F, T, P	84	Left	HH	Unimpaired	Impaired
3	65/m	I	F, T, P, BG	3	Left	Q	Impaired	Impaired
4	65/m	I	T	15	Left	No	Unimpaired	Unimpaired
5	70/f	H	BG	2	Left	No	Impaired	Impaired
6	62/m	I	T	1	Left	No	Unimpaired	Impaired
7	59/m	I	P, O	1	No	No	Unimpaired	Unimpaired
8	72/f	I	T	2	Left	HH	Unimpaired	Unimpaired
9	50/m	I	T	2	Left	No	Unimpaired	Unimpaired
10	51/m	I	BG	1	Left	No	Unimpaired	Unimpaired
11	70/m	I	T	1	Left	No	Impaired	Impaired
12	67/m	I	T, F	1	Left	No	Unimpaired	Unimpaired
13	79/f	I	T, F	2	Left	No	Impaired	Impaired
14	84/f	I	F, T	12	Left	No	Unimpaired	Unimpaired
15	72/m	I	T, P	1	Left	Q	Unimpaired	Unimpaired
16	70/m	I	T	2	Left	No	Impaired	Impaired
17	70/m	I	F	35	Left	No	Impaired	Unimpaired
18	42/f	I	T, BG	1	No	No	Unimpaired	Unimpaired
19	76/f	I	F, T, P, O	1	Left	HH	Unimpaired	Impaired
20	53/f	I	O	3	No	HH	Unimpaired	Unimpaired
21	51/m	H	P	1	No	Q	Unimpaired	Unimpaired
22	57/f	H	T, P	3	Left	No	Unimpaired	Impaired
23	67/f	I	F	1	Left	No	Impaired	Unimpaired
24	44/m	H	F, T, P	3	Left	No	Unimpaired	Unimpaired
	Mean: 63.6 yrs	20 I, 4 H		Median: 2 month	20/24 im-paired	7/24 impaired	8/24 impaired	9/24 impaired

I/H: ischemic/hemorrhagic stroke; P/T/F/O/BG: parietal/temporal/frontal/ occipital/basal ganglia; TSL: time since lesion; HH: homonymous hemianopia, Q: quadrantanopia.
[a] Based on a cutoff-value of +/− 2.0° for the constant error in this task derived from Kerkhoff (1999).
[b] Based on a cutoff-value of +/−2,5° for the constant error in this task derived from Kerkhoff (1999).

until the participant reported that the sensation had disappeared (second threshold). This procedure was repeated a second time and the median of these 4 threshold values was defined as the sensory threshold. This value of current intensity was then used for the CL and CR sessions. The mean threshold level across all patients was 0.7 mA (range: 0.4–1.5 mA). This strategy of subliminal GVS eliminates any "spatial cueing" effects as a consequence of the tingling sensation typically felt by the participant when *above-threshold* electrical current is delivered to the anode on the mastoid.

After the threshold determination for GVS all participants performed the two verticality tasks (SVV, STV; described below) *while* the electrodes of the stimulation device were fixed over the mastoids but not active, thus creating a sham condition. To this purpose, after fixing the electrodes, the current was initially turned on until the participant perceived a tingling sensation, after which the current was smoothly turned off within 30 s, without the patient being aware of this (due to the subthreshold stimulation, see above). The stimulator was always invisible for the participant. This created an effective sham-stimulation since the individuals were not able to discriminate between the conditions where real current was applied and those where the current was turned off due to the imperceptible sub-threshold intensity of the stimulus. In sessions 2 and 3, the patients repeated all experimental tasks, but received subliminal, *real* GVS (either CL or CR). The sequence of these 2 experimental conditions was counterbalanced within each group, with one half of the participants receiving CL in session 2 and CR in session 3, and the other half receiving the opposite sequence. The study design was single-blinded, i.e. only the participants were blinded for the experimental conditions (CL, CR, and Sham).

The three sessions were performed on three separate days. The total experiment was completed within 5 days. Each session lasted approximately one hour, but GVS stimulation was always limited to 20 minutes per session. GVS-stimulation started a few seconds before the task instruction by the experimenter and terminated immediately after completion of the two tests.

2.3. Experimental verticality tests

2.3.1. Subjective visual vertical (SVV)

The subjects were tested using specific software (VSWin; Kerkhoff and Marquardt, 1995) for the measurement of the SVV in the frontal or roll plane. VS is based on the method of limits (Engen, 1971). In the measurement of the SVV, the experimenter is required to orient an oblique white line (100 mmx2 mm) presented on a black background until the subject indicates that it lies exactly vertical. The line is then rotated further until the subject indicates that the line is no longer vertical. With this method, two psychophysical parameters are calculated: the constant error and difference threshold. The constant error denotes the difference between the subject's mean estimate (the point of subjective equality) and the objective correct orientation (here: 90°). Hence, the constant error gives information about the central tendency or central error of the subject. A positive constant error value represents a clockwise deviation from veridical and a negative value represents anticlockwise deviation. The interval of uncertainty indicates the complete range during which the subject considers the displayed line as exactly vertical within each trial. From this value the difference threshold is calculated which is defined as one half of the interval of uncertainty (Engen, 1971). Finally, the range was computed for each subject in this task which denotes the distance between the minimum and maximum score (across *all* trials). Ten trials were performed, 5 with a clockwise rotation and 5 with a counterclockwise rotation. The starting position was always 30° away from the objective vertical (hence either at 60° or 120°, while vertical was defined as 90°). The head and body of the subject were oriented earth-vertical within an experimental chair with a supporting head- and chinrest. All measurements were taken in total darkness with the chassis of the PC-monitor covered by an oval-shaped mask to eliminate any visual reference cues. No visual cues were visible except the bar for estimating the SVV. Subjects were tested at a distance of 0.5 m from a monitor with spectacle corrections where necessary. For the statistical analysis, the constant errors, difference thresholds and ranges (all in °) were analyzed.

2.3.2. *Subjective tactile vertical (STV)*

The STV was measured via a rotatable metal bar (15 cm long, 12 mm wide) which was fixed on a wooden board (0.4×0.5 m^2; Kerkhoff, 1999). The board was mounted perpendicularly on a table in front of the patient at a distance of 0.5 m. Participants were sitting on a chair with their head supported by a head-and chinrest such that his/her body and head were oriented earth-vertical. The rod was continuously adjustable in the frontal plane. A scale was drawn on the board, hidden from participants, indicating their tactile-spatial judgment in degrees. The scale ranged in steps of 1° from 0° indicating the right horizontal over 90° denoting the objective vertical to 180° indicating the left horizontal. Prior to each experimental session, the apparatus and rod were calibrated according to the earth vertical. Participants were required to adjust the bar blindfolded according to their subjective tactile vertical with their right (nonparetic) hand. There were two different starting positions, one 30° rotated from the veridical vertical in clockwise direction (120°), the other 30° rotated from the objective vertical in counterclockwise direction (60°). After 5 practice trials, participants had to perform 10 experimental trials, 5 from each starting position, their order pseudo-randomized. Participants were only allowed to touch the metal rod, not the outer edges of the board. The tactile-spatial tests were performed with the same experimental chair as in the SVV (see above) at a distance of 0.5 m from the tactile board. Subjects were blindfolded before starting the five practice trials per task (which were not counted) to familiarize the subjects with the tasks. Constant errors and ranges from the 10 measurements were calculated.

2.4. *Statistics*

For the analysis of stimulation effects on constant errors, range values and difference thresholds (only SVV), 2 × repeated-measures ANOVAs were conducted with the between-subjects factor group (impaired, unimpaired) and the within-subjects factor GVS (Sham, CR, CL), separately for each measure. The results of the ANOVAs were Greenhouse-Geisser corrected when sphericity was violated according to significant Mauchly-Tests.

3. Results

3.1. *Subjective visual vertical (SVV)*

Repeated measures ANOVAs revealed a main effect of GVS on constant error [$F(2, 44)=12.03$, $p<.001$, $\eta_p{}^2=.35$], difference threshold [$F(1.19, 26.11)=5.55$, $p=.02$, $\eta_p{}^2=.20$] and range [$F(2, 44)=11.69$, $p<.001$, $\eta_p{}^2=.35$], each with the lowest values under CL stimulation. Concerning the constant error, there was a main effect of group [$F(1, 22)=26.80$, $p<.001$, $\eta_p{}^2=.55$], indicating the impaired group having a greater error reduction depending on the experimental manipulation as compared to the unimpaired group. Additionally, the interaction between both variables on constant error values was also significant [$F(2,44)=7.05$, $p=.002$, $\eta_p{}^2=0.24$] showing that the impaired group had a higher benefit of GVS under CL-stimulation than the unimpaired group. Pairwise comparisons showed the error reduction in the RBD+ group to be significantly lower under CL- as compared to Sham-stimulation [$t(7)=$ 5,79, $p=.001$, $r=.91$] as well as marginal significantly lower under CL- as compared to CR-stimulation [$t(7)= -1.98$, $p=.08$]. Across both groups, difference thresholds were significantly lower under CL-stimulation than under sham stimulation [$t(23)=$ 2.70, $p=.01$, $r=.49$] as revealed by post-hoc comparisons. There additionally was a numerical, though non-significant trend towards reduced thresholds in the CR as compared to the Sham/Baseline condition [$t(23)=$ 1.83, $p=.08$]. Concerning range, post-hoc analyzes revealed a significantly greater reduction in the CL [$t(23)=$ 2,48, $p=.02$, $r=.46$] and the CR condition [$t(23)=$ 2,68, $p=.01$, $r=.49$] for both groups as compared to sham stimulation.

Fig. 1 illustrates the influence of GVS on error, threshold and distribution (range) values in both patient groups.

3.2. *Subjective tactile vertical (STV)*

There was a non-significant trend to an interaction between GVS and group on constant error [$F(1.25, 27.55)=3.76$, $p=.055$, $\eta_p{}^2=.15$] indicating that error values were the lowest under CL stimulation in both groups (see Fig. 2). Concerning range, repeated measures ANOVAs revealed no significant effects. However, there was a numerical trend towards lower range values under GVS stimulation in the impaired as compared to the unimpaired group (see Fig. 2).

4. Discussion

Several findings are apparent from our study: 1) CL-GVS, but less CR-GVS influenced the SVV and STV in patients who were impaired in these tasks. 2) GVS affected not only constant errors,

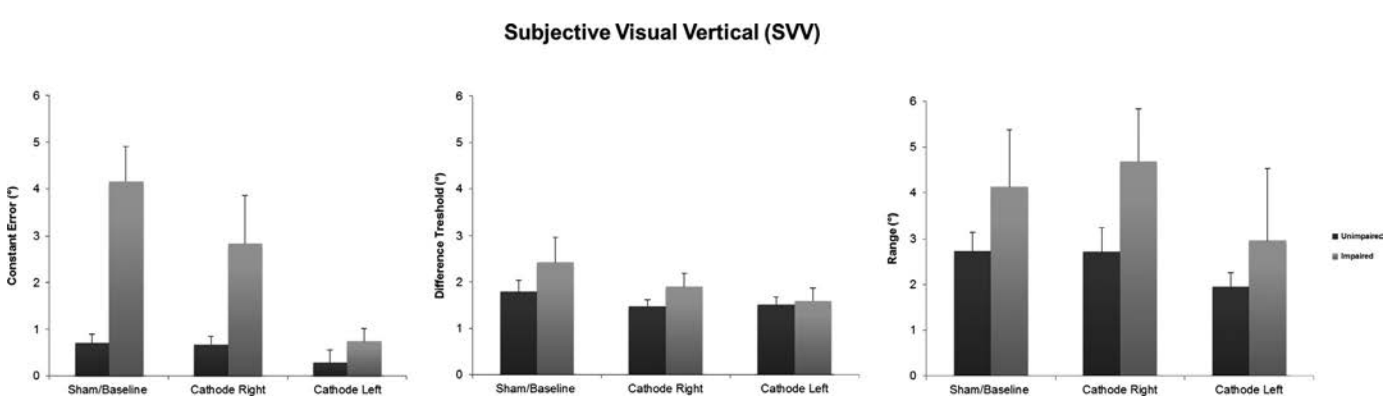

Fig. 1. Results of GVS on the SVV (constant errors, difference thresholds, range, all in °) across the three experimental conditions (Sham; cathode right=CR, cathode left=CL). Error bars indicate 1 SEM. See text for details.

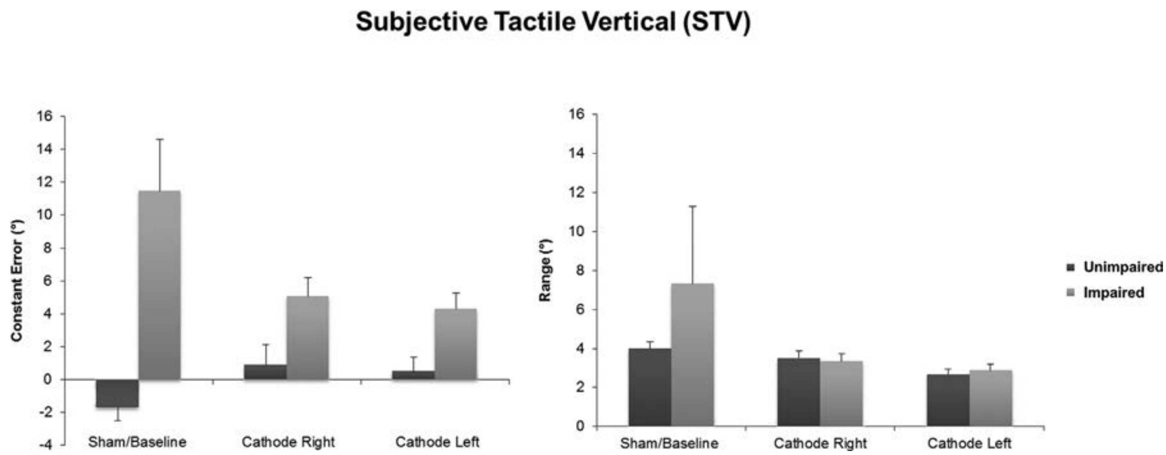

Fig. 2. Results of GVS on the STV (constant errors, range, all in °) across the three experimental conditions (Sham; cathode-right = CR, cathode-left = CL). Error bars indicate 1 SEM. See text for details.

but also difference thresholds and ranges in the SVV. Similar effects were seen for the STV, but did not reach statistical significance.

4.1. SVV

Our results are in accordance with those of Saj et al. (2006) who also found a reduction of the constant error with CL-GVS in right-hemisphere stroke patients. Furthermore, the present study extends these findings by showing that the same positive effect is also found for the difference thresholds and ranges, which decreased significantly with CL-GVS. This shows that GVS not only influences the directional error (hence the tilt), but also improves the general spatial precision in the tasks, regardless of the direction of the tilt. Put differently: the patients were much more accurate and consistent in the task when stimulated with GVS. This observation is clinically relevant as it shows that the frequently observed large variability of patients with right-sided stroke in visuo-spatial or tactile-spatial perceptual judgments (Kerkhoff, 1999; Funk et al., 2013) can be significantly reduced by vestibular input. This offers therapeutic options in neurorehabilitation, as GVS could be applied in addition to behavioral–perceptual treatments (i.e. Funk et al., 2013).

4.2. STV

We found largely the similar pattern of results for the STV as for the SVV, with one exception: the deviations in the latter were typically larger than in the prior, which is related to the fact that tactile estimation is more difficult than visual judgement of the verticality in the roll/frontal plane. This nicely agrees with similar findings from visual and tactile vertical tests of other studies (Kerkhoff, 1999; Utz et al., 2011a; Funk et al., 2010a, 2010b). Moreover, the modulatory effect of GVS largely to be similar in the tactile as in the visual modality (in terms of reduction of the errors in °), although the reduction of the range values were not significant for the STV in the impaired group (Fig. 2). This latter finding is probably due to the large variabilities in our data which might have prevented significant effects for the range values. Nevertheless, the current data are in agreement with the GVS-modulatory effect on the STV found in studies with normal subjects and higher current values as the present (Mars et al., 2001; Volkening et al., 2014). This shows a strong influence of vestibular input onto the somatosensory system and is in accord with similar GVS-modulatory effects on tactile extinction (Schmidt et al., 2013b). Anatomically, this influence may result from the partially overlapping cortical projection zones of the vestibular and somatosensory systems that terminate in the parietal lobe (Lopez et al., 2012), so that vestibular stimulation also activates in parallel the somatosensory system.

4.3. Implications

In accordance with previous studies for the SVV (Saj et al., 2006) and similar studies in visual neglect (Oppenländer et al., 2014) our results show that *subliminal* GVS is a promising and effective technique for non-invasive, bottom-up stimulation of brain damaged patients with multimodal spatial disorders of verticality. The technique is easy to administer, low-cost, safe, and has been shown to modulate a wide range of neurocognitive or neurosensory functions transiently (Utz et al., 2010 for review). A recent study showed *lasting* effects of a small number of repetitive GVS sessions on tactile extinction (Schmidt et al., 2013b), thus showing its feasibility and efficacy of repetitive GVS as a treatment. In this sense we would expect that *repetitive* GVS could permanently recalibrate the distorted visual and tactile vertical in patients suffering from right-hemisphere stroke – but this hypothesis has to be tested in subsequent studies. Repetitive GVS might also speed up the recovery from the marked balance problems so often reported for this patient group (Bonan et al., 2007).

4.4. Limitations of the study

As a limitation of our study, we cannot completely rule out practice effects as sham stimulation was always administered first. However, some of our findings argue against that possibility: first, the unimpaired unimpaired patient group did not show any improvement, which theoretically could have occurred in their results (because they were not perfect in the tasks). Second, we found that CL-GVS had the strongest effect on all parameters of both axes, regardless of whether this was the second or third session (given that the two real GVS stimulation sessions were pseudo-randomized in their sequence). This speaks against a practice or mere repetition effect. Taken together, even if we cannot completely rule out the contributing effects of test practice, these appear unlikely. Moreover, the thresholding procedure for GVS in the beginning of the Sham session could have influenced the results, although it lasted only 30 s. This could have been circumvented by adding another (fourth) session devoted only to the threshold determination 1 or 2 days before starting with the sham-session. This was not possible due to time constraints in the neurorehabilitation setting. Nevertheless, sham GVS was less effective or completely ineffective as compared to *real* GVS thus highlighting the specificity of the latter. Moreover, the subliminal stimulation excluded any subtle attentional cueing effects arising from the tingling of the active electrode that are inevitable with suprathreshold GVS.

5. Conclusions

Subliminal GVS significantly reduces the tilt and improves the general precision in the SVV and STV in individuals with right-sided stroke.

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