Mareike Kardinal

Adaptive Times

Modulating Time Perception in Neglect Patients and Healthy Individuals

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General Abstract

In our daily experience, time and space are rarely separated. Over the past decades, there have been increasing indications that time and space are linked not only in the physical world, but also interact in the mind. Some authors suggest that durations in the interval range are represented along a mental time line, with shorter durations encoded on the left and longer durations on the right side. Evidence for spatial codes in the representation of time comes from time-space interferences in healthy individuals. They also stem from observation of severe time deficits in patients with spatial neglect, calling upon the need for therapy possibilities. However, while visuospatial distortions in these patients have been thoroughly investigated and may be confronted with well-established treatments, there are only sparse studies examining time deficits and their possible modulation. From anthropological psychology comes the notion that space processing might differ between East Asians and Westerners. Sensory stimulation techniques known to modulate space perception might thus exert differential effects in individuals from different cultures. Further investigation for this matter is needed.

The present dissertation aims at examining the interaction of time and space processing in neglect patients and healthy individuals. More concretely, it has three objectives: (i) to investigate effects of well-established space modulation techniques on time deficits in neglect patients, (ii) to further elucidate time-space interactions in the sense of a horizontal mental time line, and (iii) to reveal possible cross-cultural differences in basic time perception and susceptibility to sensory stimulation techniques which have proven to be a powerful tool in the treatment of spatial neglect. To provide an answer, three studies are conducted and presented in this thesis. In all of them, traditional space modulation techniques are employed and administered in diverse time tasks. Study 1 investigates effects of lateral head and trunk rotation on time reproduction and bisection in neglect patients and healthy individuals. Study 2 examines effects of Galvanic vestibular stimulation on temporal order judgments in right brain damaged patients with and without manifested neglect. And study 3 assesses influences of optokinetic stimulation on temporal order judgments in healthy Chinese and German participants.

In the studies, neglect patients demonstrated severe time distortions in both time reproduction and temporal order judgments. Importantly, these deficits could be overcome by lateral head and trunk rotation and Galvanic vestibular stimulation (GVS). Sustained effects after the termination of repetitive GVS treatment indicate a rehabilitation potential of this method. Trunk rotation also modulated time reproduction in healthy participants. Subjects produced shorter durations during rightward turns. These findings are in dissonance with known effects for physical space modulation, and do not support the idea of an automatic activation of a left-to-right mental time line during time tasks where spatial information is irrelevant. Optokinetic stimulation effectively influenced temporal order judgments in healthy subjects. Responses of “right stimulus first” judgments increased during leftward motion, indicating a shift of attention to the side of the incoming movement. Performance between Chinese and German subjects was comparable in the task, suggesting no cultural differences in basic time perception and sensibility to background optokinetic stimulation.

To conclude, the present work confirms previous studies on time-space interactions in healthy individuals and patients with spatial neglect. While no indications were found for a horizontal mental time line or cross-cultural differences in time perception, I report as a novel finding that time distortions in neglect can be ameliorated by familiar sensory stimulation techniques, especially recommending Galvanic vestibular stimulation to be a strong candidate for therapy treatment.

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Abbreviations

ANOVA	analysis of variance
ATOM	a theory of magnitude
BG	basal ganglia
BL	baseline
BL-R	body left rotation
BR-R	body right rotation
CCT	cranial computed tomography
CI	capsula interna
CL-GVS	cathode left Galvanic vestibular stimulation (application of the cathode over the left mastoid)
cm	centimeter
CR-GVS	cathode right Galvanic vestibular stimulation (application of the cathode over the right mastoid)
DLPFC	dorsolateral prefrontal cortex
e.g.	for example
fMRI	functional magnetic resonance imaging
GVS	Galvanic vestibular stimulation
HFD	high field-dependence
HL-R	head left rotation
HR-R	head right rotation
i.e.	that is
ICB	intracerebral bleeding
ISI	interstimulus interval

LBT	line bisection task
LFD	low field-dependence
LIP	lateral intraparietal area
LLQ	left lower quadrant
LPS	*Leistungsprüfsystem*
mA	milliAmpere
MCA	middle cerebral artery
min	minute(s)
MNL	mental number line
MRI	magnetic resonance imaging
ms	millisecond
MTL	mental time line
n.a.	not assessed
n.s.	not significant
NET	*Neglect-Test*
OKN	optokinetic nystagmus
OKS	optokinetic stimulation
OTI	objective time interval
PPC	posterior parietal cortex
RBD	right brain damaged
(r)TMS	(repetitive) transcranial magnetic stimulation
SD	standard deviation
SEM	standard error of the mean
SI	stimulus interval
SMA	supplementary motor areas
SNARC	spatial-numerical association of response codes
SOA	stimulus onset time
STARC	spatial-temporal association of response codes
TB	time bisection
TBI	traumatic brain injury
tDCS	transcranial direct current stimulation
Thal	thalamus
TL-R	trunk left rotation
TOJ	temporal order judgment

TR	time reproduction
TR-R	trunk right rotation

Theoretical Background and Rationale

1.1. General introduction to time perception

Telling time is essential for most activities in daily life. It allows e.g. to develop the urge to wake up, to estimate how long it takes to brew coffee, and to unconsciously know when to move the hands to clap a certain rhythm. In order to deal with time, we rely on distinct timing systems (Buhusi & Meck, 2005). Circadian timing operates on a 24 hour range and unconsciously controls the sleep-wake cycle and our appetite. The millisecond timing system lies on the other end of the time range, and is important for motor control, thus enabling speech and music generation. Interval timing comprises conscious time perception in the seconds-to-minutes-to-hours range, and is the focus of the present dissertation. The perception of interval durations is subserved by two distinct subsystems: a metric versus an ordinal system (Buhusi & Meck, 2005; Battelli, Pascual-Leone, & Cavanagh, 2007). The first refers to a continuous-event, cognitively controlled timing, which is necessary for the judgment of a duration, or an interval between events. Continuous timing is measured in time estimation, comparison or reproduction tasks. The second subsystem corresponds to a rather automatic and discrete-event (discontinuous) timing, which is used for the judgment of the temporal order of event in a series. Event timing can be analyzed in temporal order or simultaneity judgment tasks. Both subsystems work in parallel (Buhusi & Meck, 2005).

Although the perception of time guides many of our behaviors, time is highly abstract: we cannot see, hear, smell nor haptically feel it. Thus, for the processing of temporal intervals, more concrete measures are needed. The theory of embodied cognition states that the mental representation of abstract concepts builds on physical experiences in perception and motor actions (Wilson, 2002; Boroditsky & Ramscar, 2002). The primary dimension we deal with, and which is part of all sensorimotor experiences since birth, is space.

1.2. Interactions between time and space

In our daily experience, time and space are rarely separated. We need two hours to go from Saarbrücken to Paris by train, we reach out to catch a falling porcelain vase in time, and we move our body to dance to music rhythms. Interestingly, we even talk about time in spatial codes, i.e. about the future which lies "ahead" of us, or leaving the past "behind". Over the past few decades, there has been increasing evidence that time and space are linked not only in the physical world, but also interact in the mind. Indications for time-space interactions stem from several research lines: behavioral data in healthy individuals, clinical reports of patients with deficits in space processing, and anatomical studies involving the application of transcranial magnetic stimulation (TMS), functional neuroimaging, and electrophysiology.

1.2.1. Time-space interactions in the healthy state

First evidence for the interaction between time and space comes from Piaget's observation that children intuitively do not differentiate between the concepts of time and space. For them, "longer [duration] is equivalent to further" (Piaget, 1969; as cited by Levin, 1977; see also Levin, 1979). Consecutive studies showed that the observation of differentially size-scaled model environments influences the subjective passage of time in adults. Compressed environments lead to a likewise compression of subjective time relative to clock time. The effect proves to be stronger in highly compressed than in full-sized models (De Long, 1981; Mitchell & Davis, 1987). Since these first indications, numerous following investigations have corroborated the idea of time-space associations (see Oliveri, Koch, & Caltagirone, 2009 for a review). Subjects judge larger stimuli to last longer than smaller stimuli (Xuan, Zhang, He, & Chen, 2007). They overestimate the duration of stimuli presented on the right side of visual space, and underestimate them when presented in the left hemi-space (Vicario et al., 2008; Oliveri et al., 2009). Also, participants respond faster to short durations or stimulus onset times with their left hand; and to longer durations or onset times with their right hand. The later phenomenon has been denominated STARC (*S*patial-*T*emporal *A*ssociation of *R*esponse *C*odes) effect (Conson, Cinque, Barbarulo, & Trojano, 2008; Ishihara, Keller, Rosetti, & Prinz, 2008; Vallesi, Binns, & Shallice, 2008). Moreover, subjective time perception is influenced by the speed of visual stimuli, i.e. when viewing speed-altered movie scenes (Levin, 1977; Levin, 1979; Grivel, Bernasconi, Manuel, Murray, & Spierer, 2011).

Given that time and space processing interact in the brain, it is not surprising that techniques which modulate space perception can alter subjective time sensation, too. The adaptation to left- or rightward deviating prism lenses shifts visuospatial attention to the side of the induced aftereffect (Rossetti et al., 1998). Interestingly, subjects underestimate temporal durations after being exposed to prisms inducing leftward attentional shifts, and likewise overestimate them for opposing aftereffects (Frassinetti, Magnani, & Oliveri, 2009; Magnani, Oliveri, Mancuso, Galante, & Frassinetti, 2011). Similarly, participants underestimate the duration of stimuli after the exposure to leftward optokinetic stimulation (OKS), and overestimate them after rightward OKS (Vicario, Caltagirone, & Oliveri, 2007). OKS further influences the perception of temporal order of two events (Teramoto, Watanabe, Umemura, Matsuoka, & Kita, 2004; Teramoto, Watanabe, & Umemura, 2008).

As a striking notion, research over the last years suggests that culture may be a fundamental modulator of basic space perception, as well (for a review see Nisbett & Miyamoto, 2005). In the rod-and-frame, test participants are asked to adjust a rod to the vertical upright, while ignoring a tilted frame surrounding the rod (Asch & Witkin, 1948a; Asch & Witkin, 1948b). Distinct individual performance in this task has been related to field-dependence, which defines the degree to which a subject can disembed an object from its environment with ease (Witkin, 1950; Witkin et al., 1954; Zhang, 2004). Interestingly, East Asians show greater difficulties in the rod-and-frame task than Westerners, suggesting that they find it more challenging to perceive an object as being independent from its surrounding (Ji, Peng, & Nisbett, 2000). Converting evidence for cultural differences in space perception comes from similar cross-cultural studies (Abel & Hsu, 1949; Masuda & Nisbett, 2001; Kitayama, Duffy, Kawamura, & Larsen, 2003; Masuda & Nisbett, 2006). Regarding time-space interactions, it yet remains a subject open to investigation whether people from a different cultural background differ in their perception of time, too. Interestingly, there are indications from linguistic research suggesting that the metaphoric time concept varies across cultures. Fuhrman and Boroditsky found an analog STARC effect in a picture task showing “earlier” (e.g. whole banana) and “later” events (e.g. eaten-up banana). English speaking subjects are faster to make “earlier” judgments with their left hand (and vice versa “later” responses with their right hand), while Hebrew speaking participants demonstrate a directly opposing stimulus-response phenomenon. The authors conclude that the metaphoric time concept follows a left-to-right orientation in Westerners and a right-to-left orientation in Hebrews, thus mirroring writing habits in both cultures (Fuhrman & Boroditsky, 2007; Santiago, Lupiáñez, Pérez, & Funes, 2007; Ulrich & Maienborn, 2010). In other cultures, the spatial layouts for the representation of past-future events include e.g. a vertical top-to-bottom orientation in Chinese subjects (Boroditsky, 2001; Boroditsky, Fuhrman, & McCormick, 2011) and a horizontal front-to-back orientation in Aymara people living in the Andean highlands of South America (Núñez & Sweetser, 2006). Importantly, if space and possibly time perception differs across cultures, then East Asians and Westerners might respond differentially to experimental manipulation known to influence perception. Regarding neurological patients, it raises the question whether neuropsychological tests and methods coming from studies in one culture might be generalized to patients from other cultures as well (Nell, 1999; Brickman, Cabo, & Manly, 2006; Hsieh & Tori, 2007). Therefore, it is worth examining the effectiveness of conventional modulation techniques across East Asian and Western cultures.

1.2.2. Spatial neglect and time deficits

In 1953, the neurologist Critchley wrote “pure temporal disorientation […] occurring independently of spatial disorders, is a rarer phenomenon, for more often, the two are combined” (Critchley, 1953; as cited by Walsh, 2003). Since then, there has been increasing evidence of associated space and time deficits in neuropsychological patients (Petrovici & Scheider, 1994; Becchio & Bertone, 2006). Hemispatial neglect (synonymously termed spatial neglect, or simply neglect in the following) is a heterogeneous, multimodal syndrome consisting of the failure to acknowledge, react and act to stimuli in the contralesional hemispace, in the absence of primary sensory or motor deficits (Kerkhoff, 2001; Heilman, Watson, & Valenstein, 2011). Neglect usually occurs after unilateral brain damage, being more prevalent after right than left brain damage (Ringman, Saver, Woolson, Clarke, & Adams, 2004). The most frequent etiology leading to neglect is an infarct of the middle cerebral artery; other causes are traumatic brain injuries, tumors, or degenerative diseases (Vallar, 1993; Heilman, Valenstein, & Watson, 2000; Kerkhoff, 2003a). Affected brain areas involve the posterior parietal cortex (PPC) including the temporo-parietal junction, the superior temporal cortex, the frontal premotor cortex, and the insula. Subcortical areas associated with neglect are the basal ganglia, the thalamus,

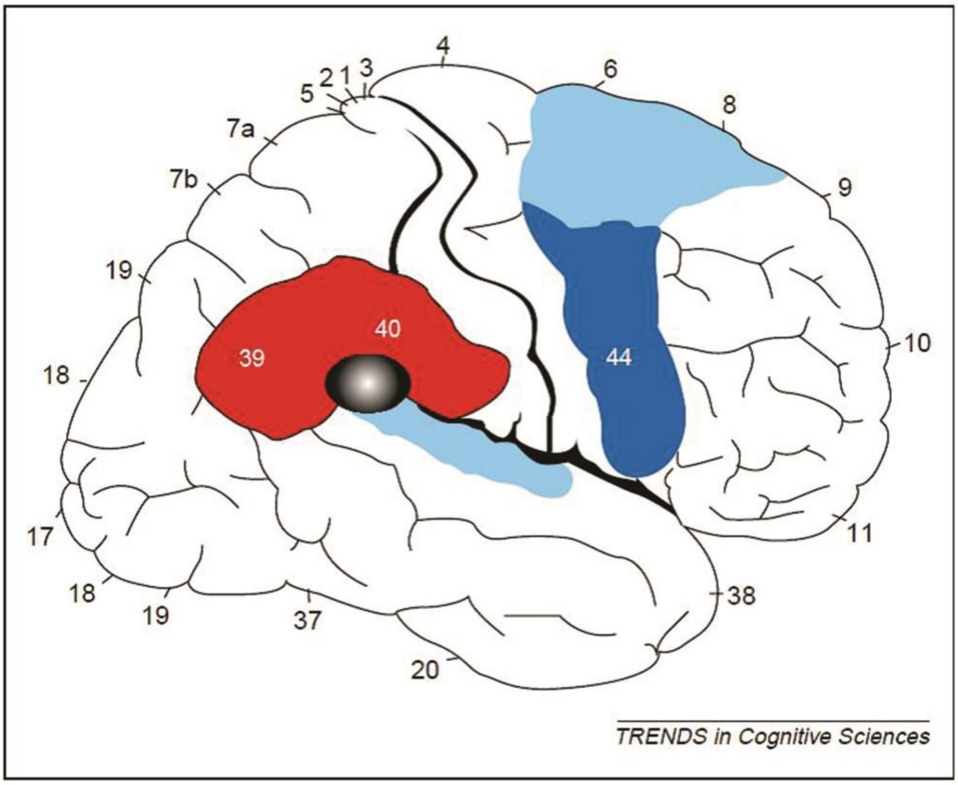

Figure 1. Cortical anatomical correlates of unilateral visuospatial neglect. Involved regions include the right inferior parietal cortex (highlighted in red), in particular the supramarginal gyrus at the temporo-parietal junction (black-gray area). Neglect is also associated with damages to the superior temporal gyrus (light blue area), and to the frontal premotor cortex (light and dark blue areas). Not shown are subcortical areas involved in neglect. The numbers refer to Brodmann areas. From: Halligan, Fink, Marshall, Vallar (2003). Spatial cognition: evidence from visual neglect. Trends in Cognitive Sciences, 7(3), 125–133. Copyright 2013 by Elsevier. Reprinted with permission.

and white matter fiber tracts (Halligan, Fink, Marshall, & Vallar, 2003; Karnath, Fruhmann Berger, Küker, & Rorden, 2004; Karnath & Rorden, 2012; see also figure 1). Notably, functionally different deficits of this rather heterogeneous syndrome draw upon selective damages to distinct anatomical sites (Chechlacz, Rotshtein, & Humphreys, 2012; Karnath & Rorden, 2012). Every year, three to five million individuals are affected by neglect worldwide, thus making neglect a noteworthy disorder (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005). About two thirds of the patients recover within the first year of injury; however, especially patients with large diffuse lesions develop chronic neglect, handicapping them in their private and professional lives (Kerkhoff, 2003a; Karnath, Rennig, Johannsen, & Rorden, 2011; Saj, Verdon, Vocat, & Vuilleumier, 2012). Regarding the underlying mechanism leading to neglect, several diverging theories have been established (see Kerkhoff, 2001, for an overview). Some of them stress the importance of disturbances in attentional processes (e.g. Kinsbourne, 1987; Posner & Driver, 1992); while others point out the impairment of contralesional space representation (Bisiach & Luzzatti, 1978; Bisiach, Capitani, Luzzatti, & Perani, 1981). Another theory considers a disturbed multisensory transformation process to be the primary cause of neglect (Karnath, Christ, & Hartje, 1993; Karnath, 1997). This later hypothesis is of particular importance for study 1 of the present work, and is explained in detail in the respective chapter.

Neglect (1) affects many activities in everyday life. Symptomatically, right brain damaged neglect patients shave or put on make-up only on the right side of their face; they neglect to eat food located on the left side of the plate; or bump into doorframes and other objects in their contralesional hemispace (Mesulam, 1981). Neglect has also been reported to extend to representational space. When asked to describe familiar places, patients omit to mention objects in the contralesional hemispace (Bisiach & Luzzatti, 1978; Guariglia, Padovani, Pantano, & Pizzamiglio, 1993). Also, they ignore details on this side when requested to draw objects from memory (Beschin, Cocchini, Della Sala, & Logie, 1997; Halligan & Marshall, 2001, see figure 2). In clinical settings, hemispatial neglect becomes visible in ipsilesional deviations in line bisection tasks which requests judging the midpoint of given lines, and in omissions of contralesional visual stimuli in reading and cancelling tasks (Albert, 1973; Schenkenberg, Bradford, & Ajax, 1980; Wilson, Cockburn, & Halligan, 1987; Stone et al., 1991). Importantly, neglect patients display deficits in time perception, too (Basso, Nichelli, Frassinetti, & di Pellegrino, 1996; Snyder & Chatterjee, 2004; Becchio & Bertone, 2006; Danckert et al., 2007; Oliveri et al., 2009; Calabria et al., 2011). Compared to healthy individuals, they have a three times prolonged attentional blink, which is especially severe for contralesional presented stimuli (Husain, Shapiro, Martin, & Kennard, 1997; Hillstrom, Husain, Shapiro, & Rorden, 2004). In time estimation or reproduction tasks, they underestimate temporal intervals (Danckert et al., 2007; Oliveri et al., 2009; Merrifield, Hurwitz, & Danckert, 2010). Moreover, neglect patients judge left-sided stimuli to last longer than right-sided stimuli (Basso et al., 1996). Regarding temporal order judgment (TOJ) tasks, healthy individuals reliably distinguish the temporal

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(1) For the ease of reading, I refer to left spatial neglect after right brain lesions whenever using the term neglect throughout this dissertation, unless otherwise stated. Of course, right spatial neglect may also occur after a left brain damage.

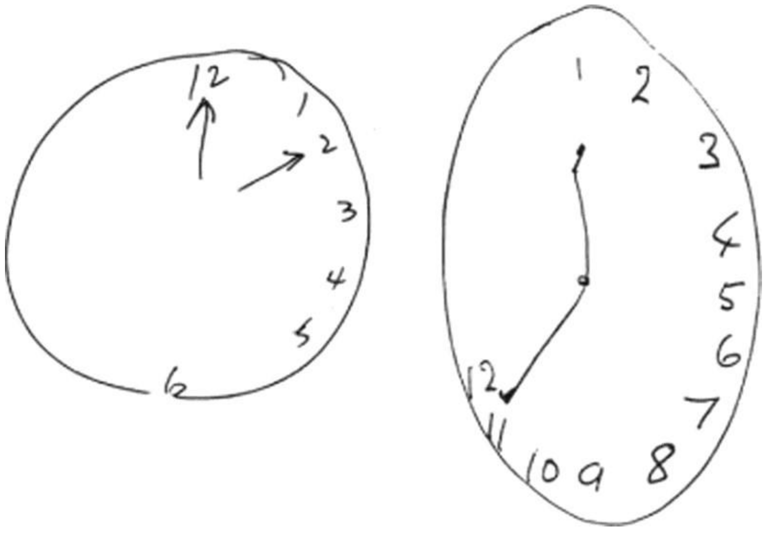


Figure 2. Characteristic left-sided neglect in a clock drawing task from memory. Adapted and modified according to Halligan & Bartolomeo (2012). Visual Neglect, Encyclopedia of Human Behavior, Second Edition, Ed.: Ramachandran, San Diego. First published in Robertson & Halligan (1999): Spatial Neglect: A Clinical Handbook for Diagnosis and Treatment. Hove: Psychology Press. Copyright 2013 by Elsevier Books. Reprinted with permission.

sequence of events if the interstimulus interval is greater than 40 ms. In contrast, patients with neglect or extinction (a related disorder) perceive the ipsilesional stimulus prior to the contralesional stimulus, unless the contralesional stimulus leads about 200 ms or more in time (Rorden, Mattingley, Karnath, & Driver, 1997; Robertson, Mattingley, Rorden, & Driver, 1998; Berberovic, Pisella, Morris, & Mattingley, 2004; Sinnett, Juncadella, Rafal, Azañón, & Soto-Faraco, 2007). This phenomenon is known as “prior entry” effect and has been reported for both the visual and auditory modality (Karnath, Zimmer, & Lewald, 2002; Becchio & Bertone, 2006).

Notably, correct time processing is indispensable for daily life functioning for neglect patients. For example, they need to be able to plan how much time they need to dress and eat, or how long the way takes from their home to the neuropsychological treatment facility. Also, a timely perception of objects (such as door frames) is essential to prevent from visually neglecting them. In fact, time deficits may be one crucial factor leading to neglect: if objects in the ipsilesional hemispace are perceived prior to those in the contralesional hemifield, it is not surprising that patients guide their attention primarily to the ipsilesional items. The above mentioned time deficits might therefore aggravate the visuospatial deficits and slow down the general rehabilitation process. It is therefore important to treat time deficits in patients, too. Neuropsychological treatment approaches for patients with neglect include visual exploration training, alertness training, and limb activation training. Furthermore, various bottom-up sensory stimulation techniques such as prism adaptation, optokinetic stimulation, neck muscle vibration, caloric vestibular stimulation, and trunk rotation permanently or transiently improve visuospatial neglect symptoms (Kerkhoff, 2001; Kerkhoff, 2003a; Kerkhoff, 2003b; for a recent review see Kerkhoff & Schenk, 2012). Several studies suggest Galvanic vestibular stimulation (GVS) as a new effective therapy method for diverse neglect deficits (Rorsman, Magnusson, & Johansson, 1999; Utz, Dimova, Oppenlander, & Kerkhoff, 2010; Utz, Keller, Kardinal, & Kerkhoff, 2011; Utz et al., 2011). However, the current treatment of neglect does not involve the attendance of time distortions. Also, investigations on modulating the time deficit in neglect have been sparse and are mainly restricted to alertness cues (Robertson et al., 1998), and prism adaptation (Berberovic et al., 2004; Oliveri, Magnani, Filipelli, Avanzi, & Frassinetti, 2013). It is an open question whether further techniques known to manipulate space perception ameliorate timing deficits in neglect patients.

1.3. Anatomy of time perception and processing

Time processing is associated with the activation of many diverse neuronal structures. Involved areas include the dorsolateral prefrontal cortex (DLPFC, Rao, Mayer, & Harrington, 2001; Macar et al., 2002; Koch, Oliveri, Torriero, & Caltagirone, 2003; Jones, Rosenkranz, Rothwell, & Jahanshahi, 2004; Tregellas, Davalos, & Rojas, 2006), the inferior frontal gyrus (Smith, Taylor, Lidzba, & Rubia, 2003), the supplementary motor areas (SMA, Macar et al., 2002; Smith et al., 2003; Tregellas et al., 2006), the insula (Tregellas et al., 2006), the cerebellum (Rao et al., 2001; Smith et al., 2003; Smith et al., 2011), and the basal ganglia (Rao et al., 2001; Tregellas et al., 2006; Smith et al., 2011). While the basal ganglia and the cerebellum have been proposed as general time generators, the frontal areas, especially the DLPFC, are related to working memory processes, and are thus thought to mediate the cognitive control of time perception (Lewis & Miall, 2003; Koch, Oliveri, & Caltagirone, 2009; Smith et al., 2011). Notably, an increasing number of studies further point towards the posterior parietal cortex (PPC) as playing an essential role in time processing and time-space interactions (Battelli et al., 2007; Bueti, Bahrami, & Walsh, 2008; Oliveri et al., 2009). The PPC is viewed as the neural substrate for visuospatial attention (Corbetta, Miezin, Shulman, & Petersen, 1993; Coull & Nobre, 1998; Bjoertomt, Cowey, & Walsh, 2002) and perception of the body in space (Brotchie, Andersen, Snyder, & Goodman, 1995; Bremmer, Pouget, & Hoffmann, 1998; Mullette-Gillman, Cohen, & Groh, 2005). Evidence for its further involvement in time processing comes partially from neurolopsychological reports of neglect patients with time deficits (Roberts, Lau, Chechlacz, & Humphreys, 2012; also see section 1.2.2). Besides, there are indications from studies using TMS which induces virtual lesions in healthy individuals. When applied over the right PPC, TMS disturbs judgments of temporal order (Woo, Kim, & Lee, 2009), as well as the comparison (Bueti et al., 2008) or the reproduction of time intervals (Oliveri et al., 2009). Functional imaging data have revealed the activation of the temporo-parietal junction during temporal order judgments (Davis, Christie, & Rorden, 2009). In addition, they demonstrated the involvement of the intraparietal sulcus (IPS) and the posterior inferior area of the parietal cortex during temporal cueing tasks (Coull & Nobre, 1998), as well as during time reproduction (Macar et al., 2002), and time comparison of visual (Onoe et al., 2001) or auditory stimuli (Rao et al., 2001). Final evidence for the important role of the PPC in time processing comes from electrophysiological studies in non-human primates. Neuronal activation in the IPS of the monkey's brain is associated with the integration of visual stimuli over time (Nieder, Diester, & Tudusciuc, 2006). Moreover, neurons in the lateral intraparietal cortex (area LIP) of the IPS are selectively activated during time comparisons tasks (Leon & Shadlen, 2003). To conclude, the observation that the PPC holds both the neuronal structures for time *and* space processing further nourishes the notion that time and space interact in the brain.

1.4. Mental representation of interval time

To sum, healthy individuals show a left-right stimulus response compatibility phenomenon for small versus long durations (STARC effect) in the interval timing range. They underestimate the duration of left-sided stimuli and likewise overestimate right-sided stimuli (see section 1.2.1.). Second, patients with left-sided visuospatial neglect demonstrate profound time distortions. These deficits are more severe in the contra- than the ipsilesional hemispace (see section 1.2.2.). And third, time perception is manipulated by techniques such as prisms and OKS, shifting visual attention to the left or right hemifield. In neglect patients, the time deficits are reduced by leftward (but not rightward) OKS—

similar to the modulation of hemineglect in physical space. These observations lead some authors to suggest that interval time is represented along a so-called horizontal mental time line (MTL), with shorter durations encoded in the left, and longer durations in the right space (Ishihara et al., 2008; Oliveri et al., 2009). A similar encoding format has been reported for the representation of numbers, with smaller numbers mapped to the left of larger numbers on a mental number line (MNL, Dehaene, Bossini, & Giraux, 1993; Hubbard, Piazza, Pinel, & Dehaene, 2005; Nieder, 2005). However, unlike the MNL whose existence has been repetitively confirmed by research over the last decade, the idea of a horizontal MTL is still a subject for debate.

In “A Theory of Magnitude” (ATOM), Walsh suggested that the processing of quantities such as time, space, and number rely on common neuronal networks in the parietal cortex (Walsh, 2003; Bueti & Walsh, 2009). In fact, number processing is disturbed in neglect patients, too (Zorzi, Priftis, & Umiltà, 2002; Vuilleumier, Ortigue, & Brugger, 2004; Zorzi, Priftis, Meneghello, Marenzi, & Umiltà, 2006; Priftis, Zorzi, Meneghello, Marenzi, & Umiltà, 2006; Umiltà, Priftis, & Zorzi, 2009). Moreover, time and numbers have been shown to interact in the brain (Dormal, Seron, & Pesenti, 2006; Roitman, Brannon, Andrews, & Platt, 2007; Javadi & Aichelburg, 2012). For example, numerically larger digits are judged to last longer than smaller digits (Xuan et al., 2007; Vicario et al., 2008; Oliveri et al., 2008). Numeric information also manipulates performance in the temporal order judgment task (Casarotti, Michielin, Zorzi, & Umiltà, 2007; Schwarz & Eiselt, 2009). Importantly, if time and number representation follow similar structures, then orienting in time space should resemble orienting in number space. In this sense, number processing is likewise influenced by OKS (Salillas, Grana, Juncadella, Rico, & Semenza, 2009), and prism adaptation (Rossetti et al., 2004). Furthermore, it can be manipulated by lateral head rotation (Lötscher, Schwarz, Schubiger, & Brugger, 2008). It remains to be investigated whether head rotation may modulate time processing in a similar fashion, thus corroborating the hypothesis of a MTL.

1.5. Rationale of the present investigations

The present work has three objectives. First, it aims at investigating the modulation of time deficits in neglect patients. Second, it focuses on further elucidating general time-space interactions in the sense of a horizontal mental time line. And third, it targets to reveal possible cross-cultural and individual

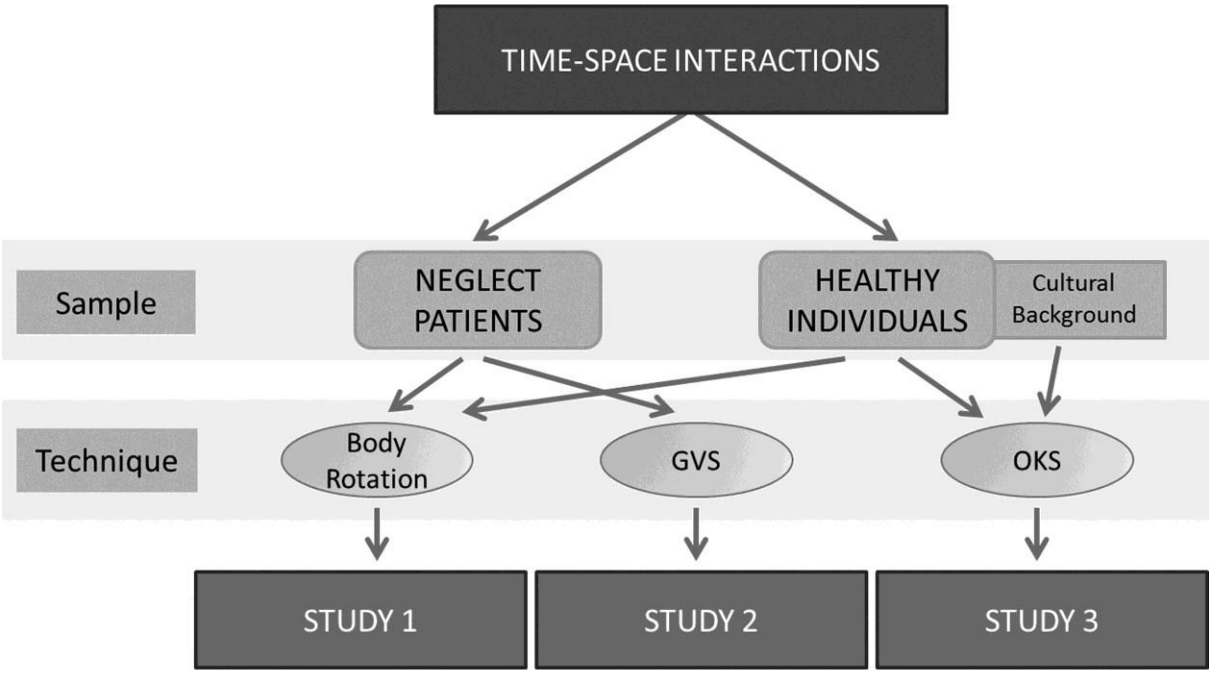


Figure 3. Schematic overview of samples and techniques involved in the diverse studies of this dissertation. GVS: Galvanic vestibular stimulation, OKS: optokinetic stimulation.

differences in basic time perception and sensitiveness to stimulation techniques which establish strong tools in the treatment of visuospatial neglect. To accomplish these objectives, techniques known to modulate space perception—namely trunk rotation, optokinetic stimulation, and Galvanic vestibular stimulation—were applied in conventional timing tasks. In study 1, I used a time reproduction and a time bisection task. Time perception in these tasks has been successfully manipulated by prism adaptation in healthy subjects (Frassinetti et al., 2009) and right brain damaged patients with and without neglect (Magnani et al., 2011; Oliveri et al., 2013). The present work investigated effects of lateral head and trunk rotation on time reproduction/bisection in neglect patients and healthy individuals. In study 2 and 3, I focused on the temporal order judgment task. Judging the sequence of two adjacent stimuli is a more concrete example of time-space interactions. Previously, TOJ have been modulated by large-field OKS in healthy individuals (Teramoto et al., 2004; Teramoto et al., 2008), as well as prism adaptation (Berberovic et al., 2004) and lateralized alerting tones in neglect patients (Robertson et al., 1998). Study 2 of the present work examined effects of GVS on TOJ in right brain damaged patients with prior entry phenomenon. In Study 3, I investigated influences of small-field OKS on TOJ in healthy Chinese and German participants, which allowed exploring cross-cultural differences in responsiveness to this method. Figure 3 gives an overview of the samples tested and the techniques used in the respective studies of the present work.

Effects of Head and Trunk Rotation on Time Reproduction

2.1. Introduction

Time seems to flow from left to right: recent research suggests the involvement of horizontal spatial codes in the mental representation of temporal intervals. Subjects underestimate the duration of stimuli presented in the left side of space and overestimate it for right-sided stimuli (Vicario et al., 2008; Oliveri et al., 2009). Also, participants respond faster to small durations or short stimulus onset times with their left, and to longer durations or onset times with their right body side. This is the so-called STARC (_S_patial-_T_emporal _A_ssociation of _R_esponse _C_odes) effect (Conson et al., 2008; Ishihara et al., 2008; Vallesi et al., 2008). Interestingly, duration judgments made while imagining the left or the right side of a clock face correlate with the strength of left- or rightward deviations in a line bisection task (Zäch & Brugger, 2008). Converging evidence for horizontal time-space interactions comes from clinical research in patients with left-sided visuospatial neglect. Neglect is a heterogeneous neurological disorder, which usually occurs following right brain damage. It is defined by the failure to perceive, respond, or orient to stimuli in the contralesional hemispace, despite the absence of sensory or motor deficits (Kerkhoff, 2001; Heilman et al., 2011). While having severe difficulties in space exploration, individuals suffering from neglect also demonstrate distortions in time perception and processing (Calabria et al., 2011; see Becchio & Bertone, 2006 for a review). Neglect patients judge left-sided stimuli to last longer and to occur later than right-sided stimuli (Basso et al., 1996; Snyder & Chatterjee, 2004; Berberovic et al., 2004; see also chapter 3). Moreover, they underestimate the objective passage of time in tasks requiring raw time estimation or time bisection (Danckert et al., 2007; Oliveri et al., 2009; Merrifield et al., 2010). The above findings lead some authors to suggest the existence of a horizontal mental time line (MTL). Following this hypothesis, shorter/earlier durations are represented to the left of longer/later temporal intervals, in analogy to a conventional time course on a Cartesian x-axis (Ishihara et al., 2008; Oliveri et al., 2009). A similar representation mode has been firmly confirmed for numbers, with smaller numbers mapped to the left and larger numbers to the right of a mental number line (Dehaene et al., 1993; Hubbard et al., 2005; Nieder, 2005).

Interestingly, a few current studies have indicated that time perception can be modulated by lateralized manipulation of spatial attention in the sense of a left-to-right MTL. Vicario and colleagues reported that participants underestimated the duration of stimuli after the exposure to leftward optokinetic stimulation, while they overestimated their duration after rightward OKS (Vicario et al., 2007). Prismatic adaption has yielded similar results: subjects underestimated time durations after being exposed to prisms inducing leftward shifts of spatial attention, and likewise overestimated them for opposing aftereffects (Frassinetti et al., 2009; Magnani et al., 2011). In patients with neglect, prisms producing leftward attentional shifts ameliorated the severe time underestimation (Oliveri et al., 2013). It remains to be investigated if further sensory stimulation techniques may influence time perception according to the MTL as well.

Body rotation is an effective and easily implemented method that influences spatial deficits in neglect by shifting the egocentric reference. In healthy individuals, horizontal trunk rotation induces lateral biases in covert visual attention (Grubb & Reed, 2002). In patients with neglect, trunk rotation has been demonstrated to improve visuospatial deficits of the contralesional side (Karnath, Schenkel, & Fischer, 1991; Karnath et al., 1993; Chokron & Imbert, 1995). For example, Schindler and Kerkhoff reported that turning the head or trunk to the left reduces the typical rightward line bisection bias as well as reading errors in neglect patients (Schindler & Kerkhoff, 1997). Notably, manipulations through head and trunk rotation extend to representational space, such as mental images of known places or the mental number line (Meador, Loring, Bowers, & Heilmann, 1987; Lötscher et al., 2008). The underlying mechanism of these effects has been attributed to alterations of afferent retinal, eye- and neck-propioceptive information. These signals are integrated into a global, body- or egocentric reference frame which allows an adequate orientation in space. During the rotation, the afferent information is changed, thereby leading to a shift of the internal body-centered coordinates. The anatomical substrate for the integration and transformation process seems to be the posterior parietal cortex (Brotchie et al., 1995; Duhamel, Bremmer, Benhamed, & Graf, 1997; Bremmer et al., 1998; Bremmer, Graf, Ben Hamed, & Duhamel, 1999; Mullette-

Gillman et al., 2005). Noteworthy, the right posterior inferior parietal cortex has also been suggested to establish a principal anatomical site of time processing and time-space interactions. Evidence comes from a variety of research lines including neuropsychological reports (Oliveri et al., 2009), TMS distortion studies (Bueti et al., 2008; Oliveri et al., 2009; Koch et al., 2009), neuroimaging (Coull & Nobre, 1998; Onoe et al., 2001; Macar et al., 2002; Rao et al., 2001), and electrophysiological studies (Leon & Shadlen, 2003; Nieder et al., 2006). These findings raise the question whether lateral head or trunk rotation influences time perception, too.

The current study aims to further elucidate the interaction between time and space using the body rotation technique. For this reason, I applied a time reproduction and a time bisection task which have previously shown to be susceptive to time-space modulations (Frassinetti et al., 2009; Oliveri et al., 2009; Magnani et al., 2011; Oliveri et al., 2013). Experiments 1 and 2 examined whether horizontal body rotation leads to altered time estimation in healthy individuals. Participants were passively rotated with their head and trunk independently from each other (experiment 1) or simultaneously (experiment 2) to the left or right side of a computer screen located directly in front of them. In experiment 2, I further analyzed if performance in the time reproduction task is influenced by individual field-dependence. Field-dependence defines the degree to which a person may disembed an object from its surroundings. High field-dependent subjects are stronger influenced by their body position in space during visuospatial judgments than low field-dependent individuals (Witkin, 1950; Witkin et al., 1954; Zhang, 2004). According to the hypothesis of the MTL, high field-dependent participants should demonstrate stronger modulations of time perception during horizontal body rotation. In experiment 3, I analyzed whether body posture has an impact on time production in neglect patients. Five patients with manifested or residual neglect completed a time reproduction task while turning their head or trunk laterally to each side in an identical fashion to experiment 1.

2.2. Material and methods

2.2.1. Experiment 1

2.2.1.1. Participants

Sixteen healthy participants (6 males and 10 females, mean age: 23.9 ± 0.8 years) volunteered in the experiment either for financial reimbursement or for class fulfillments. All but one were right-handed according to the German version of the Edinburgh handedness inventory (Salmaso & Longoni, 1985; Hermsdörfer, Mai, Rudroff, & Münßinger, 1994), and had normal or corrected-to-normal vision with a visual acuity yielding 0.8 or higher for near space (0.4 m). None of them reported neurological or psychiatric disorders. Except for one subject, they were naïve regarding the theoretical background of the experiment.

2.2.1.2. Time reproduction (TR) and time bisection (TB) task

The experiment comprised two tasks: a time reproduction (TR) and a time bisection (TB) task. The design was an adapted version of those used in previous studies (Frassinetti et al., 2009; Oliveri et al., 2009). The procedure in the TR and the TB task was nearly identical and differed only in the instruction of how to respond to the stimuli. At the beginning of a trial, a fixation cross appeared for 500 ms at the center of the screen (see figure 4A). Then a reference stimulus (blue square of 1 x 1 cm) was shown for a defined duration. The temporal intervals of the stimulus were 1200, 1600, 2000, 2400, and 2800 ms. Afterwards, the screen went blank for 1000 ms, which was followed by the demonstration of a fixation cross for 500 ms. Then a test stimulus (red square of 1 x 1 cm) appeared and remained on the screen until participants responded. In the reproduction task, participants were instructed to answer when the duration of the test stimulus equaled the duration of the reference stimulus. In the bisection task, they had to respond when the duration of the test stimulus equaled exactly half of the duration of the reference stimulus. Responses were given by pressing a key. All stimuli were presented on a white background. There was a training block of 25 trials at the beginning of each task. Data for these trials were discarded. Stimuli were then administered in 5 experimental blocks. Each temporal interval was randomly presented 10 times during a block. Thus, there were 50 trials per block, and 250 trials in total per task. Participants finished one block per rotation condition. They were instructed to prevent inner counting while completing the task.

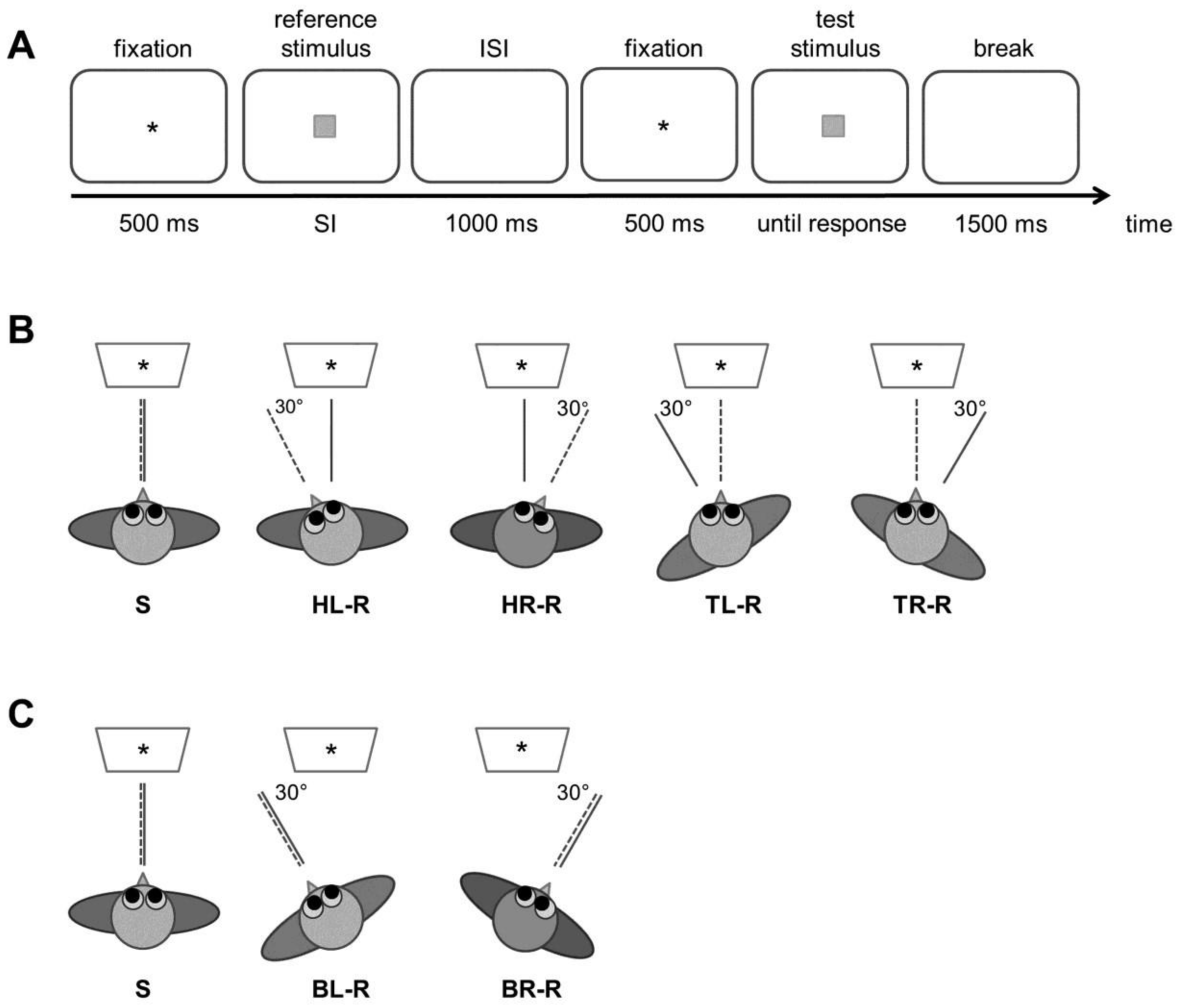


Figure 4. A: Demonstration of a typical trial in the time reproduction (TR) and the time bisection (TB) task. A blue square served as the reference stimulus, and a red square as the test stimulus. In the TR task, participants were instructed to respond when the duration of the test stimulus was identical to the duration of the reference stimulus. In the TB task, participants had to respond when the duration of the test stimulus equaled half of the duration of the reference stimulus. Participants gave their answers by pressing a key. **B:** Schematic overview of the experimental conditions in experiments 1 and 3, and **C:** in experiment 2. Fixation was always directed towards the central fixation point (marked by an asterisk). The dashed lines denominate the head axis; the continuous lines display the objective trunk midline. BL-R: body left; BR-R: body right; HL-R: head left; HR-R: head right; SI: stimulus interval; ISI: interstimulus interval; S: body straight; TL-R: trunk left, TR-R: trunk right

2.2.1.3. Head and trunk rotation

There were five different experimental conditions (see figure 4B). In the baseline (straight, S) condition, head and trunk were positioned facing the computer screen. In the head left rotation (HL-R) or head right rotation (HR-R) condition, the head was passively turned 30° to the left or right, while the objective trunk axis remained straight ahead. In the trunk left rotation (TL-R) or the trunk right rotation (TR-R) condition, participants had their trunk turned 30° to the respective side, while their head remained facing at the monitor straight ahead. Head rotation angles were realized by rotation of a head/chin rest. Trunk rotation was achieved by rotation of the subject's chair, on which the subject body was fixed. The position of the head was secured by the chin-rest throughout all conditions. The viewing distance was 0.4 m for all participants.

2.2.1.4. Design and experimental procedures

The experiment was split into two subsequent test sessions on different days, which lasted about one hour each. Participants completed one task per session. Half of the subjects performed the TR task in the first session, the other half completed the TB task. The order of rotation conditions in the task was pseudo-randomized across the subjects. Participants were given a break of approx. 3 − 5 min between each test block to prevent possible aftereffects that might have been caused by the rotation. During this time, demographic data were assessed. In addition, participants completed a line bisection task (LBT) including 20 horizontal lines (lengths: 8.4 − 17.1 mm) aligned in parallel on a 0.297 m x 0.21 m sized white sheet of paper (adapted and modified from Schenkenberg et al., 1980).

2.2.1.5. Data analysis

For both the TR and the TB task, response deviations (in ms) were computed as follows: first, the objective time interval (OTI) was subtracted from the subjective time interval reported by the participant. Hence, answers that were made before the OTI had passed yielded negative deviations, while responses given after the OTI resulted in positive biases. The OTI equaled 100% of the duration of the reference stimulus in the TR task and 50% of its duration in the TB task. Noteworthy, the production of time intervals shorter than the reference interval are referred to as time overestimation, while intervals longer than the OTI are taken as time underestimation. General deviations from the OTI were analyzed separately for each experimental condition using one-sample t-tests.

Modulations of head and trunk rotation were then investigated by a repeated measures analysis of variance (ANOVA) run over all experimental conditions. To further examine the effect of left- versus rightward rotation, deviations to the baseline were calculated for every rotation condition (HL-R, HR-R, TL-R, and TR-R). This was done by subtracting the computed response deviations in the S condition from the data obtained in the respective rotation condition. The data were then compared using paired-samples t-tests. Response deviations (in mm) in the LBT were computed similarly to analyses in the TB task. Biases to the left of the true midpoint resulted in negative values, deviations to the right in positive values. Pearson's correlation coefficient was used to determine the correlation between performance in the line bisection test and the TB task at baseline. Statistical analyses were carried out using IBM SPSS Statistics, version 19.

2.2.2. Experiment 2

2.2.2.1. Participants

45 healthy participants (22 males and 23 females, mean age: 23.2 ± 0.5 years) volunteered in the experiment either for financial reimbursement or for class fulfillments. None of them had participated in the previous experiment and all were naïve regarding the theoretical background and right-handed according to the German version of the Edinburgh handedness inventory (Salmaso & Longoni, 1985; Hermsdörfer et al., 1994). They had normal or corrected-to-normal vision and demonstrated visual acuity of 0.8 or higher for near space (0.4 m). Two participants yielded lower visual acuity (0.5 and 0.63, respectively). However, this should not have impaired their performance as stimuli were large enough and clearly distinguishable by their color (see section 2.2.1.2). No subject reported neurological or psychiatric disorders.

2.2.2.2. Time reproduction (TR) task

The experiment comprised a TR task which was identical to the one in experiment 1, with the exception that the training block was increased to 50 trials. In addition, the task embraced only 150 experimental trials, due to the reduced number of rotation conditions, and consequently, of experimental blocks.

2.2.2.3. Body rotation

The experiment included three different rotation conditions (see figure 4C). During the baseline, head and trunk were positioned straight ahead (S). In the body left rotation (BL-R) condition, both head and trunk were rotated 30° to the left. In the body right rotation (BR-R) condition, head and trunk were turned 30° to right. The rotation angles were accomplished by the simultaneous rotation of the subject's chair and a head/chin rest. The position of the head was secured by the chin-rest throughout all conditions. The viewing distance was 0.4 m.

2.2.2.4. Design and experimental procedures

Participants were tested during one session which lasted about 45 min. The order of rotation conditions was pseudo-randomized across subjects. Participants were given a 3 – 5 minute break between the different rotation conditions. Spatial field-dependence was measured in 23 participants applying the subtest 10 of the German *Leistungsprüfungssystem* (Horn, 1983). Participants were then assigned to a high or low field-dependent group according to a median split based on the performance in the task. The median split equated 85% of correct answers.

2.2.2.5. Data analysis

The fundamental data analyses were identical to experiment 1. In the present experiment it was further explored whether field-dependence modulated responses. This factor was assessed in a subgroup of participants and was therefore analyzed in a separate 2 (rotation condition) x 2 (field-dependence) mixed design ANOVA.

2.2.3. Experiment 3

2.2.3.1. Patients

Five right brain damaged patients (mean age: 54.2 ± 13.6 years) with manifested or residual neglect symptoms participated in the experiment. Their clinical and demographic data is displayed in table 1. Patients 1 and 2 were originally assessed as experimental pilots at the Clinical Neuropsychology Unit, Saarland University. Patient 1 has been described in detail as patient CJ in Kerkhoff et al. (2011). Patients 3 – 5 were tested at Schön Clinic Bad Aibling, Germany.

2.2.3.2. Handedness, visual field testing, and neglect assessment

Handedness was tested according to the German version of the Edinburgh handedness inventory (Salmaso & Longoni, 1985; Hermsdörfer et al., 1994). In patients 3 – 5, visuospatial neglect was assessed with seven conventional screening tests, including line cancellation, star cancellation, letter cancellation, paragraph reading of a 140-word reading test, and figure copy (star, rhomb, flower). These are subtests from the *Neglect-Test*, NET (Fels & Geissner, 1997), which is the German Version of the Behavioral Inattention Test (Wilson et al., 1987). The patients were further given a number cancellation task (20 targets among 200 distracters with 10 targets per hemispace), and a line bisection task which was identical to the one in experiment 1. All tests were presented on a 0.297 m x 0.21 m sized white sheet of paper with its center perpendicular to the patient’s trunk midline. Viewing distance was 0.3 – 0.4 m from the patient’s eyes. Patients were considered to have manifested visuospatial neglect when they demonstrated three or more omissions in a test, or more than 15.3 mm rightward deviation in the line bisection task (Ferro, Kertesz, & Black, 1987), and were impaired in at least 3 out of 7 neglect screening tests. In patient 1, visuospatial neglect had been already assessed prior to the present testing (but in close temporal proximity). The patient showed a chronic, discrete left-sided neglect. Her performance is reported in detail in Kerkhoff et al. (2011). Patient 2 had also been previously screened for neglect, using a star cancellation, a letter cancelation, and a figure copy (star, rhomb, flower) test. Furthermore, he underwent a 180-word reading task and a line bisection task that consisted of a single horizontal 20 cm long, horizontal line. Patient 2 was considered as showing mild left visuospatial neglect. In all patients, binocular visual fields (for the central visual field area) were mapped via static binocular campimetry using the special software EyeMove (Kerkhoff & Marquardt, 2009, also see section 3.2.2 for a detailed description of the program).

2.2.3.3. Time reproduction (TR) task

The patients completed a TR task which was identical to experiment 1, except for some minor changes. As the main difference, all patients underwent only one rotation condition per session to prevent possible after-effects interfering with the performance in the subsequent condition. Patients 1 and 2, who were tested with an early version of the program, completed the task in five blocks à 25 trials which sum up to 125 trials per condition. For patients 3 – 5, the TR task was administered in two blocks à 50 trials, making it a total of 100 experimental trials per session. There was a training block at the beginning of each session, which comprised 20 trials for patients $1-2$, and 50 trials for patients $3-5$. Data for these trials were discarded. The background color of the screen was further changed to black (except for patient 2). This was done since previous participants had repetitively indicated that this would be more comfortable to the eyes.

2.2.3.4. Head and trunk rotation

Rotation conditions were identical to experiment 1, with the exception that the patients turned their head and trunk only 20° to each side due to greater physical constraints as a result of motor impairments and shoulder pain due to hemiplegia.

2.2.3.5. Design and experimental procedures

In contrast to healthy participants, neglect patients were tested during five separate sessions on different days. A single session lasted about 30 minutes and included only one rotation condition. The rotation order was pseudo-randomized across the patients.

2.2.3.6. Data analysis

Data analysis was identical to experiment 1.

Table 1. A: Clinical and demographic data of the patients enrolled in experiment 3. **B:** Performance of the patients in the neglect screening tests.

A

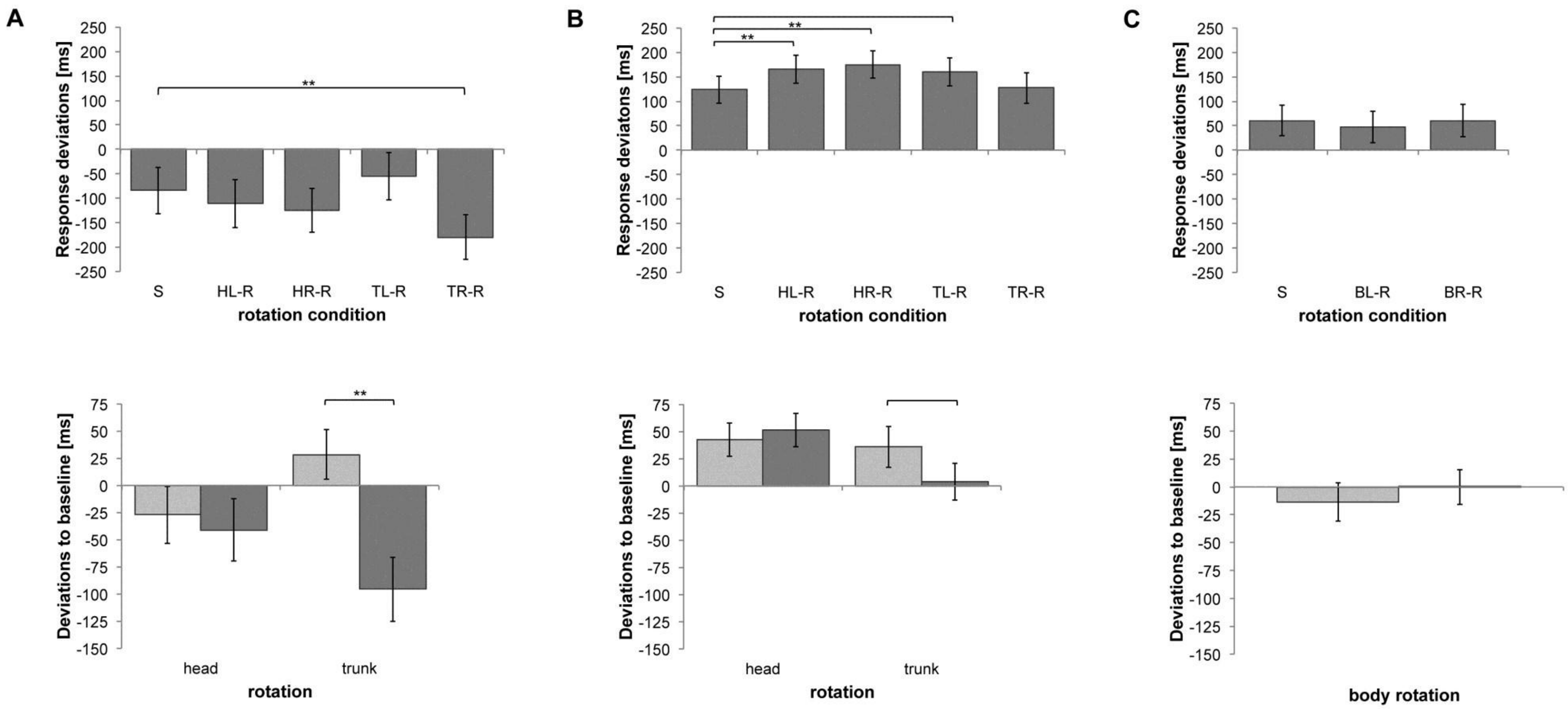
Patient	Neglect	Age	Gender	Handedness laterality score	Etiology	Locus of lesion	Time post lesion	Visual field defect	Visual acuity near space (0.4 m) in %
Patient 1	Residual	43	Female	+100	Stroke	Right orbitofrontal and parietal	78 month	Incomplete left hemianopia >10°	1.0
Patient 2	Residual	41	Male	+100	Stroke	Right parieto-temporal	34 month	Normal	0.8
Patient 3	Yes	71	Female	+100	Stroke	Right temporo-parietal	14 weeks	Normal	0.63
Patient 4	Residual	50	Male	+100	Stroke	Right temporo-parietal	50 month	Normal	1.25
Patient 5	Residual	66	Female	+100	Stroke	Right fronto-temporal	11 weeks	Normal	0.80

B

Patient	Line cancellation omissions *left*	Star cancellation omissions *left*	Letter cancellation omissions *left*	Number cancellation omissions *left*	Reading omissions *left*	Figure copy omission score	Line bisection (deviation in mm)
Patient 1	< 2	n.a.	n.a.	< 2	n.a.	0	+2
Patient 2	n.a.	0	2	n.a.	3	0	+7
Patient 3	0	3	3	8	0	0	-36
Patient 4	0	2	1	0	1	1	-38
Patient 5	0	0	3	0	0	1	+37

Handedness laterality score: +100: strongly right-handed

Abbreviations: n.a.: not assessed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Response deviations [ms]
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TR-R
rotation condition
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body rotation

2.3. Results

2.3.1. Experiment 1

In the TR task, participants tended to overestimate the time interval they reproduced at the baseline (straight condition), i.e. that they gave answers that were marginally shorter than the reference interval, $t(79) = -1.76$, $p = .08$, see figure 5A (top). A similar overestimation was observed during head rotation to the left [$t(79) = -2.26$, $p < .05$] and right [$t(79) = -2.78$, $p < .01$], as well as during trunk rotation to the right, $t(79) = -3.96$, $p < .001$. When the trunk was turned to the left, durations of reproduced time intervals did not differ from the reference interval, $t(79) = -1.15$, $p > .05$, *n.s.*. An ANOVA across all rotation conditions was highly significant, $F(3.32, 277.85) = 6.11$, $p < .001$. Planned contrasts revealed shorter time intervals in the trunk right condition than in the baseline, $F(1, 79) = 10.47$, $p < .01$. When performance was compared specifically between left- and rightward rotation, trunk rotation had a significant influence on estimated time intervals. Participants reproduced longer intervals when the trunk was turned to the left than when it was rotated to the right, $t(79) = 4.33$, $p < .001$, see figure 5A (bottom). Head rotation had no influence on performance, $t(79) = .54$, $p > .05$, *n.s.*.

Figure 5. A (left page): Effects of head and trunk rotation on time reproduction in healthy subjects (experiment 1). **B:** Effects of head and trunk rotation on time bisection in healthy subjects (experiment 1). **C:** Effects of body rotation on time reproduction in healthy subjects (experiment 2). The depicted data in the upper row represent response deviations from the reference stimulus (in ms ± SEM). Positive values indicate that the participants produced longer durations; negative values indicate that the subjects made shorter duration compared to the length of the reference interval. Asterisks indicate significant p-values of planned contrasts: ** $p < .01$. The data in the lower row illustrate deviations from the baseline performance in the respective task (in ms ± SEM). Positive values indicate that the participants produced longer intervals; negative values indicate that the subjects made shorter intervals in the respective rotation condition compared to the baseline. Asterisks indicate significant p-values of paired t-test: ** $p < .01$. BL-R: body left rotation; BR-R: body right rotation; HL-R: head left rotation; HR-R: head right rotation; S: straight (baseline); TL-R: trunk left rotation; TR-R: trunk right rotation

When participants were asked to bisect temporal intervals (TB task), they underestimated the time interval they produced. Thus, the subjects pressed the button after the objective midpoint of the reference interval had passed. This difference was significant at baseline [$t(79) = 4.51$, $p < .001$] as well as during all rotation conditions: head left [$t(79) = 5.73$, $p < .001$], head right [$t(79) = 6.30$, $p < .001$], trunk left [$t(79) = 5.65$, $p < .001$], and trunk right [$t(79) = 4.02$, $p < .001$]. An ANOVA across all rotation conditions revealed significant changes across conditions, $F(4, 316) = 3.90$, $p < .01$, see figure 5B (top). Planned contrasts indicated that produced time intervals were significantly longer during the head left [$F(1, 79) = 7.69$, $p < .01$] and head right rotation [$F(1, 79) = 11.24$, $p < .01$] than in the baseline (straight condition). Differences between the baseline and the trunk left condition were marginally significant, $F(1, 79) = 3.64$, $p = .06$. When comparing performance during left- and rightward rotation, I found that trunk rotation had a marginal effect on time bisection, $t(79) = 1.71$, $p < .09$. Bisected intervals tended to last longer during trunk rotation to the left than to the right, see figure 5B (bottom). Head rotation had again no influence on response bias, $t(79) = -.67$, $p > .05$, *n.s.*. Response bias for time bisection in the straight condition did not correlate with deviations in the LBT, $r = -.07$, $p > .05$, *n.s.*.

2.3.2. Experiment 2

In contrast to experiment 1, participants marginally overestimated reproduced time intervals in the straight condition of the TR task, $t(224) = 1.96$, $p = .05$. The same response pattern was observed when the body was turned to the right, $t(224) = 1.80$, $p = .07$. Reproduced time intervals during the body rotation to the left did not differ from the reference intervals, $t(224) = 1.48$, $p > .05$, *n.s.*. An ANOVA across all three rotation conditions indicated no modulation of responses by body rotation, $F(2, 448) = .44$, $p > .05$, *n.s.*, see figure 5C (top). A further analysis of performance between deviations to the baseline during left and rightward rotation confirmed that body rotation had no influence on response bias, $t(224) = -.80$, $p > .05$, *n.s.*, see figure 5C (bottom). Moreover, a separate ANOVA run over 23 participants yielded no main effect of field-dependence on response bias [$F(1, 113) = 1.42$, $p > .05$, *n.s.*] as well as no interaction between field-dependence and rotation condition [$F(1, 113) = 1.86$, $p > .05$, *n.s.*. The position of the body had therefore no differential influence on time reproduction in field-dependent and independent subjects.

2.3.3. Experiment 3

Neglect patients underestimated the time interval they reproduced. They gave responses that lasted significantly longer than the reference stimulus in the baseline condition, $t(24) = 2.43$, $p < .05$. Noteworthy, this deviation was eliminated under head and trunk rotation. Reproduced intervals did not differ from the reference stimulus in neither condition: head left [$t(24) = 1.64$, $p > .05$, *n.s.*], head right [$t(24) = .60$, $p > .05$, *n.s.*], trunk left [$t(24) = 1.58$, $p > .05$, *n.s.*], and trunk right [$t(24) = .39$, $p > .05$, *n.s.*]. Head and trunk rotation had a marginal effect on time reproduction, $F(4, 96) = 2.25$, $p = .07$, see figure 6A. Planned contrasts indicated significant changes to the baseline performance under head right [$F(1, 24) = 5.94$, $p < .05$] and trunk right rotation, $F(1, 24) = 7.02$, $p < .05$. When taking a closer look at differences between left and rightward rotation, it can be seen that head rotation had no influence on time reproduction, $t(24) = 1.44$, $p > .05$, *n.s.*. However, trunk rotation marginally modulated responses, $t(24) = 1.81$, $p = .08$. Patients reproduced shorter intervals when the head was turned to the right, see figure 6B.

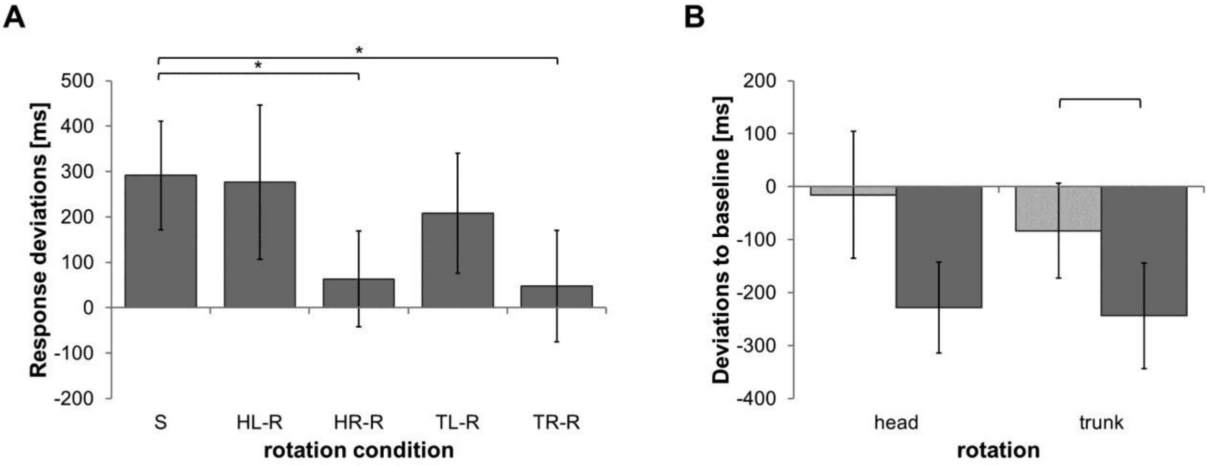


Figure 6. Effects of head and trunk rotation on time reproduction in neglect patients (experiment 3). **A:** The data represent response deviations from the reference stimulus (in ms ± SEM). **B:** The data are deviations from the baseline performance (median ± SEM). Positive values indicate that the patients produced longer intervals; negative values indicate that the patients made shorter intervals. Asterisks indicate significant p-values of planned contrasts: * $p < .05$. HL-R: head left rotation; HR-R: head right rotation; S: straight (baseline); TL-R: trunk left rotation; TR-R: trunk right rotation

2.4. Discussion

These are the main findings of the present study: (i) neglect patients severely underestimated reproduced intervals. This bias was reduced by turning the head or trunk to either side. A systematic difference between performances during left- and rightward rotation was only found for trunk rotation. Patients reproduced shorter durations when the trunk was turned right. In healthy participants, trunk rotation modulated time perception in a similar fashion. Head or whole body rotation showed no systematic influence on performance. (ii) Nevertheless, the reported results are in contrast with the hypothesis of the left-to-right MTL. I will discuss these findings in detail below.

2.4.1. Effects of head and trunk rotation on time reproduction

Neglect patients underestimated the time they reproduced, giving intervals that were significantly longer than the reference interval. This result confirms and extends previous findings which report time underestimations in neglect patients (Danckert et al., 2007; Oliveri et al., 2009). In healthy individuals, I found no consistent over- or underestimation in the TR task. In the TB task, subjects significantly overestimated the temporal interval they produced. This behavior mirrors Vierordt’s law, which states that short durations are judged as longer, and long duration as shorter compared to their actual length, with an “indifference point” lying between two and three seconds (Vierordt, 1868). The mean duration to reproduce was 1000 ms in the TB task, and 2000 ms in the TR task; hereby lying under, or reaching the indifference point, respectively.

As novel finding, I report that trunk rotation modulated time perception. Rotation to either side reduced the severe underestimation of time intervals in neglect patients. Importantly, reproduced intervals were significantly shorter during rightward than leftward turns. This holds true for both neglect patients and healthy individuals, suggesting a systematic modulation of trunk rotation on time perception. In contrast, head or body (simultaneous head and trunk) rotation had less consistent impact on performance in the present study. Although head turns generally ameliorated time reproduction deviations in neglect patients, I found no modulation differences between left- and rightward rotation. In healthy subjects, head or body rotation had no influence in the TR task. In the TB task, head turns generally increased the overestimation bias; however, there were again no differences during left- and rightward rotation. I may thus conclude that head rotation exerted no systematic manipulation on time perception. Until now, various studies have described the manipulation of space perception by trunk rotation. In neglect patients, a decrease of left-sided deficits is found following trunk rotation in tasks such as contralesional stimuli detection (Karnath et al., 1993), straight-ahead pointing (Chokron & Imbert, 1995), and line bisection and paragraph reading (Schindler & Kerkhoff, 1997). Also, trunk turns improve the pathologically increased saccadic reaction times to the contralesional space (Karnath et al., 1991). In healthy individuals, trunk rotation has been demonstrated to manipulate visual attention in a Posner covert attention paradigm, and to shift the subjective sagittale to the same side of the rotation during a straight-ahead pointing task (Chokron & Imbert, 1995; Grubb & Reed, 2002). Notably, related techniques such as neck muscle vibration and caloric vestibular stimulation similarly improve neglect or may, in contrast, induce neglect-like biases in healthy individuals during ocular space exploration (Karnath, Fetter, & Dichgans, 1996; Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002; Johannsen, Ackermann, & Karnath, 2003). Regarding head rotation, literature reports are inconsistent about its effect. Some authors found improvement of neglect deficits during leftward head turns (Schindler & Kerkhoff, 1997; Kooistra & Heilman, 1989), whereas others report no modulations (Karnath et al., 1991; Karnath et al., 1993). In healthy subjects, one study showed that head turns manipulate the orientation in representational space (Lötscher et al., 2008). In contrast, two other studies found no systematic influence of head or body rotation in “real” visuospatial tasks (Schindler & Kerkhoff, 1997; Nicholls, Mattingley, Bradshaw, & Krins, 2003). The first authors interpreted the observation of increased behavioral variability during a LBT task as a consequence of greater incommodity caused by the head fixation. Hence, I might attribute the deteriorated performance in the TB task during head rotation rather to increased reaction times due to the unfamiliar body posture than to an altered time perception. Along this line, I found that simultaneous head and trunk rotation—which should be considerably more pleasant—did not manipulate time reproduction, corroborating the idea that the position of the head does not influence time perception.

Noteworthy, I found that *right*ward trunk rotation alleviated more strongly the pathological time underestimation than leftward turns in neglect patients. This is in surprising contrast to literature findings. All previous studies have reported positive effects exclusively for *left*ward rotation; and even worsened performance for rightward rotation (Karnath et al., 1991; Karnath et al., 1993; Chokron & Imbert, 1995; Schindler & Kerkhoff, 1997). Importantly, my results

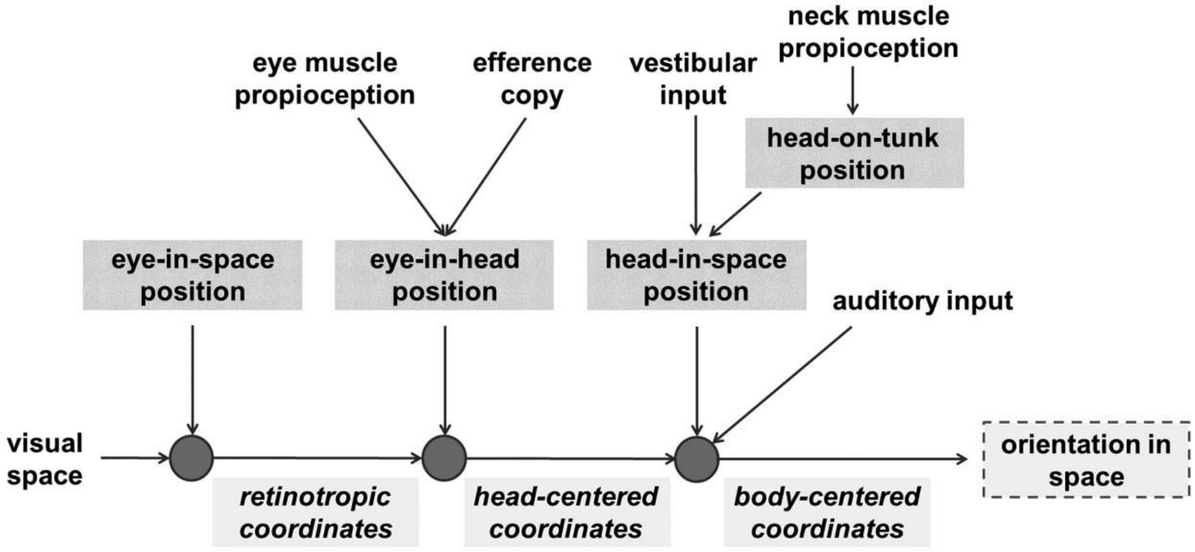


Figure 7. Transformation hypothesis of visuospatial neglect (adapted and modified according to Karnath, 1994). Multimodal information are integrated and transformed to build up body-centered coordinates which allow for a successful orienting in space. In neglect, this process is disturbed; leading to an ipsilesional deviation of the body-centered coordinates.

are also in striking contrast to the proposed mechanisms of head and trunk rotation in healthy subjects and neglect patients. For a successful orientation in space, it is required that afferent information from the retina (stimulus-on-retina position), the eyes (eyes-in-head position), and the neck (head-on-trunk position), as well as signals from the vestibular system are integrated and transformed to build up a global, ego-centered reference frame which represents the body position in space (see figure 7). The transformation hypothesis of neglect suggests that this integration process is disturbed in the patients, entailing an ipsilesional (rightward) deviation of the body-centered coordinates (Karnath, 1994; Karnath, 1997). Head or trunk rotation to the left causes a lengthening of the neck muscles and changes of the gaze direction. The retinal, eye- and neck-propioceptive information is hereby altered, leading to a compensatory leftward shift of the subjective sagittal head or trunk axis, which add up to the global, body-centered reference. This in turn ameliorates the typical inattention to the left side in neglect. Head or trunk rotation to the right, in contrast, leads to a rightward shift of the subjective sagittale and therefore to some further impairments. In healthy individuals, trunk rotation seems to similarly guide visual attention to the side of rotation (Grubb & Reed, 2002). Consequently, if subjects relied on the orientation on an internal MTL with increasing durations from left to right during the reproduction or bisection of temporal intervals, they were expected to produce *longer* intervals during rightward rotations. However, I found that both neglect patients and healthy participants made *shorter* intervals during right turns. These findings argue against an automatic left-to-right orientation of mentally represented time intervals. In addition, I also observed no effects of field-dependence on time perception during the body rotation. Field-dependence affects verticality judgments during head or body tilts (Witkin & Asch, 1948a; Witkin & Asch, 1948b; Witkin, 1949). The present study thus suggests that time perception and processing may not hold such fundamental spatial features as it has been indicated before. Regarding the ameliorative effects of head and trunk rotation to either side in the neglect patients, I might—in turn—speculate that an altered body posture gave rise to a general increased arousal which led to improved performance. This idea is in line with reports by Robertson who found improved time perception in a temporal order judgment task following spatially non-lateralized altering cues in neglect patients (Robertson et al., 1998).

2.4.2. Time-space modulations and the mental number line

Research done by Oliveri and colleagues suggests that time perception can be influenced according to the orientation on a left-to-right mental time line. The authors have repetitively reported that prismatic adaptation inducing a leftward orientation of spatial attention produced an underestimation of time intervals, whereas prismatic adaptation inducing a rightward attention shift led to an overestimation of temporal intervals in time reproduction tasks. The effect held true for both healthy individuals and right brain damaged patients with and without neglect (Frassinetti et al., 2009; Magnani et al., 2011; Oliveri et al., 2013). If time is represented in horizontal spatial codes, then it is plausible to assume that changes of the subjective egocentric sagittale do not only lead to systematic alterations during external space exploration, but also during the orientation in time. In fact, several studies have demonstrated that the exploration of physical and representational space share striking similarities. For example, left-sided visuospatial neglect and non-neurological inattention to the right hemi-space (pseudoneglect) extend to imagined space (Bisiach & Luzzatti, 1978; Brugger, Surbeck, & Lötscher, 2007). Also, deviations during physical line bisection correlate with deviations for the bisection of representational space, such as the mental number line, whose left-to-right encoding has been firmly confirmed over the last decade (Zorzi et al., 2002; Zorzi et al., 2006; Longo & Lourenco, 2007). In accordance, head rotation successfully manipulates the orientation in mental number space. Subjects generate larger numbers when looking to the right, and smaller ones when looking left during random number generation (Lötscher et al., 2008). In the present study, participants reproduced shorter durations when the trunk was turned right, hereby behaving in direct contrast to the hypothesis of a mental time line. Hence, the current results may not extend Oliveri and colleague's findings demonstrating that time perception may be modulated in a horizontal left-to-right fashion. Interestingly, not all previous studies on time perception may lead to the conclusion of a horizontal MTL with increasing duration from left to right. Vicario reported that rightward optokinetic stimulation induced an overestimation of time intervals that had to be compared to a standard duration (Vicario et al., 2007). However, the authors applied fast rightward OKS (38°/sec), which elicited monitored reflectory saccades to the *left* (optokinetic nystagmus, OKN). The OKN has been shown to shift attention towards the side opposing the OKS movement (Pizzamiglio, Frasca, Guariglia, Incoccia, & Antonucci, 1990; Teramoto et al., 2004; Teramoto et al., 2008). Thus, according to a left-to-right MTL, Vicario and colleagues should have actually reported time underestimation during rightward OKS inducing leftward shifts of attention and not the reverse. Further support against a left-to-right directed time encoding might come from neuropsychology research. Severe time underestimations have not only been found in patients with neglect, but also in right brain damaged patients without neglect (Petrovici & Scheider, 1994; Magnani et al., 2011). An inattention to the left-side of space is thus no prerequisite for developing a directed time deficit.

Walsh postulated a generalized magnitude system in the posterior parietal cortex which is based on common neuronal circuits for the processing of time, space and quantity (Walsh, 2003). Regarding the present data, however, it might be possible that the neuronal populations for time and space encoding do not sufficiently overlap to allow for reasonable, i.e. left-to-right oriented modulations. Noteworthy, one study suggested that the neural mechanisms for timing of visual events are more spatially selective in world- centered than in retinal-based coordinates (Burr, Tozzi, & Morrone, 2007). Egocentric body- and external world-referenced representations of space depend on separate structures in the parietal cortex (Snyder, Grieve, Brotchie, & Andersen, 1998). It remains to be further investigated if the inconsistent results in the present study are due to a world-centered representation of the MTL, which is not affected by body rotation, or if the idea of a left-to-right coding of temporal intervals along a time line must be completely rejected.

2.5. Conclusions

Head and trunk rotation to the right ameliorates the severe time deficit in patients with neglect. Trunk rotation also modulates time perception in healthy individuals. Subjects produce shorter durations when the trunk is turned to the right than to the left, indicating a subjective overestimation of reproduced intervals during rightward rotation. These findings are in contrast to previous research on trunk rotation in visuospatial neglect which report improvement of symptoms during leftward trunk rotation. The current results also contradict existing hypotheses on the mechanism of body rotation regarding shifts of the egocentric reference. The data suggest that time and space interact to some extent; however, they do not support the idea of a left-to-right MTL with shorter durations encoded in the left and longer durations in the right space.

Effects of Galvanic Vestibular Stimulation (GVS) on Temporal Order Judgments

3.1. Introduction

Stroke patients with lesions to the right cerebral hemisphere often show left-sided visuospatial neglect. Spatial neglect is a complex syndrome defined by the failure to report, respond, or orient to stimuli in the contralesional hemi-space, despite the absence of sensory or motor deficits (Kerkhoff, 2001; Heilman et al., 2011). It is a heterogeneous disorder that encompasses various aspects of attention and space processing (Halligan et al., 2003). Often, patients with neglect and extinction (a related disorder) demonstrate further deficits in time perception and processing such as pure time estimation, time reproduction, or judging the temporal order of presented stimuli (Petrovici & Scheider, 1994; Basso et al., 1996; Snyder & Chatterjee, 2004; Danckert et al., 2007; Oliveri et al., 2009; Calabria et al., 2011).

One example of a method used to measure deficits in time perception is the temporal order judgment (TOJ) task. In this task, two identical stimuli are presented in opposing hemi-spaces with different time onsets of presentation. Neglect patients typically judge the right (ipsilesional) stimulus to appear first, even when the left (contralesional) one has a substantial lead in time (Snyder & Chatterjee, 2004). This phenomenon can be explained by the prior entry hypothesis (Rorden et al., 1997), according to which attended stimuli are perceived earlier than unattended, even if both are physically identical and presented simultaneously. The TOJ task is thus a representative task to assess between the interaction of space and time processing.

Several recent studies have investigated modulatory effects on time perception. Optokinetic stimulation (Vicario et al., 2007), prism adaptation (Frassinetti et al., 2009; Magnani et al., 2011), and rTMS (Oliveri et al., 2009) have been shown to alter time processing. Also, the perception of temporal length is influenced by both the spatial location of visual stimuli and the magnitude of numeric stimuli (Dormal et al., 2006; Xuan et al., 2007; Vicario et al., 2008; Oliveri et al., 2008; Casarotti et al., 2007). Furthermore, the speed of motion in the visual environment (i.e. when viewing a movie) may change the subjective passage of time (Grivel et al., 2011). However, studies investigating how timing deficits in neglect patients can be modulated are still sparse. Recently, Oliveri and colleagues reported that prism adaptation could ameliorate temporal distortions in neglect patients (Oliveri et al., 2013). With respect to TOJ tasks, Berberovic and co-workers demonstrated that prismatic adaptation reduced the typical neglect-related bias in the task (Berberovic et al., 2004). And, Robertson showed that spatially non-lateralized alerting tones successfully decreased the pathological advantage for right-sided stimuli in the TOJ task in neglect (Robertson et al., 1998). Interestingly, Davis reported that TOJ activate the temporo-parietal junction bilaterally (Davis et al., 2009), while other authors have underlined the importance of the right parietal lobe (Woo et al., 2009; Battelli et al., 2007).

A potentially interesting candidate for investigating the interplay between spatial and temporal processing is vestibular stimulation. Caloric vestibular stimulation has a strong modulatory influence on a variety of sensory and motor neglect phenomena (Rode, Perenin, Honoré, & Boisson, 1998; Rode et al., 1992). Galvanic vestibular stimulation (GVS) is a non-invasive, non-painful, and easily applicable vestibular stimulation technique (Utz et al., 2010). It successfully reduces various components of spatial deficits in neglect such as the typical rightward deviation in line bisection (Utz et al., 2011), the counterclockwise tilt of the subjective visual vertical (Saj, Honore, & Rousseaux, 2006), the visuo-constructional deficits in the Rey figure copy (Wilkinson, Zubko, Degutis, Milberg, & Potter, 2010), and left-sided tactile extinction (Kerkhoff et al., 2011). On the neuroanatomical and physiological level, GVS stimulates the vestibular nerve through polarization effects, which in turn activates a network of multisensory subcortical and cortical areas, including the insular, retroinsular regions, superior temporal gyrus, temporo-parietal cortex, basal ganglia, and the anterior cingulate gyrus (Utz et al., 2010). The polarity of GVS has differential brain activation effects: While right-cathodal/left-anodal GVS (further termed CR-GVS) leads to unilateral activation of the right-hemispheric vestibular system, left-cathodal/right-anodal GVS (further termed CL-GVS) stimulates bilaterally both vestibular cortices. Hence, the following three questions were addressed in the present study: (i) does GVS modulate the typical rightward TOJ deficit? (ii) Are there polarity-specific effects of GVS on TOJ? And, (iii) are there sustained effects of GVS on TOJ after the termination of stimulation?

3.2. Material and methods

3.2.1. Patients and healthy controls

3.2.1.1. Case report

First, a single case study is reported because of slightly different time intervals, followed by a group study (see 3.2.1.2.). The patient was a software engineer who had suffered from a traumatic brain injury caused by a car accident. His CCT/MRI immediately performed after the event showed subarachnoid hemorrhage, bilateral subdural hematoma, and diffuse axonal injury. MRI scans revealed a right frontal lesion, but also an affected part of the anterior pole of the temporal lobe (figure 8). The patient demonstrated symptoms of left-sided neglect (see table 2). In addition, he showed a left lower quadranopia beyond 5° of visual field sparing, which did not impair vision of the TOJ stimuli, as these were presented horizontally and fell totally in the spared visual field (see 3.2.3, below).

3.2.1.2. Group study and healthy controls

Thirteen right brain-damaged patients with or without manifested neglect symptoms participated in the study (see table 2). Two of them had to be excluded due to a complete left hemianopia that impeded their ability to complete the TOJ task successfully. Another two patients were not included in the analysis because they exhibited an atypical *left*ward bias in the task, which was beyond the normal range.

A composite neglect score based on six conventional visuospatial neglect tests did not correlate with the strength of rightward bias shown at baseline in the TOJ task ($r_s = .23$, $p > .05$, *n.s.*), although it correlated with the accuracy in the task ($r_s = -.76$, $p < .01$). Line bisection deviation did also not correlate with this rightward bias ($r_s = -.21$, $p > .05$, *n.s.*) nor with accuracy ($r_s = -.49$, $p > .05$, *n.s.*) in the TOJ task. However, line bisection, and reading, figure copying and cancellation tasks assess visuospatial performance and not temporal order deficits. Since the main interest of this study focused on modulating the TOJ deficit, a median split was computed based on the patients' averaged baseline performance ("right first" responses = 56.68%). On this basis, patients were assigned into a *prior entry group* and a *RBD control group* without the prior-entry-phenomenon. Hence, the cut off for normal behavior displayed a mean ± 3.5 standard deviations of the range obtained by healthy participants. The prior entry group comprised five patients (mean age: 67.0 years, range: 52 − 77). The average time since lesion was 16.6 weeks (± 5.5 SEM) in this group. Four patients established the RBD control group (mean age: 65.5 years, range: 51 − 72). Mean time since lesion yielded 52.0 weeks (± 45.6 SEM). There were no differences in age or time since lesion between the prior entry and the RBD control group (age: $U = 9.50$, $z = -.12$, $p > .05$, *n.s.*; weeks post lesion: $U = 7.00$, $z = -.74$, $p > .05$, *n.s.*). All patients included in the analysis demonstrated normal central visual fields.

Eight right-handed males without neurological or psychiatric disorders served as *healthy controls* (mean age: 60 years, range: 31 − 72 years). They had a visual acuity of 0.63 or better, and were tested to establish normative values in the TOJ task at baseline.

3.2.2. Handedness, visual field testing, and neglect assessment

Handedness was assessed according to the German version of the Edinburgh handedness inventory (Salmaso & Longoni, 1985; Hermsdörfer et al., 1994). Binocular visual fields (for the central visual field area) were mapped via static binocular campimetry using a special software (EyeMove, Kerkhoff & Marquardt (2009), results see table 2A). Subjects faced a computer screen (17") at a distance of 0.40 m on which a central fixation cross was permanently displayed. Seventy targets (white squares with a size of 0.5" x 0.5") were shown consecutively for 200 ms, in random order and at different positions in the four quadrants of the visual field (horizontal eccentricity: 35° for each hemifield, vertical eccentricity: 30°). Interspersed with these target trials, the fixation point randomly changed color which could only be detected through a central fixation (thus serving as catch trials). Patients were instructed to press a button with their right index finger immediately after each target presentation, or when the fixation point changed color. Visuospatial neglect was assessed with five conventional screening tests: line cancellation, star cancellation, letter cancellation, paragraph reading of a 140-word reading test, and figure copy (star, rhomb, flower) which are sub-tests from the *Neglect-Test*, NET (Fels & Geissner, 1997), the German Version of the Behavioral Inattention Test (Wilson et al., 1987). The

Table 2. A: Clinical and demographic data of all patients enrolled in the study.

A

Patient	Study	Neglect	Age	Gender	Handedness laterality score	Etiology	Locus of lesion	Weeks post lesion	Visual field defect	Visual acuity near space (0.4 m) in %
Patient 1	Case report	Yes	34	Male	+100	TBI	Right frontal	9	Scotoma 5° LLQ	0.8
Patient 2	Prior entry	Yes	69	Male	+81.8	ICB	Right frontal	13	None	0.8
Patient 3	Prior entry	Yes	71	Male	+100	Ischemia	Right frontal	4	None	0.8
Patient 4	Prior entry	No	77	Male	+100	Ischemia	Right parietal	12	None	0.4
Patient 5	Prior entry	No	66	Male	+100	Ischemia	Right BG and CI	35	Incomplete left hemianopia >5°	0.8
Patient 6	Prior entry	No	52	Female	+80	Ischemia	Right BG	19	None	1.25
Patient 7	RBD control	No	69	Male	+100	ICB	Right BG and Thal	7	None	1.0
Patient 8	RBD control	No	72	Male	+100	Ischemia	Right Thal	2	None	1.0
Patient 9	RBD control	No	51	Male	+100	ICB	Right frontal	10	None	0.4
Patient 10	RBD control	No	70	Male	+100	ICB	Right BG	189	None	0.63
Patient 11	Excluded	Yes	58	Male	+100	Ischemia	Fronto-temporo-parietal	20	None	0.63
Patient 12	Excluded	No	62	Male	+100	Ischemia	Temporo-parietal	2	None	0.5
Patient 13	Excluded	Yes	60	Male	+100	Ischemia	Temporo-parietal	13	Hemianopia	0.63
Patient 14	Excluded	Yes	54	Male	+100	Ischemia	Temporo-parietal	21	Hemianopia	0.5

Handedness laterality score: +100: strongly right-handed.

Abbreviations: BG: basal ganglia; CI: capsula interna; ICB: intracerebral bleeding; MCA: middle cerebral artery territory; LLQ: left lower quadrant; TBI: traumatic brain injury; Thal: thalamus

Table 2. B: Performance of the patients in the neglect screening tests and in the TOJ task at baseline.

B

Patient	Line cancellation omissions *left*	Star cancellation omissions *left*	Letter cancellation omissions *left*	Number cancellation omissions *left*	Reading omissions *left*	Figure copy omission score	Composite neglect score	LBT (deviation in mm)	% “right first” resp. averaged BL	Accuracy averaged BL
Patient 1	1	5	7	4	1	1	19	31	60,1	76,6
Patient 2	0	13	16	7	47	8	91	128	75,6	55,0
Patient 3	0	3	4	1	1	2	11	88	67,3	73,1
Patient 4	0	1	0	0	0	0	1	48	62,3	86,9
Patient 5	0	0	0	0	47	2	49	157	56,7	73,3
Patient 6	0	0	3	0	0	2	5	26	59,0	72,4
Patient 7	0	0	1	2	0	1	4	80	46,6	89,1
Patient 8	0	0	1	0	0	0	1	-14	55,8	93,8
Patient 9	1	0	0	0	1	1	3	51	48,8	87,4
Patient 10	0	1	2	0	1	1	5	51	49,8	91,0
Patient 11	3	8	9	5	47	3	75	85	36,2	63,1
Patient 12	0	0	0	0	0	1	1	30	37,6	77,6
Patient 13	14	27	20	10	22	6	99	183	95,9	50,5
Patient 14	8	16	20	4	47	4	99	347	51,2	67,1

The composite neglect score was determined by adding left-sided omissions in the cancellation (line, star, letter, number) and reading tasks, as well as the figure copy omission score.

Abbreviations: BL: baseline; LBT: line bisection task; Resp: responses

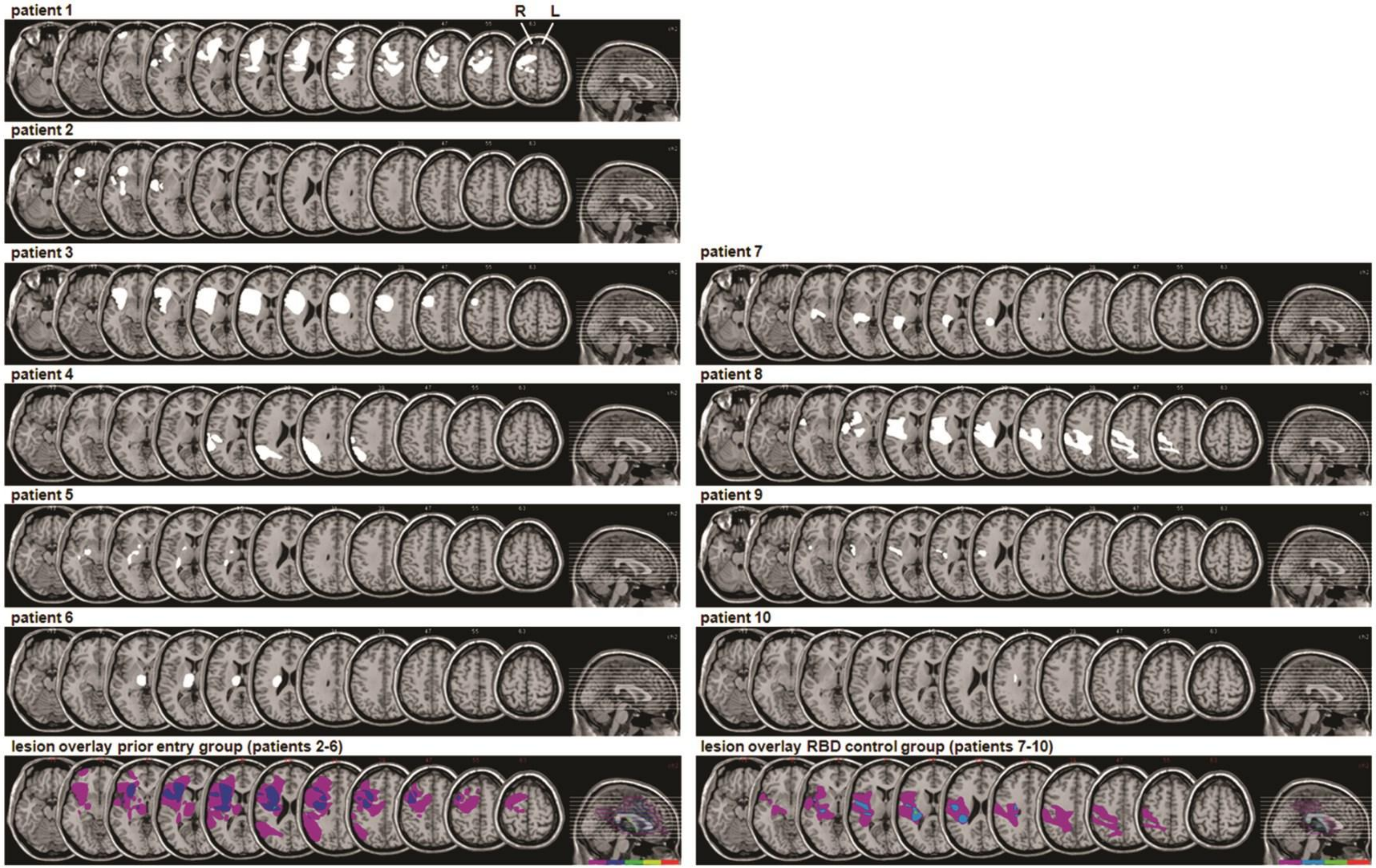


Figure 8. Reconstruction of brain lesions of the patients enrolled in the study using MRIcron. Patient 1 is the neglect patient in the case report. All other patients were tested in the group study: patients 2 – 6 are participants in the prior entry group, patients 7 – 10 are RBD controls. The right cerebral hemisphere is shown on the left side, and vice versa (R, L). Note that the scans were done partly in the acute phase, and that 5 of the patients suffered from hemorrhages. Therefore, the reconstructions may over- or underrepresent the chronic lesions.

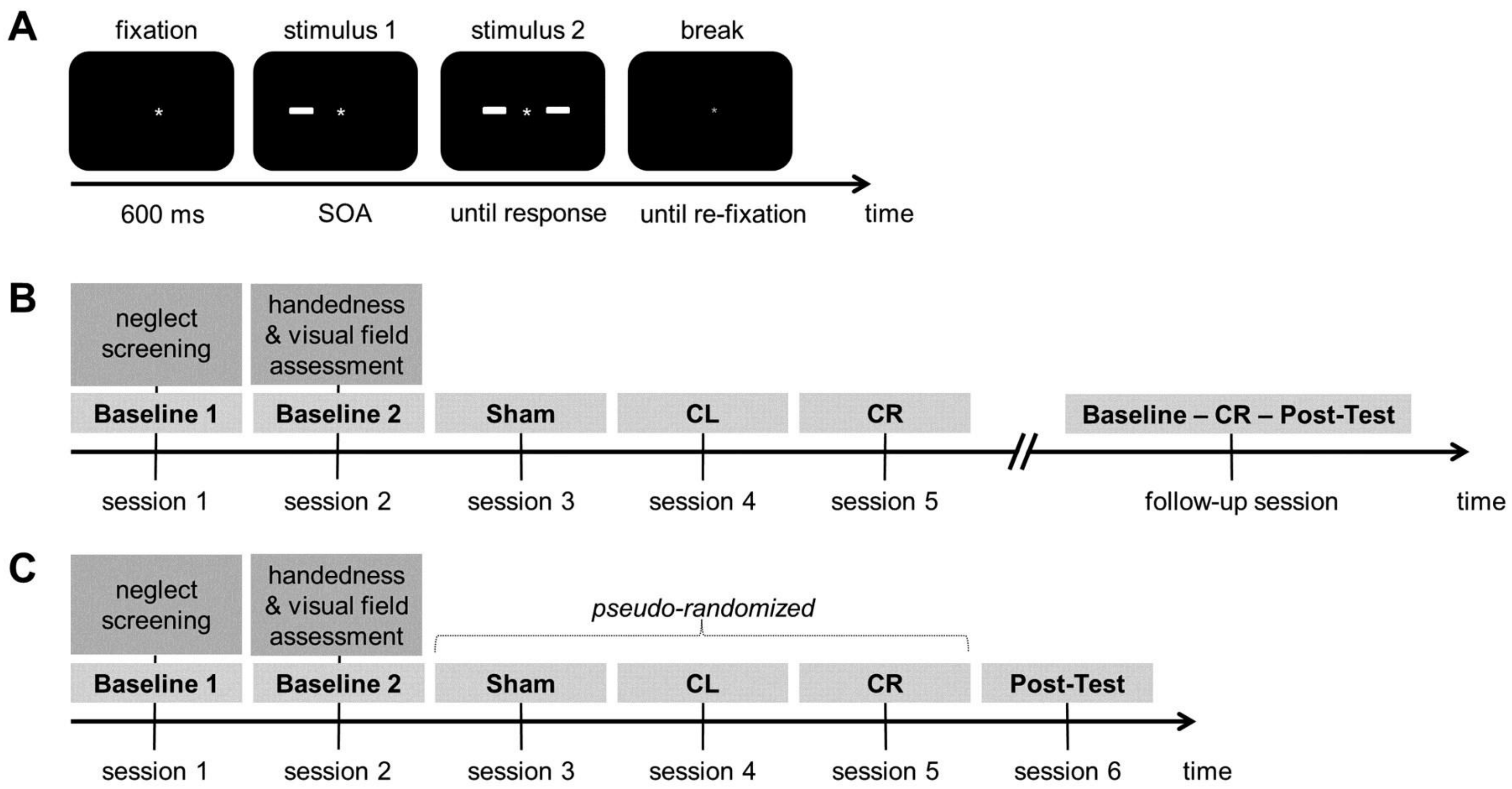


Figure 9. A: Demonstration of a typical trial in the TOJ task. As stimulus 1, a bar appeared either to the left or the right side of a central fixation cross. The patients were asked to indicate on which side the bar had appeared first. Responses were given verbally and keyed in by the experimenter. The procedure of a trial was slightly different in the case report. See text for further details. **B:** Overview of the design and GVS procedures in the case report and **C:** Overview of the design and GVS procedures in the group study. CL: cathode placed over the left mastoid and anode over the right mastoid; CR: cathode placed over the right mastoid and anode over the left mastoid; sham: electrodes in place (CL and CR pseudo-randomized), but no current; baselines and post-test: no electrodes in place. See text for further details.

patients were further given a number cancellation task (20 targets among 200 distracters with 10 targets per hemispace). Moreover, they were screened for neglect with a line bisection task (adapted and modified from Schenkenberg et al., 1980). All tests were presented on a 0.297 m x 0.21 m sized white sheet of paper with its center perpendicular to the midline of the patient's trunk, and at a distance of 0.3 – 0.4 m from the patient's eyes. A composite neglect score was established by adding omissions in the left hemispace in the various cancellation and reading tasks, as well as omissions and significant distortions in the figure copy task. Patients were considered to show visuospatial neglect if they demonstrated three or more omissions in a test, or more than 15.3 mm rightward deviation in the line bisection task (Ferro et al., 1987), and were impaired in at least 3 out of 7 screening tests.

3.2.3. Temporal order judgment (TOJ) task

The design of the temporal order judgment task was a modified version of the task used by Rorden et al. (1997) and Berberovic et al. (2004), and was identical in the case report and the group study except for minor differences. During the task, patients sat in front of a 19" screen which was aligned to the midsagittal plane of the participant. The viewing distance was 0.4 m. Patients were repeatedly instructed to maintain fixation at the center of the screen, which was assessed by the experimenter who sat behind the monitor. The sequence of a typical trial of the TOJ task is demonstrated in figure 9A. All stimuli were presented in white on a black background. At the beginning of each trial, a central fixation cross (0.9° x 0.9°) was presented for 600 ms. Then a bar (0.4° x 3.1°) appeared either to the left or right of the fixation cross which remained visible on the screen. The bar was shown at the same vertical height as the fixation cross, and the distance of its outer edge to the center of the screen was 9.8°. After a variable stimulus onset time (SOA), a second bar was displayed in the other hemi-space of the screen. Its vertical and horizontal position was identical to the one of the first bar. SOAs were: 1100, 900, 700, 500, 400, 350, 300, 250, 200, 150, 100, 80, 60, 40, 20, and 0 ms, respectively for the left and the right stimulus leading in time. Thus, both the left and the right bar appeared first with equal frequency. The targets remained visible on the screen until the participant gave his response by making a verbal forced-choice judgment regarding which stimulus he had seen first ("left" or "right"). Then the screen was cleared except for the fixation cross, which diminished in size (0.6° x 0.6°) and darkened from white to a grayish color during the break. This was done in order to give the participants a reference point where they had to fixate for the next trial. When the experimenter was sure that the participant had fixated on the screen again, she initiated the consecutive trial. Each trial was shown seven times, thus there were a total of 217 trials.

The case report patient, who was the first participant to be tested, received an earlier version of the TOJ task with some minor differences. In this version, the following SOAs were used for both the left and the right stimulus appearing first: 1200, 1000, 800, 600, 500, 400, 350, 300, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, and 0 ms. The fixation cross disappeared completely during the break. Each trial was shown 3 times, summing up to a total of 129 trials in the task. During the follow-up session, the former described version of the TOJ task was applied. One patient in the group study (patient 2) demonstrated a very strong visuospatial neglect which led him to perceive the right stimulus first in the vast majority of trials. In order to re-assure the patient that the left stimulus could also appear first, further SOAs were added. However, this was only done for the *left* bar leading in time (but not the right). The additional onset times were: 1600, 2100, 2600, 3300, 4000, and 5000 ms. Responses for these trials were not included in the analysis, as they only served as a demonstration of the nature of the task to the patient.

The procedure for healthy controls was identical to the first described above with the exception that the participants entered their responses themselves by pressing a key with their left/right index finger (Woo et al., 2009). Also, the screen was completely blanked during the break, and the next trial was initiated automatically after a 1200 ms interstimulus interval. To ensure a constant viewing distance of 0.4 m, subjects were tested with a head- and chin-rest during the TOJ task.

3.2.4. Galvanic vestibular stimulation (GVS)

The procedure of Galvanic vestibular stimulation was identical in both the case report and the group study. I applied bipolar Galvanic vestibular stimulation (NeuroConn DC stimulator; neuroConn GmbH, Ilmenau, Germany). During GVS a current of 1.0 mA (milliAmpere) was delivered. For safety reasons the maximal duration of stimulation was set to 20 min. There were three different GVS conditions (see figure 9B and 9C): left-cathodal/right-anodal GVS (termed CL-GVS), left-anodal/right-cathodal GVS (termed CR-GVS), and sham. In the CL-GVS condition, the cathode was placed over the left mastoid and the anode over the right mastoid. In the CR-GVS condition, positions of electrodes were reversed. In the sham condition, the electrodes were in place (in pseudo-randomized CR and CL-GVS order); however, no current was applied except during the first 30 sec. The short usage of current ensured that the patients experienced the typical itching underneath the electrodes at the beginning of the testing, and hereby effectively created a realistic sham GVS condition. Duration of current fade in and out was 10 sec, respectively.

The study was approved by the local ethics committee (Ärztekammer München, Germany) and was performed in accordance to the Declaration of Helsinki II. All patients had given written informed consent prior to participating in the study.

3.2.5. Design and experimental procedures

3.2.5.1. Case report

The patient was tested in five different sessions on separate days (see figure 9B). During the first two sessions, baseline data were collected, with the patient completing the TOJ task, but without having GVS-electrodes attached. In these sessions, he was further screened for neglect and visual field defects, and the visual acuity was assessed. During session $3 - 5$, GVS was applied while the patient performed the TOJ task. Stimulation sequence was: sham (in CL application), CL, and CR. There was at least a 48 h break between the single stimulation sessions to eliminate after-effects of GVS. The patient was re-tested in a follow-up session 9 weeks after the last GVS stimulation. During this session, his performance was assessed under the baseline condition, GVS stimulation (only CR), and 20 minutes post stimulation.

3.2.5.2. Group study and healthy controls

Patients were tested in six different sessions on separate days (see figure 9C). The experimental procedures of session $4 - 6$ were identical to the one described above with the exception that the sequence of GVS stimulation was pseudo-randomized to control for sequence effects. Furthermore, the type of sham (in CL vs. CR application) was pseudo-randomized across the participants. A post-test (without electrodes) was performed no sooner than two days after the last GVS application. Healthy controls were tested in one session during which the baseline performance in the TOJ task and the visual acuity were assessed.

3.2.6. Data analysis

Response frequencies “right stimulus first” and accuracy were converted in percentages for each individual. Non-parametric statistics were computed for the individual data of the patient in the case report, and for the averaged group data in the group study (IBM SPSS Statistics, version 19). There were no differences in “right stimulus first” frequency between the baseline 1 and 2 in the case report ($z = -1.11$, $p > .05$, *n.s.*), in the prior entry group ($z = -.98$, $p > .05$, *n.s.*) nor in the RBD control group ($z = -.68$, $p > .05$, *n.s.*). The accuracy was similarly comparable between the two baselines (case report: $z = -.23$, $p > .05$, *n.s.*; prior entry group: $z = -1.13$, $p > .05$, *n.s.*; RBD control group: $z = -1.16$, $p > .05$, *n.s.*). This indicates no spontaneous recovery or learning effect. Hence, all analyses refer to averaged baseline data. Friedman tests were run to test for general differences in TOJ performance across experimental conditions. Subsequent paired comparisons were performed with the two-tailed Wilcoxon sign-ranked tests. Spearman’s correlation coefficient was used to determine correlations between response bias in the TOJ task at baseline and neglect performance in conventional tests.

3.3. Results

3.3.1. Case report

3.3.1.1. Effects of GVS on left-right responses in TOJ

On average, the patient reported more often the right (ipsilesional) than the left (contralesional) stimulus to appear first across all trials in the TOJ baseline condition (figure 10A), which will be referred to as rightward bias further on. However, this was not statistically significant ($z = -.00$, $p > .05$, *n.s.*), which was probably due to the small number of observed items in the former version of the TOJ task (3 trials per SOA). GVS had a significant influence on the “right stimulus first” response frequency during the first GVS test series ($\chi^2 = 25.12(3)$, $p < .001$). Subsequent paired comparisons showed that the patient made significantly fewer rightward judgments during CR-GVS when compared with baseline data ($z = -4.33$, $p < .001$), sham ($z = -3.23$, $p < .01$), or CL-GVS ($z = -3.52$, $p < .001$). In contrast, no differences were found between baseline and sham ($z = -1.32$, $p > .05$, *n.s.*), baseline and CL-GVS ($z = -1.31$, $p > .05$, *n.s.*), or sham and CL-GVS ($z = -.27$, $p > .05$, *n.s.*). Notably, under CR stimulation, the patient reported on average more often the left than the right stimulus to appear first. However, this was again not statistically significant ($z = -.00$, $p > .05$, *n.s.*).

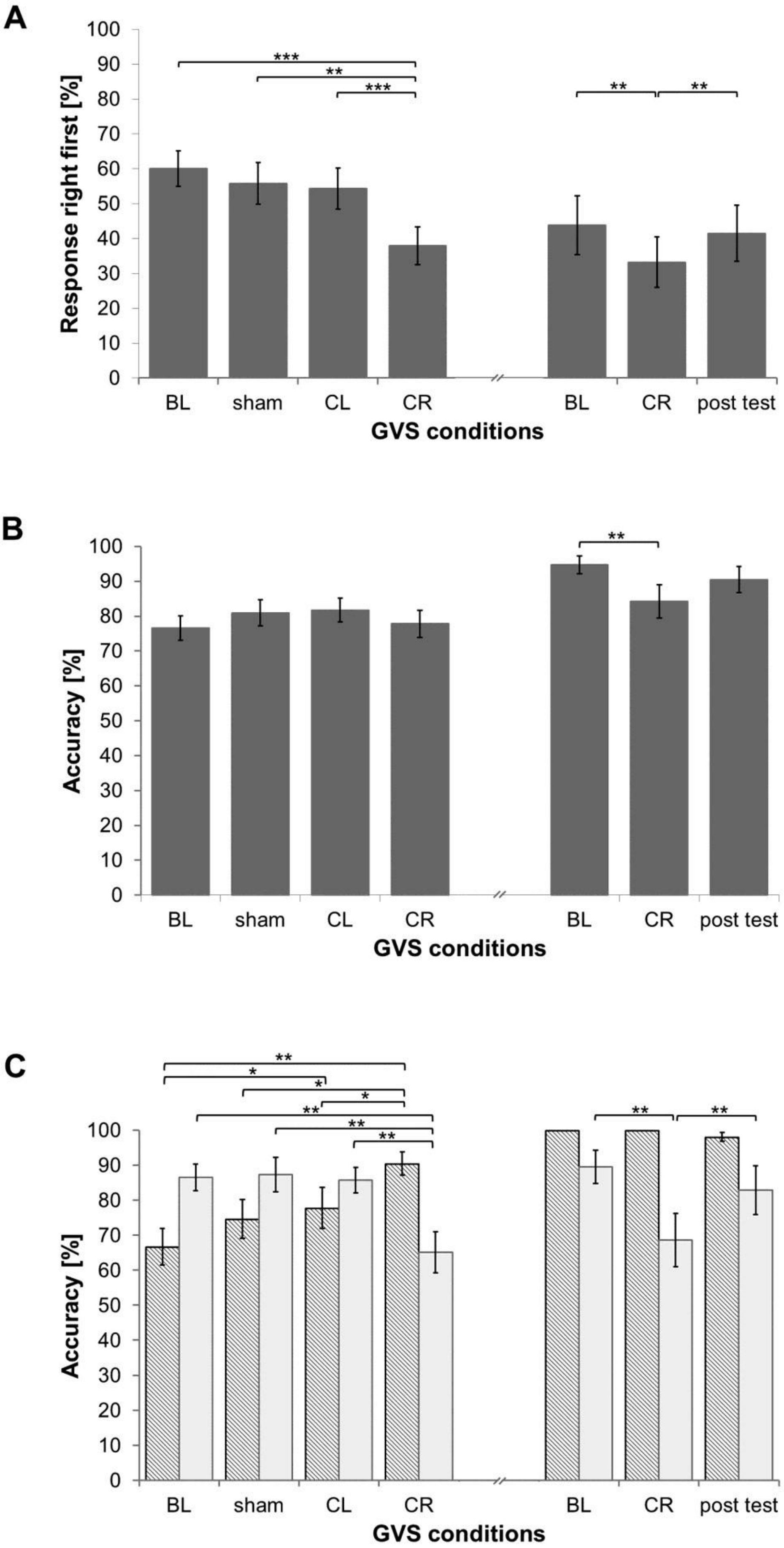
In the follow-up session 9 weeks after the first GVS study, the patient did no longer exhibit the typical rightward bias in temporal order judgments. On the contrary, already at the baseline, he perceived more often the left stimulus as appearing first. This corresponds with his reversed response pattern in the CR-GVS condition tested earlier. Yet, the percentage frequency of "stimulus left first" responses again did not differ statistically from "right stimulus first" answers ($z = -.91$, $p > .05$, *n.s.*). GVS had again a significant influence on "right stimulus first" responses ($\chi^2 = 12.72(2)$, $p < .01$). During CR stimulation, the patient reported significantly more often the left stimulus to lead in time ($z = -3.27$, $p < .01$) when compared with his responses in the baseline. This response pattern did not persist until the post-test 20 minutes after GVS. Here, he judged less often the left stimulus to appear first when compared with CR-GVS ($z = -2.69$, $p < .01$), indicating no lasting modulation of GVS on responses. Performance in the baseline and the post-test did not differ in the follow-up session ($z = -.92$, $p > .05$, *n.s.*).

3.3.1.2. Effects of GVS on the unsystematic error in TOJ

The unsystematic error in the TOJ task refers to the overall accuracy of performance. Accuracy data can be seen in figure 10B. Although GVS ameliorated the pathological rightward bias in the patient, it did not influence the unsystematic error in the test series ($\chi^2 = 3.89(3)$, $p > .05$, *n.s.*). Nevertheless, there was an effect of GVS on accuracy in the follow-up assessment ($\chi^2 = 9.64(2)$, $p < .01$). As reported above, the patient did no longer demonstrate the rightward TOJ bias at that point in time. Hence, the re-experienced reduction of "right stimulus first" responses under CR-GVS stimulation impoverished the accuracy ($z = -3.13$, $p < .01$). Accuracy during baseline and 20 min post-stimulation testing was comparable ($z = -1.92$, $p > .05$, *n.s.*), as well as during CR-GVS and the post-test ($z = -1.79$, $p > .05$, *n.s.*).

3.3.1.3. Effects of GVS on the systematic error in TOJ

The systematic error in the TOJ task refers to the accuracy for trials where the first stimulus was shown on the left side. In the course of this work, these trials will be denoted contralesional trials. Trials where the right stimulus appeared first will be correspondingly named ipsilesional trials. The presentation location of the first stimulus had a significant influence on response accuracy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sham
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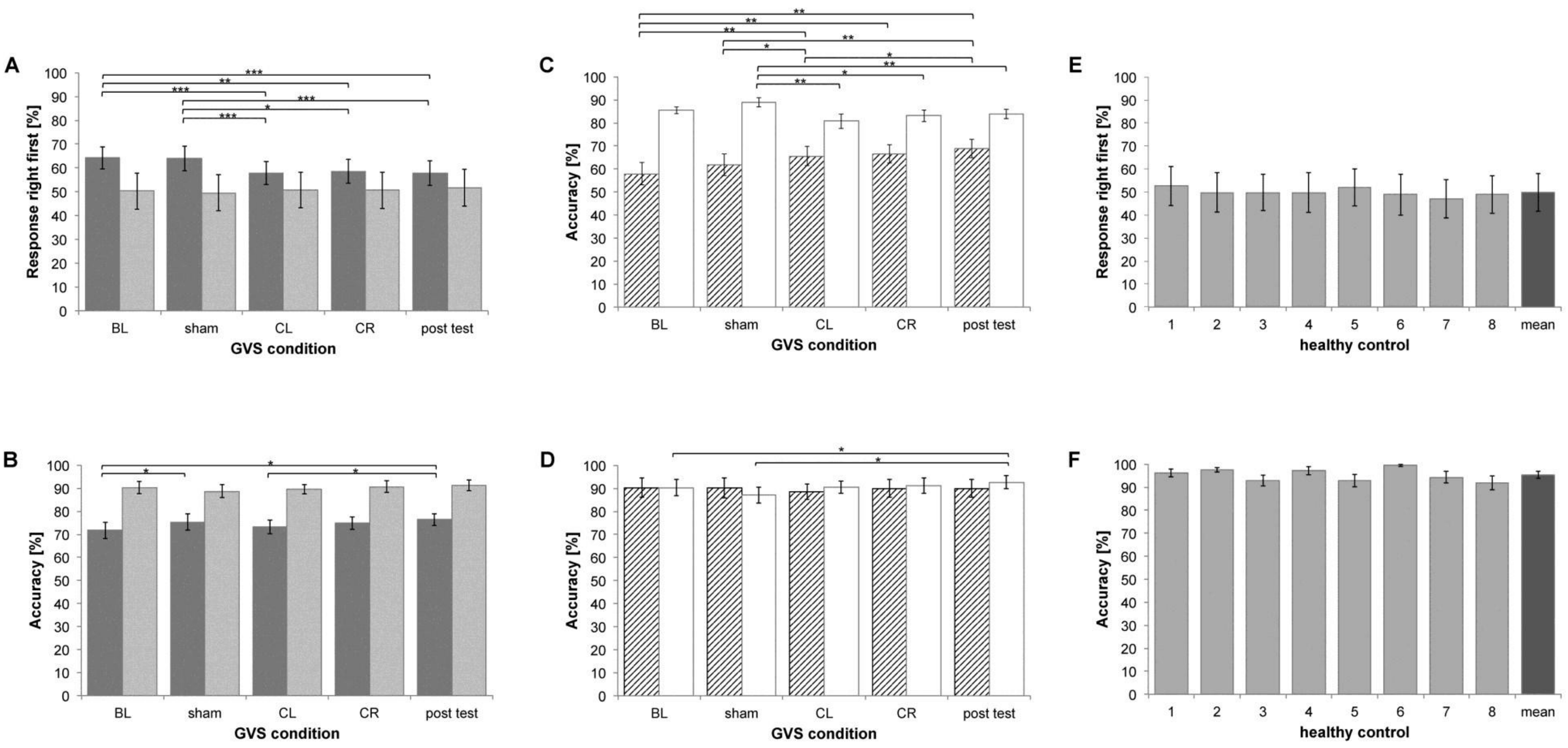
post test
GVS conditions

Figure 10 (left page). A: "Right stimulus first" responses across GVS sessions in the case report. **B:** Accuracy across GVS sessions in the case report (unsystematic error). **C:** Accuracy across GVS sessions in contra- versus ipsilesional trials in the case report. Data are means (± SEM). Hatched colored bars depict contralesional trials (left stimulus shown first); smoothly filled bars represent ipsilesional trial (right stimulus shown first). Bars to the left of the x-axis disruption generally display results for the different GVS session during the first test series; bars to the right demonstrate performance during different GVS conditions in the follow-up session. Asterisks indicate significant p-values of the Wilcoxon signed-rank test: * $p < .05$; ** $p < .01$; *** $p < .001$. BL: baseline; CL: cathode left; CR: cathode right.

during the first GVS test series (see figure 10C). When comparing performance for contralesional trials (first stimulus presented on the left) with ipsilesional trials (first stimulus presented on the right), the accuracy proved to be significantly higher for ipsilesional trials at baseline ($z = -2.33$, $p < .05$). No differences between contra- and ipsilesional trials were found during sham ($z = -1.48$, $p > .05$, *n.s.*) and CL-GVS ($z = -1.34$, $p > .05$, *n.s.*). Notably, during CR-GVS, the accuracy was better for contralesional trials ($z = -3.14$, $p < .01$).

When separately taking a look at effects of GVS for contra- and ipsilesional trials, GVS modulated the accuracy regardless when the first stimulus was presented in the left ($\chi^2 = 14.35(3)$, $p < .01$) or the right hemispace ($\chi^2 = 14.98(3)$, $p < .01$). For contralesional trials, the accuracy was highest during CR-GVS when compared with baseline ($z = -3.22$, $p < .01$), sham ($z = -2.29$, $p < .05$), and CL ($z = -2.14$, $p < .05$). Accuracy was also higher during CL-GVS than during baseline ($z = -2.04$, $p < .05$). No differences were found between baseline and sham ($z = -1.40$, $p > .05$, *n.s.*), or sham and CL-GVS ($z = -.32$, $p > .05$, *n.s.*). Interestingly, this pattern was reversed for ipsilesional trials. Here, the accuracy was comparable between the baseline and sham ($z = -.48$, $p > .05$, *n.s.*), the baseline and CL-GVS ($z = -.75$, $p > .05$, *n.s.*), and sham and CL-GVS ($z = -.31$, $p > .05$, *n.s.*). Importantly, the lowest accuracy was found during CR, with significant differences to performance during BL ($z = -2.76$, $p < .01$), sham ($z = -2.84$, $p < .01$), and CL-GVS ($z = -2.81$, $p < .01$). This finding is compatible with a shift of attention from the ipsi- to the contralesional hemispace under CR-GVS.

During the follow-up session, accuracy reached almost 100% for contralesional trials. Regardless of the condition, performance in these trials was significantly better than in ipsilesional trials (BL: $z = -2.03$, $p < .05$; CR: $z = -3.24$, $p < .01$; post-test: $z = -2.10$, $p < .05$). This observation contrasts performance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during baseline TOJ in the first GVS test series, where accuracy was higher in ipsilesional trials. Due to a ceiling effect, GVS could not modulate the accuracy for contralesional trials during the follow-up session ($\chi^2 = 4.00(2)$, $p > .05$, *n.s.*). However, GVS influenced the accuracy in ipsilesional trials ($\chi^2 = 11.23(2)$, $p < .01$). Here, the accuracy was lowest during CR-GVS when compared with the baseline ($z = -3.13$, $p < .01$) or the post-test ($z = -2.23$, $p < .05$). The accuracy was comparable during the baseline and the post-test ($z = -1.48$, $p > .05$, *n.s.*).

To conclude, GVS modulated the systematic error in trials where the left stimulus was shown first. Performance improved significantly under CR-GVS during the test series. In the follow-up session, the systematic error did no longer appear; hence GVS could only modulate accuracy in ipsilesional trials.

3.3.2. Group study and healthy controls

3.3.2.1. Effects of GVS on left-right responses in TOJ

Patients in the prior entry group reported more often the ipsilesional (right) than the contralesional (left) stimulus to appear first ($z = -2.91$, $p < .01$). Percentage frequency of left versus right stimulus first responses did not differ in the RBD control group ($z = -.26$, $p > .05$, *n.s.*). GVS significantly modulated the mean percentage of the “right stimulus first” responses in the prior entry group ($\chi^2 = 28.45(4)$, $p < .001$), but not in the control group ($\chi^2 = 9.32(4)$, $p > .05$, *n.s.*, see figure 11A). While there was no difference in “right stimulus first” response frequency during baseline and sham GVS ($z = -.22$, $p > .05$, *n.s.*), prior entry patients perceived the right stimulus first significantly less often during

Figure 11 (left page). A: “Right stimulus first” responses across GVS sessions in the prior entry (dark gray) and the RBD control (light gray) group. **B:** Accuracy across GVS sessions in the prior entry (dark gray) and the RBD control (light gray) group (unsystematic error). **C:** Accuracy across GVS sessions in contra- versus ipsilesional trials in the prior entry group. **D:** Accuracy across GVS sessions in contra- versus ipsilesional trials in the RBD control group. **E:** Individual and averaged “right stimulus first” responses of healthy control participants at baseline TOJ. **F:** Individual and averaged accuracy of healthy controls at baseline TOJ. Data are means (± SEM). In C and D, hatched colored bars stand for contralesional trials; smoothly filled bars represent ipsilesional trials. Asterisks indicate significant p-values of the Wilcoxon signed-rank test: * p < .5; ** p < .01; *** p < .001. BL: baseline; CL: cathode left; CR: cathode right; RBD: right brain damaged

CL-GVS ($z = -3.58$, $p < .001$), and CR-GVS ($z = -2.88$, $p < .01$) stimulation when compared with the baseline testing. Improved performance to baseline persisted until a post-test assessed no sooner than 48 hours after the last GVS stimulation ($z = -3.80$, $p < .001$). Accordingly, “right stimulus first” responses were also less frequent during GVS stimulation (CL-GVS: $z = -3.67$, $p < .001$; CR-GVS: $z = -2.45$, $p < .01$) and the post-test ($z = -3.83$, $p < .001$) when compared with sham GVS performance. No differences between “right first” responses were found between CL- and CR-GVS ($z = -.63$, $p > .05$, *n.s.*), or both types of GVS stimulation and the post-test (CL: $z = -.72$, $p > .05$, *n.s.*; CR: $z = -.73$, $p > .05$, *n.s.*).

3.3.2.2. Effects of GVS on the unsystematic error in TOJ

Accuracy data for both groups across experimental conditions are depicted in figure 11B. In the prior entry group, the unsystematic error significantly changed across test conditions ($\chi^2 = 10.78(4)$, $p < .05$). However, the modulation was not GVS dependent, as there were no differences between the baseline and CL-GVS ($z = -1.28$, $p > .05$, *n.s.*), or the baseline and CR-GVS ($z = -1.56$, $p > .05$, *n.s.*). The accuracy was also comparable between sham and CL-GVS ($z = -.73$, $p > .05$, *n.s.*), sham and CR-GVS ($z = -.40$, $p > .05$, *n.s.*), and sham and the post-test ($z = -.64$, $p > .05$, *n.s.*). Furthermore, there were no differences between performance during CL- and CR-GVS stimulation ($z = -.92$, $p > .05$, *n.s.*), or during CR-GVS and the post-test ($z = -1.06$, $p > .05$, *n.s.*). In contrast, patients became more accurate during sham GVS stimulation when compared with baseline TOJ ($z = -2.21$, $p < .05$). Moreover, their performance was significantly better during the post-test than during the baseline ($z = -2.45$, $p < .05$), or during CL-GVS ($z = -2.00$, $p < .05$). In the RBD control group, accuracy did not change across GVS sessions ($\chi^2 = 7.59(4)$, $p > .05$, *n.s.*).

3.3.2.3. Effects of GVS on the systematic error in TOJ

The location of the first stimulus had a significant influence on responses in prior entry patients (figure 11C). Participants were far more accurate in ipsilesional than contralesional trials in all conditions (BL: $z = -3.24$, $p < .01$; sham: $z = -3.15$, $p < .01$; CR: $z = -2.33$, $p < .05$; post-test: $z = -2.16$, $p < .05$), except for the CL-GVS condition (CL: $z = -1.93$, $p > .05$, *n.s.*). Interestingly, a systematic influence of GVS was only found for contralesional trials ($\chi^2 = 26.60(4)$, $p < .001$), indicating a modulation of the systematic error. In these trials, the accuracy significantly improved during CL-GVS ($z = -3.18$, $p < .01$), and CR-GVS

($z = -2.86$, $p < .01$) when compared with the baseline. Accuracy was also higher during CL-GVS ($z = -2.08$, $p < .05$) than during sham GVS. Responses were most accurate during the post-test. Performance in this condition was significantly better than during the baseline ($z = -3.41$, $p < .01$), during sham ($z = -2.80$, $p < .01$), and during CL-GVS ($z = -2.44$, $p < .05$). Performance in contralesional trials was comparable between CR-GVS and sham ($z = -1.33$, $p > .05$, *n.s.*), as well as between both stimulation conditions and the post-test (CL-GVS: $z = -.17$, $p > .05$, *n.s.*; CR-GVS: $z = -1.22$, $p > .05$, *n.s.*).

Regarding ipsilesional trails, there was also a significant change of the accuracy across experimental conditions ($\chi^2 = 11.01(4)$, $p < .05$). However, no direct modulation of GVS was found. Patients were most accurate during sham GVS. Performance in this condition was significantly better than during CL-GVS ($z = -2.97$, $p < .01$), CR-GVS ($z = -2.28$, $p < .05$), and the post-test ($z = -2.60$, $p < .01$). No differences were found between the baseline and all experimental conditions (sham: $z = -1.89$, $p > .05$, *n.s.*; CL: $z = -1.48$, $p > .05$, *n.s.*; CR: $z = -.94$, $p > .05$, *n.s.*; post-test: $z = -.81$, $p > .05$, *n.s.*). The accuracy was also comparable between both stimulation conditions and the post-test (CL: $z = -.77$, $p > .05$, *n.s.*; CR: $z = -.18$, $p > .05$, *n.s.*), as well as between CL- and CR-GVS ($z = -.88$, $p > .05$, *n.s.*).

In the RBD control group, the location of the first stimulus had no systematic impact on response accuracy (figure 11D). The accuracy in ipsi- and contralesional trials was comparable in all conditions: baseline ($z = -.11$, $p > .05$, *n.s.*), sham ($z = -.63$, $p > .05$, *n.s.*), CL-GVS ($z = -.43$, $p > .05$, *n.s.*), CR-GVS ($z = -.14$, $p > .05$, *n.s.*), and post-test ($z = -.24$, $p > .05$, *n.s.*). When taking a closer look specifically at contralesional trials, there was no difference in the accuracy across GVS conditions ($\chi^2 = 3.26(4)$, $p > .05$, *n.s.*). In contrast, in ipsilesional trials, the accuracy changed across experimental conditions in ($\chi^2 = 14.13(4)$, $p < .01$). This was due to an improved performance during the post-test compared to the baseline ($z = -2.05$, $p < .05$), and to sham GVS ($z = -2.00$, $p < .05$). However, no differences were found between the stimulation conditions and the baseline (CL-GVS: $z = -.21$, $p > .05$, *n.s.*; CR-GVS: $z = -.76$, $p > .05$, *n.s.*). Performance was further comparable between sham and CL-GVS ($z = -1.51$, $p > .05$, *n.s.*), sham and CR-GVS ($z = -1.83$, $p > .05$, *n.s.*), CL-GVS and CR-GVS ($z = -.64$, $p > .05$, *n.s.*), CL-GVS and the post test ($z = -1.54$, $p > .05$, *n.s.*), and CR-GVS and the post test ($z = -1.73$, $p > .05$, *n.s.*), suggesting no direct effects of GVS in the RBD control group. Additionally, there was no difference between the baseline and sham GVS ($z = -1.85$, $p > .05$, *n.s.*).

3.3.2.4. Healthy controls

None of the 8 healthy control participants showed a lateralized response pattern for baseline temporal order judgments (figure 11E). The average percentage of “right stimulus first” response” at baseline was 49.8 (± 1.8 SD). Percentage frequencies of “right” versus “left stimulus seen first” did not differ ($z = -.11$, $p > .05$, *n.s.*), indicating near-perfect symmetry for both the left- and the right-sided stimulus in temporal processing. The individual accuracy yielded 91.9% and higher in the TOJ task, the average accuracy across all participants was 95.3% (± 1.5 SD, see figure 11F). There was no difference in the mean accuracy if the first stimulus was presented on the left or on the right side ($z = -1.15$, $p > .05$, *n.s.*).

3.4. Discussion

These are the main findings of the present study: (i) CR-GVS modulated the typical rightward TOJ bias in a patient with neglect. Both CR- and CL-GVS reduced the TOJ bias in a “prior entry” group of patients (n = 5) with stronger rightward deviations at baseline, while it had no effect on a RBD control group (n = 4) without the prior entry phenomenon. (ii) In the case report, CR-GVS was slightly more effective than CL-GVS, indicating a polarity-specific effect. (iii) Significant sustained effects after termination of GVS were observed in the follow-up-session in the case report and in the post-test assessment in the prior entry group, but not in the RBD control group. These three issues will be discussed in detail below.

3.4.1. Effects of GVS on TOJ

A patient with visuospatial neglect (case report) demonstrated a clear aptitude for the perception of right- before left-sided stimuli (“prior entry” phenomenon) at baseline TOJ. This result is consistent with previous reports of the TOJ deficit in neglect (Berberovic et al., 2004; Snyder & Chatterjee, 2004), or the related disorder of extinction (Rorden et al., 1997). As a novel finding, I report that GVS significantly modulated the response bias in this patient. During CR stimulation, the patient reported significantly more often the left (contralesional) stimulus to appear before the right stimulus when compared with the baseline condition. Furthermore, accuracy improved under both CL- and CR-GVS if the first stimulus was presented on the contralesional side. This indicates a normalization of the TOJ deficit in left-sided visuospatial neglect. Interestingly, accuracy worsened under CR-GVS in trials during which the first stimulus was shown on the ipsilesional side. Obviously, GVS does not enhance attentional performance in the TOJ per se, but rather seems to act on the left-right bias by redirecting the focus of visuospatial attention to the neglected left side of space (2). Previous studies have reported that TOJ can be influenced by endogenous and exogenous cues guiding visual attention to the left or right hemifield (Shore, Spence, & Klein, 2001; Schneider & Bavelier, 2003; Spence & Parise, 2010). The positive modulatory effects of GVS are in accordance with related findings from caloric vestibular stimulation in neglect patients (Rode et al., 1998; Rode et al., 1992). As a second novel finding, I observed that GVS modulates the TOJ deficit in a group of RBD patients with strong prior entry phenomenon at baseline. During CL and CR stimulation, these patients made significantly fewer "right stimulus first" answers when compared with performance under baseline and sham GVS. This was due to a systematically increased accuracy in trials where the left (contralesional) stimulus was shown first (reduction of the systematic error). A similar improvement for exclusively right-sided items was observed by Utz (Utz et al., 2011). Interestingly, accuracy deteriorated slightly under CL- and CR-GVS in trials where the first stimulus was presented on the right side, corroborating the attention-shift hypothesis of the GVS effect. Notably, the frequency of "right stimulus first" responses and accuracy was not altered by GVS in a homogenous non-neglecting RBD control group with less severe rightward deviations at baseline TOJ.

Since group assignment was made on strength of the baseline TOJ deficit, one could argue that the reported effect in the prior entry group may be explained by a mere regression towards the mean. However, there are three arguments against this possibility: first, performance in these patients was comparable between baselines 1 and 2. If the observed effect relied on a regression towards the mean, then performance should have already differed during the first two sessions. Second, performance was furthermore similar between average

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(2) Further evidence for this hypothesis comes from patient 12, who had to be excluded from the study due to abnormal strong *leftward* deviations at baseline TOJ. This patient experienced a further leftward shift under GVS, which was highly significant ($\chi^2 = 30.45(31)$, $p < .001$).

baseline and sham GVS, which was assessed pseudo-randomized in the third until fifth test session. The improvement of TOJ strictly limited to effective GVS stimulation contradicts the regression hypothesis. And third, accuracy did not improve per se, but showed a specific lateralized improvement pattern. This additionally speaks against an unsystematic change of performance. I can thus draw the conclusion that GVS generally modulates the TOJ bias in patients with a strong "prior entry" phenomenon.

A striking finding which has to be addressed is that a rightward response pattern in the TOJ task was not restricted solely to patients with visuospatial neglect. The prior entry group comprised patients with and without manifested neglect symptoms. Noteworthy, this is the first study on TOJ that includes RBD control patients without neglect; therefore there are no previous reports I can refer to. I explain the present findings partially by the fact that many non-neglecting patients included in this study still demonstrated a small residual neglect in some neglect screening tests (see table 2B). Secondly, I have to point out that temporal order judgments differ significantly from visuospatial paper-and-pencil tests. Thus, deficits in temporal processing may not necessarily be reflected by the performance in conventional neglect test. A recent study corroborates this idea by reporting differential brain activation in neglect patients during the processing of spatial versus temporal information in the TOJ task (Roberts et al., 2012). And, thirdly, I acknowledge that only a few patients with strong neglect symptoms could be tested in this study. Note, that previous studies on temporal order processing in neglect or extinction also included very few patients (1 patient in Snyder & Chatterjee, 2004; 2 patients in Rorden et al., 1997; and 5 patients in Berberovic et al., 2004). TOJ task requirements set strict limits in advance regarding the target patient group. On the one hand, participants have to exhibit clearly defined neglect deficits; on the other hand, they must not suffer from further neurological constraints such as hemianopia, which often accompany severe neglect syndromes. Two out of 6 tested patients with manifested visuospatial neglect had to be excluded from this study due to hemianopia, and two further patients due to an atypical leftward response bias probably caused by extended damages to the frontal lobe. Therefore, only 2 neglect patients remained accessible for the group study analyses (another neglect patient was tested under slightly different circumstances and was hence analyzed separately in the case report). This impeded a reasonable analysis of "neglect" versus "non-neglecting RBD control" patients in the frame of this study. Thus, I cannot reject the hypothesis that neglect patients show indeed stronger rightward TOJ deviations than RBD controls. I also cannot rule out the possibility that TOJ deficits are a general phenomenon of damage to the right hemisphere per se, and are not related to visuospatial neglect. Importantly, patients with lesions to the left brain demonstrate no consistent left-right TOJ preference (Robertson et al., 1998). Deeper investigations of this matter should be subject to future studies.

3.4.2. Polarity-specific effects of GVS on TOJ

In the case report, CR-GVS had a slightly greater impact on the TOJ bias than CL-GVS. Notably, the patient demonstrated not only a reduction but even a reversal of the typical right-sided response pattern in TOJ during CR-GVS, suggesting polarity-specific effects. While CL-GVS activates the vestibular system bilaterally, CR preferentially activates the vestibular cortex in the right hemisphere to a greater extent. Thus, GVS might have decreased the right-sided (ipsilesional) bias during TOJ by activating preserved neuronal structures in the temporo-parietal cortex and/or the right insula cortex in this neglect patient. Since normal functioning during TOJ in healthy subjects relies on both the left and the right temporo-parietal junction, operating together as "comparators" (Davis et al., 2009), one potential explanation might be that CR-GVS had a greater effect on TOJ in neglect because it activates mainly the right-hemispheric cortical vestibular network, which in turn leads to a more symmetrical weight of the two "comparators" in both hemispheres. In contrast, CL-GVS also activates the (intact) left hemisphere in addition to the lesioned right hemisphere, which—according to this hypothesis—does not re-balance the asymmetry during TOJ in a comparable way as CR-GVS. In fact, similar polarity-dependent, but task-dependent, effects of GVS were found in related studies using GVS or tDCS in deficits in spatial neglect (Utz et al., 2011; Fink et al., 2003; Sparing et al., 2009). The most parsimonious conclusion that can be drawn from these studies is that GVS enables re-balancing of the asymmetric lateralization, or attentive orienting, typically seen in neglect or extinction, as proposed by early models of neglect (Kinsbourne, 1977). While an entire reversal of the response bias in TOJ (at least in the case report patient) may at first glance appear unusual, other authors found a similar complete, albeit temporary, normalization by direct manipulations of attentional processing using phasic alertness cues in neglect patients (Robertson et al., 1998). In line with these results, a recent single case study showed similar improvements in response bias during TOJ in a patient with right-sided chronic neglect (Dove, Eskes, Klein, & Shore, 2007), which the authors attributed to a modulation of top-down attentional strategies.

3.4.3. Sustained effects of GVS on TOJ

The positive effects of GVS on TOJ remained stable up to the post-test two days (prior entry group) or 9 weeks (case report) after the last GVS session, thus indicating sustained effects. Such prolonged effects of GVS after termination of the stimulation have been found in several recent studies using this technique (Utz et al., 2011; Kerkhoff et al., 2011), and are in accordance with physiological studies. Investigations using the related technique of transcranial direct current stimulation (tDCS) have shown that short-term effects depend on polarization effects of the neuronal membrane, whereas long-lasting effects are caused by the modulation of the NMDA receptor strength (Utz et al., 2010).

Despite the promising results in this study, a few caveats are to be mentioned. First, the sample size of manifested neglect patients was small. Future studies with larger samples have to investigate possible differences in TOJ between neglect and non-neglecting RBD control patients in greater detail. Second, the case report patient had a traumatic brain lesion (although only right-hemispheric lesions were visible on the MRI scans) and may thus represent a less typical etiology of neglect than stroke.

3.5. Conclusions

The present findings complement previous results which showed that TOJ deficits in neglect may be modulated by certain techniques such as prism adaptation. Moreover, they add to the observation that GVS not only improves a variety of spatial deficits in neglect patients, but also ameliorates temporal processing deficits in these patients as revealed in TOJ. This finding suggests clear interactions of vestibular and time-processing mechanisms in the brain. Finally, the observed sustained effects of a few GVS sessions reveal an interesting choice for treatment that should be further investigated in future studies.

Effects of Small-Field Optokinetic Stimulation (OKS) on Temporal Order Judgments

4.1. Introduction

Temporal order judgments may be modulated in neurologically healthy individuals by a variety of exogenous cues, such as peripheral flashes (Shore et al., 2001), central and peripheral visual cues (Schneider & Bavelier, 2003), uni- and multisensory distractors (Vatakis & Spence, 2006), visual flankers (Fährmann, Köpsel, Bachmann, & Huckauf, 2008), and vestibular rotatory accelerations (Figliozzi, Guariglia, Silvetti, Siegler, & Doricchi, 2005). Optokinetic stimulation is a sensory stimulation technique which involves the simultaneous one-directional movement (e.g. left- or rightward) of many homogenous single cues across the visual field. In healthy individuals, it influences attention and perception in vision (Watanabe, 2001; Na et al., 2002; Choi et al., 2005; Figliozzi, Silvetti, Rubichi, & Doricchi, 2010), space (Sándor, Bächtold, Henn, & Brugger, 2000), hearing (Cullen, Collins, Dobie, & Rappold, 1992; Otake, Kashio, Sato, & Suzuki, 2006), and touch (Gallace, Auvray, & Spence, 2007). OKS has also been demonstrated to alter time perception in duration comparison tasks (Vicario et al., 2007). Teramoto and colleagues modulated both visual and auditory TOJs using OKS in an immersive type Virtual Reality system (Teramoto et al., 2004; Teramoto et al., 2008). During the experiment, participants sat in a 2.4 m wide and 4.0 m high cylinder and completed a TOJ task, while optokinetic stimulation was projected onto the walls of the cylinder (large-screen OKS). The authors reported that subjects perceived left-sided prior to right-sided stimuli during rightward OKS, and right-sided earlier than left-sided ones during leftward OKS. They explained the finding by the optokinetic nystagmus (OKN): during visual motion, eyes slowly pursuit stimuli in the direction of movement to stabilize the retinal image, which is then alternated by fast backward saccades. Thereby, the average eye position of gaze is displaced in the direction of saccades, leading to a possible shift of attention towards the side of incoming stimuli (opposing the direction of OKS movement). Teramoto and colleagues stressed the importance of perceived self-motion for altered TOJ during OKS. For example, they found no comparable modulatory effects on auditory TOJ using a regular PC monitor, which induced no self-motion perception (Teramoto et al., 2008). However, no study so far has investigated whether visual TOJ may be influenced by small-field optokinetic stimulation.

OKS is an important tool for the treatment of spatial neglect (Kerkhoff et al., 2012). To generalize the effectiveness of a method, it is important to test the responsiveness of different populations. Psychological anthropology indicates that culture has strong influences on individual cognition such as reasoning styles and perceptual conceptualization. Recent investigations suggest that cross-cultural distinctions can even embrace “pure” perception and attention processes (for a review see Nisbett & Miyamoto, 2005). In several tasks, East Asians have been shown to focus more on the whole pattern and relate stronger to the periphery and background than Westerners do: the Rorschach cards (Abel & Hsu, 1949), the Rod-and-Frame Test (Ji et al., 2000), the framed-line test (Kitayama et al., 2003), a video recognition task (Masuda & Nisbett, 2001), and a change blindness task (Masuda & Nisbett, 2006). Differences in the performance have been related to higher field-dependence in Asians compared with Westerners (Ji et al., 2000; Nisbett, Peng, Choi, & Norenzayan, 2001; Kitayama et al., 2003; Nisbett, 2003). Field-dependence represents a perceptual ability and defines the degree to which an individual may see an object as discrete and separate from its surroundings or background. High field-dependent subjects are less accurate and show longer reaction times to disembed things from the environment than low field-dependent individuals (Witkin, 1950; Witkin et al., 1954; Zhang, 2004). Interestingly, some studies suggest that cross-cultural differences in attention and perception are reflected by differences in eye movement (Chua, Boland, & Nisbett, 2005; Goh, Tan, & Park, 2009). While Westerners look sooner and longer at focal objects, Chinese individuals make more alternating eye movements between objects and their background and generally look longer at the background. These findings raise the question, whether peripheral optokinetic stimulation has a differential influence on Westerners and Asians, or high and low field-dependent individuals.

In the present study, I investigated whether peripheral small-field OKS modulates visual TOJ, and whether there are cross-cultural or individual differences in this modulation. Given the strong success of OKS in the rehabilitation of neglect, it is worth examining whether its effectiveness differs across cultures or among low versus high field-dependent subjects. Two hypotheses were formulated: (i) small-field OKS has an influence on temporal order judgments. Participants make more “right first” responses during leftward OKS than during rightward OKS. (ii) There is an effect of culture and field-dependence on participants’ influenceability of TOJ by OKS. Chinese and high field-dependent subjects will exhibit greater modulation by OKS than German and low field-dependent subjects. This will be measured via reaction times and accuracy scores in the TOJ task.

4.2. Material and methods

4.2.1. Participants

Twelve Chinese university students (4 males and 8 females, mean age: 22.7 ± 1.1 years) and 12 German university students (5 males and 7 females, mean age: 21.8 ± 1.7 years) participated in this study. Chinese and German participants were equivalent in age ($U = 52.00$, $z = -1.19$, $p > .05$, *n.s.*) and gender ratio ($p > .05$, *n.s.*, Fisher’s exact test). There was a small difference in education duration measured as number of completed university semesters (Chinese: 8.9 ± 2.2 semesters, Germans: 5.1 ± 2.5 semesters; $U = 18.50$, $z = -1.19$, $p < .01$), due to differences in the educational system. All participants were naïve to the purpose of the study. They were all right-handed according to the German version of the Edinburgh handedness inventory (Salmaso & Longoni, 1985; Hermsdörfer et al., 1994), and had normal or corrected-to-normal vision with a corrected visual acuity yielding 0.8 or higher for near space (0.4 m). None of them reported vestibular dysfunctions or other neurological or psychiatric disorders. Spatial field-dependence was assessed using the German *Leistungsprüfungssystem* (LPS), subtest 10 (Horn, 1983), which is an embedded figures test. Based on the performance in this task, participants of both cultures were then split into a high versus low field-dependent group, respectively. Median split equated 85% correct answers in the Chinese sample and 75% correct in the German one. All subjects participated for a fee and gave informed consent before the experiment.

4.2.2. Temporal order judgment (TOJ) task

All stimuli were displayed on a 19” external monitor that was controlled by a Lenovo R61 laptop. Participants sat in front of the screen at a viewing distance of 0.4 m. Their heads were secured by a chin-rest. The TOJ task was a modified version of the task applied in study 2 (see section 3.2.3) and the task used by Figliozzi et al. (2005). TOJ stimuli were displayed in black on a light gray background field (38° x 7.2°) on an otherwise black screen (see figure 12A). At the beginning of each trial, a fixation cross with the size of 0.9° x 0.9° appeared for 600 ms at the center of the screen. Then a 3.1° x 0.4° bar was shown at the same vertical height either on the left or the right visual field of the screen. After a certain stimulus onset-asynchrony (SOA), a second bar was presented in the opposing visual field. The horizontal distance from the center of the bars to the center of the screen was 16°, which has been demonstrated to exert the greatest effects (see Teramoto et al., 2004). Participants had to make a forced choice between which of the bars had appeared first. Both stimuli remained visible on the monitor until the response was given by pressing either a left or a right key. Then the monitor went blank for 1000 ms until the beginning of the next trial. Subjects were instructed to answer as fast and accurate as possible. Adding the pressure to respond quickly might result in co-measuring a motor component of information processing (Shore et al., 2001; Figliozzi et al., 2005). However, the main interest of the present study lies on the intercultural differences, and time for motor execution should not differ between both groups. Instead, any difference in response times between Chinese and German participants could indicate different degrees of distractions by peripheral OKS. Furthermore, I decided to use *simultaneous* trials as experimental trials, expecting to increase the sensitivity of the TOJ task for subtle differences. Thus, in each OKS condition, fifty percent of the administered trials were synchronous (SOA = 0 ms). The other half comprised asynchronous trials, using seven different SOAs (16, 32, 48, 64, 80, 96, and 128 ms), which were shown 16 times each. On half of these trials, the left bar was presented first; on the other half, the right bar was delivered first. Both synchronous and asynchronous trials made up a total of 224 per condition. They were administered in two blocks, with a short break between them.

4.2.3. Small-field optokinetic stimulation (OKS)

While participants completed the TOJ task, OKS was presented in the peripheral space surrounding the TOJ background field (figure 12A). There were five different conditions depending on the absence or the direction of optokinetic stimulation: baseline, leftward OKS, rightward OKS, static, and random OKS. As OKS stimuli, yellow dots of the size of 2.7° x 2.7° appeared in random positions on a black background. Dots moved at a constant speed of 30°/sec either to the left (leftward OKS), or to the right (rightward OKS), or randomly in all directions (random). The dots were shown but did not move during the static condition. No dots were displayed during the baseline (BL). Both the static and the random condition served as control conditions.

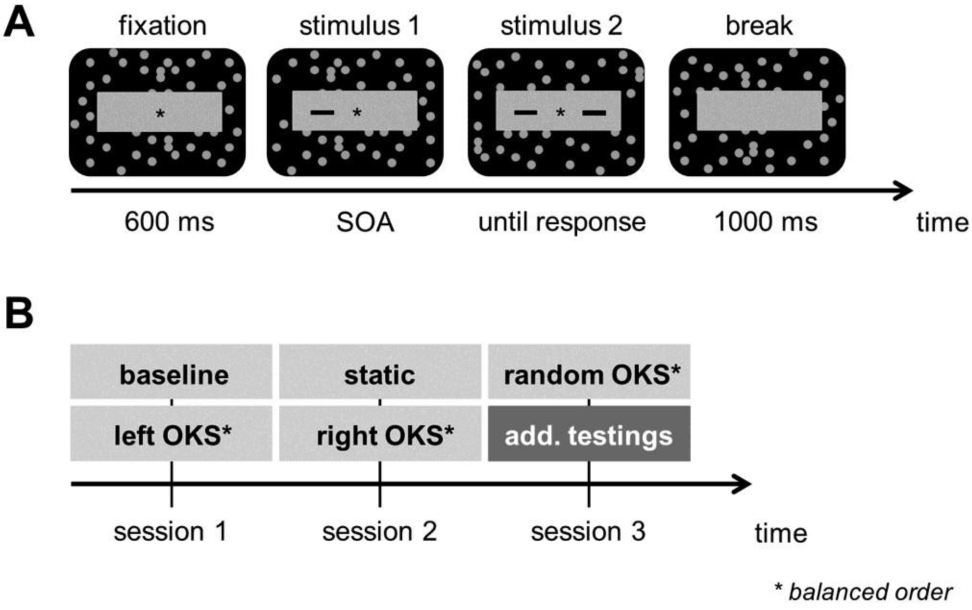

Figure 12. A: Demonstration of a typical trial in the TOJ task. As stimulus 1, a bar appeared either to the left or the right side of a central fixation cross. Participants had to indicate on which side they had seen the bar first by pressing either a left or a right key. Meanwhile, OKS was run in the background. For this, yellow dots either moved leftward (left OKS), rightward (right OKS), or into random directions (random OKS). They could also be static (static) or absent (baseline). **B:** Testing procedure of OKS stimulation. There was at least a 24-hour break between single sessions. The order of the conditions left OKS, right OKS, and random OKS was balanced across participants. Additional tests during session 3 included the assessment of field-dependence using the LPS subtest 10.

4.2.4. Design and experimental procedures

Participants were tested during three separate sessions on different days (figure 12B). Two conditions were tested during session 1 and 2, and one condition during session 3. To prevent OKS after-effects interfering with performance in the consecutive condition during the first two sessions, the BL and the static condition (which should not lead to after-effects) were assessed first. The order of the remaining conditions (leftward OKS, rightward OKS, and random OKS) was balanced across the participants. There was one practice block at the beginning of each session where each SOA was shown twice. No OKS was delivered in the background at that time. Participants then underwent two blocks of each condition. OKS presentation started at the onset of each block and was continuously maintained until the end of the block. There was a two minute break between each block during which the screen was completely cleared. Each session lasted approximately 30 minutes.

4.2.5. Data analysis

Response frequencies “right stimulus first” in synchronous trials and accuracy in asynchronous trials were converted in percentages for each individual and each condition. Reaction times were computed across both synchronous and asynchronous trials. Data were then analyzed performing a mixed design analysis of variance (ANOVA), with OKS condition as within-subject factor, and culture and field-dependence as between-subject factors (IBM SPSS Statistics, version 19). Demographic data of cultural samples were not normally distributed and thus compared using Mann-Whitney U-tests, if not stated otherwise.

4.3. Results

4.3.1. Effects of OKS on TOJ

There was a main effect of OKS on response frequencies “right first” in the TOJ task, [$F(4,80) = 4.26$, $p < .01$], see figure 13A. Planned contrasts revealed a significant increment of “right stimulus seen first” responses during leftward OKS [$F(1,20) = 3.16$, $p < .05$, one tailed] and a marginal decrement of “right stimulus first” answers during rightward OKS [$F(1, 20) = 2.97$, $p = .05$, one-tailed] when compared with the performance during baseline. An additional

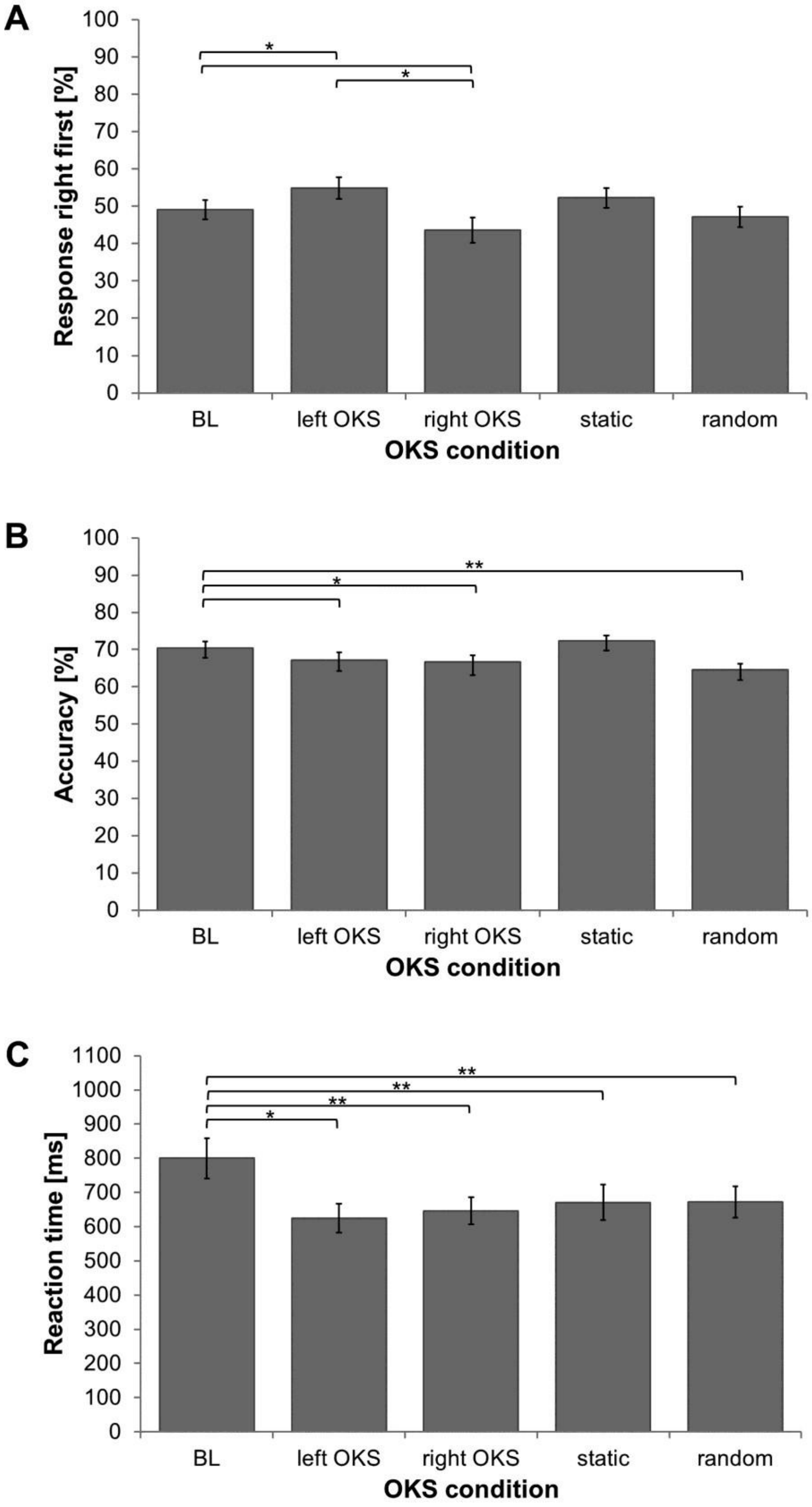

Figure 13. A: “Right stimulus first” responses across OKS conditions. **B:** Accuracy, and **C:** reaction times across OKS conditions. Data are means ± SEM. Asterisks indicate significant p-values of planned contrasts: * $p < .5$; ** $p < .01$. BL: baseline; left OKS: leftward OKS; right OKS: rightward OKS

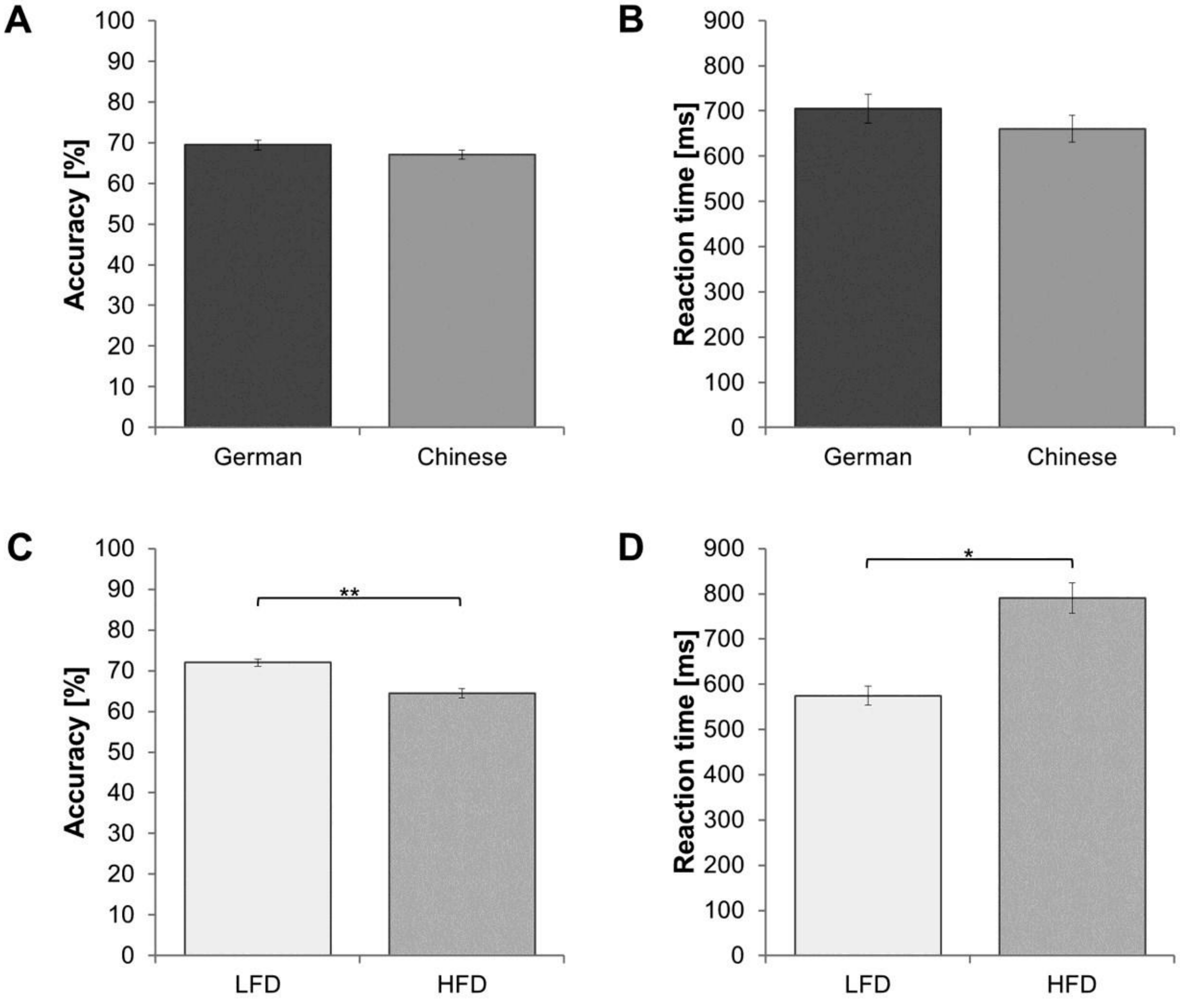

Figure 14. **A:** Accuracy, and **B:** reaction times in Chinese versus German participants. **C:** Accuracy, and **D:** reaction times (± SEM) in low field-dependent (LFD) versus high field-dependent (HFD) subjects. Data are means ± SEM. Asterisks indicate significant main effects: * p < .5; ** p < .01.

comparison confirmed that participants reported significantly more often the right stimulus to appear first during leftward than during rightward OKS [$t(23) = 3.43$, $p = .01$]. Importantly, no differences in “right first” response frequencies were found between the baseline and the two control conditions: static [$F(1, 20) = 1.56$, $p > .05$, *n.s.*] and random OKS [$F(1, 20) = .26$, $p > .05$, *n.s.*]. I further found a main effect of OKS on response accuracy, $F(4, 80) = 7.73$, $p < .001$, see figure 13B. Contrasts showed that accuracy worsened significantly under random [$F(1, 20) = 9.86$, $p < .01$] and rightward OKS [$F(1, 20) = 4.67$, $p < .05$], and marginally under leftward OKS [$F(1, 20) = 3.38$, $p = .08$] as compared with the baseline. On the other hand, accuracy was identical in the static dot condition and the baseline [$F(1, 20) = 1.53$, $p > .05$, *n.s.*], suggesting that accuracy in the TOJ task was not negatively influenced by peripheral objects per se, but rather by the movement. Analyses also revealed a main effect of OKS on reaction times ($F(4, 80) = 11.83$, $p < .001$, figure 13C). Participants were much slower during the baseline compared with their reactions during all the other experimental conditions: leftward OKS [$F(1, 20) = 36.75$, $p < .001$], rightward OKS [$F(1, 20) = 15.00$, $p < .01$], static [$F(1, 20) = 15.27$, $p < .01$], and random [$F(1, 20) = 10.43$, $p < .01$], indicating a learning effect, as the baseline was assessed at the very beginning of the test series in each participant.

4.3.2. Effects of culture and field-dependence on TOJ during OKS

Detailed data of Chinese and German participants' performance as well as low and high field-dependent subjects across OKS conditions can be seen in figures 14 and 15. The main prerequisite for OKS modulation of TOJ was apparent self-motion in the studies of Teramoto and colleagues (2004; 2008). Interestingly, compared to German participants, Chinese experienced more often a sense of self-motion during small-field OKS. Five out of 12 Chinese subjects reported this phenomenon, while none of the German participants stated this experience. Nevertheless, the performance of Chinese and German participants was comparable in this study. I found no interaction between culture and OKS for "right first" response frequencies [$F(4, 80) = 1.27$, $p > .05$, *n.s.*], response accuracy [$F(4, 80) = .49$, $p > .05$, *n.s.*], or reaction times [$F(4, 80) = .26$, $p > .05$, *n.s.*], indicating that peripheral OKS had similar influences on Chinese and German participants. Also, there was no main effect of culture on response accuracy [$F(1, 20) = .92$, $p > .05$, *n.s.*] and on reaction times [$F(1, 20) = .31$, $p > .05$, *n.s.*], suggesting that performance of Chinese and Germans was generally identical in the TOJ task. Notably, analyses revealed a marginal but non-significant main effect of culture on "right first" response frequency in TOJ [$F(1, 20) = 3.17$, $p = .09$]. On average, German participants tended to report the right stimulus to appear first more often (mean: 52.8% ± 2.0 SEM) than Chinese subjects (mean: 45.9% ± 1.6 SEM).

While the cultural background had no influence on performance in the TOJ task, field-dependence had a significant effect. There was a main effect of field-dependence on response accuracy [$F(1, 20) = 9.52$, $p < .01$] as well as on reaction times [$F(1, 20) = 7.22$, $p < .05$]. Participants with low field-dependence were generally faster and more accurate in the TOJ task than high field-dependent subjects. Strength of field-dependence (measured as percentage of

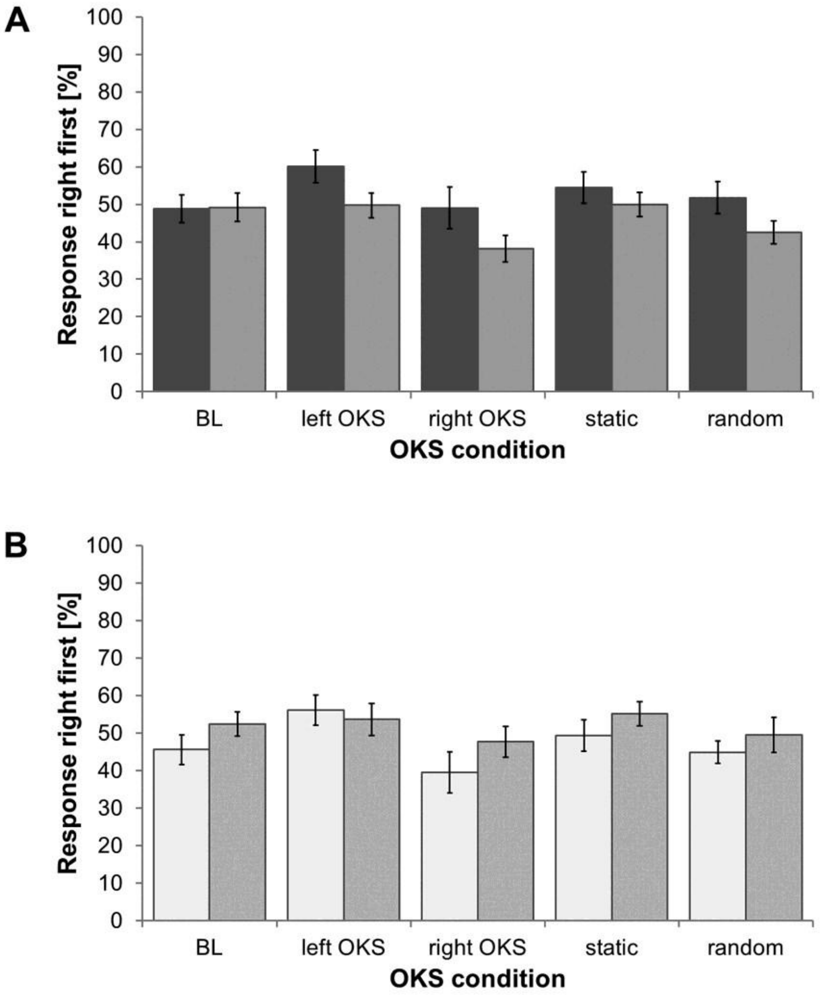

Figure 15. A: "Right stimulus first" responses in Chinese versus German participants. Dark gray bars indicate data of German subjects; light gray bars represent data of Chinese participants. **B:** "Right stimulus first" responses in high field versus low field-dependent subjects. Light grays depict data of low field-dependent subjects; dark gray bars represent data of high field-dependent subjects. Data are means ± SEM.

correct responses in the LPS subtest 10) further correlated with accuracy ($r = .41$, $p < .05$) and reaction times ($r = -.44$, $p < .05$). No main effect of field dependence on the "right first" response frequency was found [$F(1, 20) = 1.38$, $p > .05$, *n.s.*], indicating that low and high field-dependent subjects did not demonstrate an unexpected opposing preference for a visual hemi-field. Also, no interaction between field-dependence and OKS stimulation were found for the following dependent variables: "right first" response frequency [$F(4, 80) = .96$, $p > .05$, *n.s.*], accuracy [$F(4, 80) = 1.05$, $p > .05$, *n.s.*], and reaction time [$F(4, 80) = .41, p > .05$, *n.s.*].

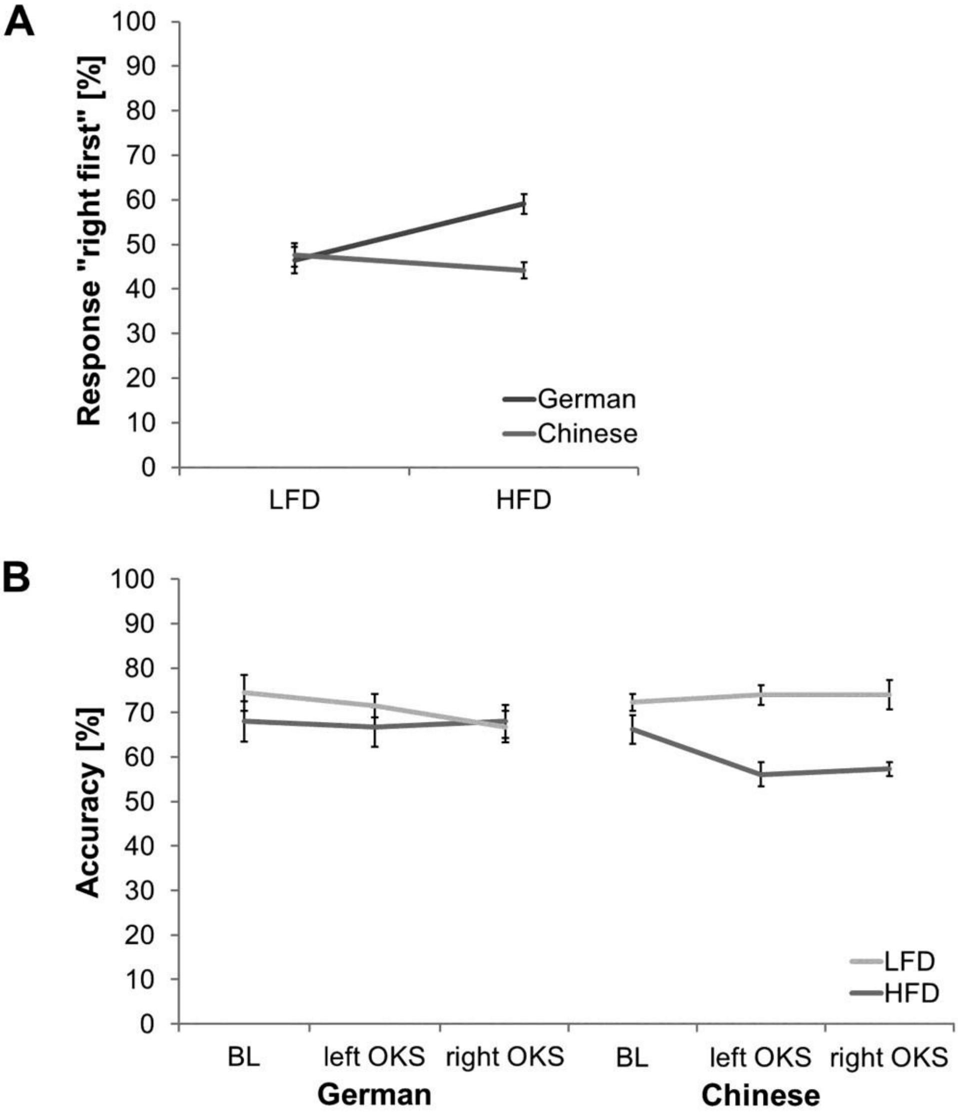

Figure 16. A: Marginal interaction between culture and field-dependence for "right first" response frequency. **B:** Interaction between OKS, culture, and field-dependence. Data are means ± SEM. HFD: high field-dependent subjects; left OKS: leftward OKS; LFD: low field-dependent subjects; right OKS: rightward OKS

The data suggest that, generally, the Chinese sample did not exhibit stronger visual field-dependence than the German one in the present study. Performance of Chinese and German participants was comparable in the LPS task, $t(22) = .60$, $p > .05$, *n.s.*. I also found no interaction between culture and field-dependence for response accuracy [$F(1, 20) = 1.00$, $p > .05$, *n.s.*] and reaction time [$F(1, 20) = 1.16$, $p > .05$, *n.s.*] in the TOJ task. Notably, though, there was a marginal interaction between culture and field-dependence for "right first" response frequency [$F(1, 20) = 4.26$, $p = .05$], see figure 16A. High field-dependent Germans made on average more "right first" judgments than high field-dependent Chinese, whereas there were no differences between low field-dependent German and Chinese participants. Furthermore, there was a 3-way interaction between OKS x culture x field-dependence for accuracy [$F(4, 80) = 5.08$, $p < .01$]. Contrasts showed a difference between rightward OKS and baseline [$F(1, 20) = 6.94$, $p < .05$], as well as a trend for a difference between leftward OKS and baseline [$F(1, 20) = 3.87$, $p = .06$], indicating that OKS modulated performance differently in low and high field-dependent Chinese and German participants. To further break down this interaction, I computed two distinct mixed 2 (field-dependence) x 3 (OKS condition) ANOVAs for Chinese and German participants, respectively. Analyses revealed that there was a significant interaction between OKS condition and field-dependence in the Chinese [$F(2, 20) = 4.52$, $p < .05$], but not in the German sample [$F(2, 20) = 1.19$, $p > .05$, *n.s.*]. The interaction graphs in figure 16B suggest that compared to low field-dependent participants, high field-dependent Chinese subjects deteriorated in accuracy during OKS stimulation while such an effect was not found in the German sample. Furthermore, there was a main effect of field-dependence [$F(1, 10) = 26.27$, $p < .001$] in the Chinese, but not in the German sample [$F(1, 10) = .53$, $p > .05$, *n.s.*].

4.4. Discussion

My hypotheses were confirmed in major parts. These are the main findings: (i) small-field OKS modulated "left right" responses in visual TOJ. Leftward OKS lead to more "right first" responses whereas rightward OKS led to fewer "right first" judgments. (ii) While I found no differences between Chinese and German participants, general performance in the TOJ task was co-related with field-dependence. High field-dependent subjects were slower and less accurate than low field-dependent subjects. I will discuss these findings in detail below.

4.4.1. Effects of OKS on TOJ

As a novel finding, I report that *small-field* OKS modulated which stimulus was seen first in the TOJ task. During leftward OKS, participants perceived stimuli presented on the right side prior to simultaneous stimuli presented on the left side, and vice versa. This is in line with previous work by Teramoto and colleagues, who found identical modulations of visual TOJ using large-field OKS

(Teramoto et al., 2004). OKS drives covert attention towards the “incoming” side of OKS stimuli, thereby facilitating the detection of TOJ stimuli in the visual hemifield opposed to the direction of OKS movement. The underlying mechanism has been attributed to a gaze shift caused by the OKN, a reflectory rapid change between slow and fast eye movements elicited during visual motion perception (Pizzamiglio et al., 1990; Teramoto et al., 2008). However, the OKN does not seem to be necessary for the modulatory effects of OKS: several studies have shown that OKS may influence visual perception even while explicit OKN are suppressed (Mattingley, Bradshaw, & Bradshaw, 1994; Kerkhoff, Kriz, Keller, & Marquardt, 1999; Watanabe, 2001). The occurrence of OKN depends on the speed of OKS motion; fast movements (above 8°/sec) facilitate OKN (Kerkhoff, 2001; Kerkhoff, 2003a). On the anatomical level, OKS activates multiple cortical and subcortical areas, such as the temporo-parietal cortex, the basal ganglia, the brain stem, and the cerebellum (Dieterich, Bucher, Seelos, & Brandt, 1998; Konen, Kleiser, Seitz, & Bremmer, 2005; Bense et al., 2006). Some of them, namely the temporo-parietal junction and the right posterior parietal cortex, have been identified to be involved in temporal order judgments (Davis et al., 2009; Woo et al., 2009).

The present data suggest that leftward OKS has slightly stronger modulatory effects than rightward OKS on TOJ. These results are in contrast with studies of OKS on visual and haptic line bisection in healthy participants, which found modulation exclusively for rightward OKS (Sándor et al., 2000; Gallace et al., 2007). Likewise, Vicario observed stronger effects of rightward OKS in a time estimation task (Vicario et al., 2007). Importantly, studies applying a TOJ task did not report differences of modulation strength between left- and rightward OKS (Teramoto et al., 2004; Teramoto et al., 2008). Judgments of temporal orders might thus differ from “pure” visuospatial or time processing tasks.

Temporal order judgments have been modulated by a variety of techniques in neurologically healthy participants. Similar results were found for vestibular rotatatory accelerations (Figliozzi et al., 2005). In this study, participants sat upright on a chair which was rotated either rightward (clockwise) or leftward (counter-clockwise) around the vertical head-body axis. During the midpoint of acceleration, they were asked to make visual or tactile temporal-order judgments. The authors reported that subjects perceived stimuli presented on the side of the rotation direction prior to simultaneous stimuli presented on the opposite side. Interestingly, neck-vibration and caloric-vestibular stimulation—being comparable bottom-up stimulation techniques—could not modulate visual TOJ in healthy individuals (Rorden, Karnath, & Driver, 2001).

Notably, while previous studies found modulations of temporal order judgments using large-field OKS, they reported no effects of small-field OKS (Teramoto et al., 2008). However, Teramoto and colleagues applied a cross-modality task design, using auditory TOJ stimuli. This might have increased the threshold for OKS influences on performance. The present results indicate a sound modulation of small-field OKS on *visual* TOJ. Advantages of small-field OKS on a regular PC screen entail lower costs and greater flexibility in terms of location and thus an easier implementation for therapeutic treatment in diseases where TOJ are disturbed, such as in neglect and extinction (Snyder & Chatterjee, 2004; Rorden et al., 1997). OKS has already proven to be a powerful tool for these disorders (Kerkhoff, 2003a; Kerkhoff, 2003b; Kerkhoff, Keller, Ritter, & Marquardt, 2006; Kerkhoff et al., 2012). It ameliorates deficits in the visual modality, such as line bisection errors (Pizzamiglio et al., 1990; Mattingley et al., 1994), deviations of the subjective straight ahead (Karnath, 1996), size distortions (Kerkhoff, Schindler, Keller, & Marquardt, 1999; Kerkhoff, 2000), poor distance judgments (Schindler & Kerkhoff, 2004), and neglect dyslexia (Reinhart, Schindler, & Kerkhoff, 2011). Also, OKS improves deficits in the auditory (Nico, 1999; Kerkhoff et al., 2012), and tactile modality (Kerkhoff, 2003b), and even neglect in representational space, such as the mental number line (Salillas et al., 2009; Priftis, Pitteri, Meneghello, Umiltà, & Zorzi, 2012). In patients with neglect, OKS modulation is based on smooth pursuit eye movements rather than on fast saccades during the OKN, which is in striking difference to modulation in healthy subjects (Kerkhoff, 2001; Kerkhoff, 2003a; Kerkhoff et al., 2012). In fact, fast OKS which elicits OKN aggravates neglect deficits (Bisiach, Pizzamiglio, Nico, & Antonucci, 1996). Future studies should address whether OKS may also modulate the typical TOJ deficit in neglect and extinction.

4.4.2. Effects of culture and field-dependence on TOJ during OKS

As a second novel finding, I report that field-dependence had an influence on temporal order judgments. High field-dependent subjects were generally less accurate and had longer reaction times in the TOJ task than their low field-dependent counterparts. This observation has been made in other tasks as well: the rod- and-frame test (Asch & Witkin, 1948a; Asch & Witkin, 1948b), the body adjustment task (Witkin & Asch, 1948a; Witkin & Asch, 1948b; Witkin, 1949), and the embedded figures test (Witkin, 1950; Witkin, Oltman, Raskin, & Karp, 1971). Field-dependence is further related to scholastic achievement in geometry, a subject which strongly requires visual disembedding (Zhang, 2004). A recent study reported differences between low and high field-dependent individuals in the capacity to direct, shift and maintain attention. The authors suggest that low field-dependent subjects find it generally easier to selectively attend to the relevant stimuli and to further sustain the attention on this given information, particularly in the presence of distracting elements (Guisande, Páramo, Tinajera, & Almeida, 2007). This offers a good explanation for the differential outcome between low and high field-dependent participants in the present TOJ task. According to this hypothesis, the low field-dependent subjects were better at guiding and maintaining attention exclusively on the TOJ background field while ignoring unrelated information in the periphery. This in turn led to improved performance in the task, measured as higher accuracy and shorter reaction times for temporal order judgments.

A few studies have indicated perceptual differences between East Asians and Westerners which are associated with field-dependence. For example, Ji and colleagues reported that East Asians are less accurate in the rod-and-frame test than Americans (Ji et al., 2000). Japanese subjects also perform better in the relative than the absolute version of the related framed-line test, indicating that they rely more on the context-dependent information than American subjects in this task (Kitayama et al., 2003). It has further been suggested that East Asians allocate their attention more broadly than Westerners during visual information processing (Boduroglu, Shah, & Nisbett, 2009). However, while I found a sound effect of field-dependence, there were no differences between Chinese and Germans participants in the TOJ task. Peripheral OKS exerted a comparable modulation of TOJ in all participants. A reasonable explanation is that field-dependence did not differ in the Chinese and German samples as measured by the LPS task. I had expected the Chinese participants to demonstrate higher field-dependence and, consequently, to be more influenced by peripheral OKS in the TOJ task than their German counterparts. The lack of cross-cultural differences in field-dependence might also be due to the relatively small sample size in the study. I followed the experimental designs of previous (non cross-cultural) studies on modulations of TOJ in healthy individuals who used an equal or even smaller number of participants. Nevertheless, any differences in general field-dependence across cultures might be too subtle to become visible in such small groups. Sample sizes embraced 2-4fold more participants in the above mentioned rod-and-frame and framed-line tests. Noteworthy, only Chinese but no German participants reported perceived self-motion during OKS in my study, which has been demonstrated to be an indicator for strength of OKS modulation of TOJ, if not even a prerequisite (Teramoto et al., 2004; Teramoto et al., 2008). Thus, there might be some cultural differences in perceptual response to peripheral OKS in the present samples that were simply too small to be measured as differences in behavioral response in the TOJ task. On the other hand, cross-cultural differences involving "pure" attention and perception are still under discussion. Although using comparably large sample sizes, Rayner and colleagues could not replicate Chua's findings of cross-cultural differences in eye movements during visual information processing tasks (Chua et al., 2005; Rayner, Williams, Cave, & Well, 2007). They report that Chinese participants did not spend more time looking at the background than their American counterparts during tasks such as reading, scene perception, and visual search. Further indications are given by recent fMRI studies which found equivalent brain activation during the processing of scene backgrounds between East Asians and Westerners (Gutchess, Welsh, Boduroglu, & Park, 2006; Goh et al., 2007). Given that the modulation in the present task depended on attending to OKS stimuli in the background of the central TOJ field, these findings support the negative cross-cultural results. As a limitation of this study, the exclusive analysis of the behavioral performance should be noted. If OKS modulation depends on a gaze shift caused by the OKN in healthy individuals, an examination of elicited reflectory eye movements could have shed further light on cultural differences in fundamental physiological processes. As a second constraint, only healthy participants were tested in the present study. The data indicate that Westerners and East Asians respond comparably to OKS, suggesting that the effectiveness of its neurological treatment might be generalized across these two cultures. However, further investigations in patient samples are needed to confirm this hypothesis. Interestingly, there were individual differences in the sensitiveness to OKS modulation. High-field-dependent subjects responded more strongly to OKS treatment than low field-dependent participants. These findings propose that the individual field-dependence may be a predictor for the effectiveness of OKS therapy in neglect patients. Field-dependence can be measured by simple paper-and-pencil tasks, and might thus be easily integrated in the diagnostic process helping to choose an individualized treatment that offers the best outcome possible. Hence, I strongly suggest examining effects of field-dependence in future patient studies as well.

Until today, there is a debate about whether field-dependence represents a pure perceptual ability or stands for a broad cognitive pattern that embraces an analytic versus a context-dependent style (Shade, 1984; Zhang, 2004). Nisbett and his colleagues have taken the field-dependence construct to explain cross-cultural differences in behavior and thinking (Nisbett et al., 2001; Nisbett, 2003). They suggest that East Asians generally act more holistically and context-dependent, while Westerners are more analytic and context-independent. Over the last few decades, there has been increasing evidence for cross-cultural differences in higher cognitive processes, such as perceptual categorization (Chiu, 1972; Norenzayan, Smith, Kim, & Nisbett, 2002; Ji, Zhang, & Nisbett, 2004; Kriukova, 2012). While Westerners group objects on basis of shared features (e.g. cow and pig are grouped together, because both are animals), East Asians categorize objects on basis of relational-contextual information (e.g. cow and grass are grouped together, because cows eat grass). Similar cultural differences have been shown in reasoning styles. While Westerners tend to attribute events to internal causes, East Asians rather emphasize the context and attribute causality to the situation, thus being less susceptible to the fundamental attribution error (Norenzayan & Nisbett, 2000; Nisbett, 2003). Proposed underlying mechanisms for these culture specific cognitive styles are different child rearing practices and language usage during the socialization process, as well as distinct daily affordances which might arise from living in rather complex (Asians) versus low complex (Western) societies (Fernald & Morikawa, 1993; Tardif, Shatz, & Naigles, 1997; Miyamoto, Nisbett, & Masuda, 2006; see also Nisbett & Miyamoto, 2005). It remains a subject for further investigations whether culture only shapes higher cognitive functions, or if it can indeed modulate basic attentional and perceptual processes, too.

4.5. Conclusions

The present results show that small-field OKS modulates temporal order judgments in healthy individuals. The results complement previous investigations on bottom-up modulation of TOJ. They further confirm previous studies demonstrating that OKS guides covert attention to the "incoming" side of stimuli in healthy participants. Notably, I found effects of field-dependence in the TOJ task, proposing clear interactions between space perception and time-processing mechanisms in the brain. Performance between Chinese and German participants was comparable in this study, suggesting no differences in basic perceptual processes and responsiveness to OKS modulation across cultures.

General Discussion and Final Conclusions

5.1. Summary of the present findings

The present work had three objectives: (i) to investigate the modulation of time deficits in neglect patients, (i) to further elucidate general time-space interactions in the sense of a horizontal mental time line, and (iii) to reveal possible cross-cultural differences in time perception and susceptibility to sensory stimulation techniques. In order to accomplish these aims, three studies were conducted and presented in this dissertation. I will first give an overview of the current findings and then discuss their implications for current research in the light of the three objectives, hereby raising perspectives for further future investigations.

Study 1 and 2 were carried out to explore effects of sensory modulation techniques on distinct time deficits in neglect patients. In study 1, the patients completed a time reproduction task. The method of choice to manipulate time perception/reproduction was lateral head and trunk rotation. At baseline, the patients gave intervals that lasted significantly longer than the references ("underestimation"), suggesting that subjective time is compressed in relation to clock time in neglect patients. I could show that this time deficit was reduced by lateral head and trunk rotation to the right. Study 2 investigated effects of Galvanic vestibular stimulation on the "prior entry" phenomenon in temporal order judgments. I found that CR-GVS overcame the typical TOJ advantage for right-sided stimuli in a patient with neglect. Moreover, both CR- and CL-GVS modulated this bias in a "prior entry" group of patients with stronger rightward deviations at baseline, while it had no effect on a RBD control group with less severe response deviations (no prior-entry phenomenon). After termination of GVS, significant sustained effects were observed in both the single case and the prior entry group, indicating a treatment potential of this technique.

The second objective of study 1 aimed to assess time-space interactions in the sense of a horizontal MTL. In this regard, I further tested the performance of healthy individuals in a time reproduction and a time bisection task while completing lateral head, trunk, or whole body rotation. The analyses revealed that neglect patients as well as healthy participants produced shorter durations during rightward turns of the trunk, which opposes the idea that participants orientated on a MTL with increasing interval length mapped from left to right during “metric” time perception. Regarding “ordinal” time processing, I examined effects of optokinetic stimulation on visual TOJ in healthy individuals in study 3. Small-field OKS modulated the frequency of left-right judgments similarly to its effectiveness in visuospatial tasks: during leftward motion—which causes attentional shifts to the right—healthy subjects perceived the right stimulus prior to the left.

Regarding the third objective of this thesis, the TOJ task in study 3 was further administered to a group of Chinese participants. As a novel finding, I report that the accuracy and reaction times in the TOJ task were related to individual field-dependence. Comparison between German and Chinese participants indicated that Chinese subjects reported more often a sensation of self-motion during the influence of peripheral OKS, which has been taken as an indicator for OKS effectiveness. However, I observed no cultural differences in TOJ performance, suggesting that time processing and susceptibility to optokinetic stimulation is comparable between East Asians and Westerners.

5.2. Implications of the present findings for current research

5.2.1. Modulating the timing deficit in neglect

The present work confirms that patients with visuospatial neglect suffer from additional timing deficits (Critchley, 1953; Petrovici & Scheider, 1994; Becchio & Bertone, 2006). As a novel finding, this dissertation shows that these distortions may be overcome by Galvanic vestibular stimulation and lateral head or trunk rotation. So far, very few studies have investigated effects of sensory modulation techniques on time deficits in neglect. The most thoroughly examined method in this regard is prism adaptation. Oliveri and colleagues have demonstrated that prism adaptation ameliorates the typical overestimation of temporal intervals in a time bisection task (Magnani et al., 2011; Oliveri et al., 2013). In addition, Berberovic and co-workers have reported that it also reduces the typical rightward TOJ bias in neglect (Berberovic et al., 2004). Apart from this technique, the only other stimulation method examined until now is the application of spatially non-lateralized alerting tones, which successfully decreases the pathological TOJ advantage for right-sided stimuli in neglect patients (Robertson et al., 1998).

Over the last decades, research has repetitively shown that visuospatial deficits in neglect improve after trunk rotation or Galvanic vestibular stimulation. Body rotation is an inexpensive propioceptive stimulation method, which can be easily integrated into everyday rehabilitation treatment (Fong et al., 2007). Several studies have reported reduction of left-sided deficits after trunk turns to the contralesional side. Improved performance was found for contralesional stimuli detection (Karnath et al., 1993), straight-ahead pointing (Chokron & Imbert, 1995), as well as line bisection and paragraph reading (Schindler & Kerkhoff, 1997). Trunk rotation further overcomes pathologically enhanced saccadic reaction times to contralesional stimuli (Karnath et al., 1991), and also affects delayed visual evoked potentials for the left hemi-field in patients with left-sided neglect (Spinelli & Di Russo, 1996). Besides, leftward turns of the head are associated with increased recall of items imagined in contralesional space (Meador et al., 1987). Regarding the long-term effects of trunk rotation, results are controversial. One study reported improved performance in conventional visuospatial neglect- and “activities of daily living”-tests after one month of daily training (Wiart et al., 1997). A more recent 1-month training study indicated no sustained effects of trunk rotation on visuospatial or motor performance in patients with neglect (Fong et al., 2007). Contralesional neck muscle vibration—a related propioceptive stimulation technique—induces stable lasting recovery in visual neglect for longer than one year after treatment (Schindler et al., 2002; Johannsen et al., 2003).

Galvanic vestibular stimulation is a painless, non-invasive, and easily applicable vestibular stimulation technique (Utz et al., 2010). Current research indicates that it successfully reduces various components of spatial neglect deficits including the typical rightward deviation in line bisection (Utz et al., 2011), the counterclockwise tilt of the subjective visual vertical (Saj et al., 2006), and the visuo-constructional deficits in the Rey figure copy (Wilkinson et al., 2010). Similar positive impacts on visuospatial neglect deficits come from transcranial direct current stimulation (tDCS) —a comparable technique—when applied over the lesioned parietal cortex (Sparing et al., 2009). Regarding long-term effects, repetitive application of GVS induces lasting improvements in left-sided tactile extinction (Kerkhoff et al., 2011). Nevertheless, there are still too few studies to allow a validated judgment on long-term therapeutic potentials of GVS (Kerkhoff & Schenk, 2012).

The present results imply that primary sensory stimulation techniques do not only improve a variety of *spatial* neglect symptoms, but also modulate *temporal* processing deficits in this disorder. This finding suggests a clear interaction of multimodal space and time-processing mechanisms in the brain. The mediating mechanism for this seems to rely on the manipulation of attention. It remains to be investigated whether the amelioration of time deficits in neglect patients depends on a general increased attentional arousal, as suggested by results in study 1 and the work from Robertson and colleagues on alerting cues (Robertson et al., 1998); or whether it works through guiding attention in physical or representational (time) space, as indicated by study 2 and previous findings on prism adaptation (Frassinetti et al., 2009; Magnani et al., 2011; Oliveri et al., 2013). Thus, as a first perspective, I suggest investigating effects of OKS on distorted TOJ and time reproduction in neglect. As demonstrated so far, OKS achieves to mediate attention to the contralesional side in these patients (Kerkhoff, 2001; Kerkhoff, 2003a; Kerkhoff et al., 2012). In this way, it ameliorates visual and auditory deficits (Pizzamiglio et al., 1990; Mattingley et al., 1994; Kerkhoff et al., 1999; Kerkhoff, 2000; Schindler & Kerkhoff, 2004; Reinhart et al., 2011), inducing long-lasting improvements (Kerkhoff et al., 2012). The effects of OKS on TOJ in healthy participants observed in study 3 suggest positive influences on the prior entry phenomenon in neglect patients. As a second perspective, I point out that the observed sustained effects of a few GVS sessions reveal an interesting choice for treatment that should be further investigated in future studies.

5.2.2. Time-space interactions and the mental time line

In study 1, trunk rotation similarly affected performance of healthy individuals and neglect patients while reproducing temporal intervals. Both samples generated shorter intervals when the trunk was rotated to the right. This is in contrast to a hypothesized shift of the egocentric reference to the right side of a mental time line. It also opposes known effects of body rotation on visuospatial tasks (Chokron & Imbert, 1995; Schindler & Kerkhoff, 1997; Grubb & Reed, 2002), and tasks involving representational space (Meador et al., 1987; Lötscher et al., 2008). Hence, the data oppose the hypothesis of exploring a left-to-right MTL during time reproduction/bisection. In study 3, I observed that temporal order judgments were influenced by OKS to the side of directed attention in space. The TOJ task is a more concrete example of time-space interactions, as the subsequent presentation of adjacent stimuli holds both spatial and temporal information (Roberts et al., 2012). It may thus not disentangle whether changed performance depends on an altered exploration of physical, or of temporal representational space. To conclude, the present work implies that time and space processing interact in the brain; however, it may not support the idea of a systematic left-right modulation of time perception in tasks were spatial information is irrelevant.

Current research points towards attention as being the critical link for time-space interactions (Vicario et al., 2007; Frassinetti et al., 2009). For example, healthy subjects judge attended stimuli to last longer than non-attended stimuli, analog to the everyday notion and the saying “a watched pot never boils” (Mattes & Ulrich, 1998; Enns, Brehaut, & Shore, 1999; Tse, Intriligator, Rivest, & Cavanagh, 2004; Yeshurun & Marom, 2008; Cicchini & Morrone, 2009; Seifried & Ulrich, 2011). The same effect holds true for neglect patients (Basso et al., 1996). Attention also influences the perception of temporal order. Temporal order judgments can be modulated by both endogenous and exogenous cues guiding visual attention in space (Shore et al., 2001; Schneider & Bavelier, 2003; Spence & Parise, 2010; Teramoto et al., 2004; Teramoto et al., 2008). The present work gives further evidence to these investigations by demonstrating that small-field OKS effectively alters TOJ in healthy individuals.

The observation that directing attention to the left or right hemispace also influences performance in “pure” time perception tasks, led some authors to suggest that time intervals are represented in a horizontal time line with shorter durations encoded to the left of longer durations. Thus, according to this MTL, prism adaptation shifting attention leftwards leads healthy subjects to reproduce smaller intervals in comparison to their performance after opposing prism effects (Frassinetti et al., 2009). The result has been confirmed in patients, too (Magnani et al., 2011; Oliveri et al., 2013). Leftward OKS similarly modulates time reproduction (Vicario et al., 2007); nevertheless, the interpretation of a systematic effect according to the MTL is questionable in this study (see discussion in section 2.4.2.). Notably, the automatic activation of a left-to-right MTL during the perception or reproduction of time intervals is definitely not confirmed at the moment. Vallesi and colleagues report that they did not observe a STARC effect when duration was task irrelevant (Vallesi et al., 2008). A recent work indicates that performance in time reproduction tasks is highly susceptible to methodological artifacts (Riemer, Trojan, Kleinböhl, & Hölzl, 2012). Other studies suggest that the nature of time-space interactions might generally be based on task affordances (Yates, Lötscher, & Nicholls, 2012; Fabbri, Cancellieri, & Natale, 2012). Regarding Walsh's ATOM theory, asymmetries between the processing of time, space, and other quantities seem to exist (Yates et al., 2012). In contrast to the STARC effect, the SNARC effect does not depend on the relevance of magnitude information to the task, indicating an automatic activation of the mental representation of numbers (Dehaene et al., 1993; van Galen & Reitsma, 2008). Also, numerical information interferes with time processing, but temporal information does not interact with number processing, hereby challenging the idea of a general magnitude system in the brain (Droit-Volet, Clément, & Fayol, 2003; Dormal et al., 2006; Roitman et al., 2007). In the light of this background, the present work gives further evidence for time-space interactions by showing that sensory stimulation techniques known to modulate space perception affect the processing of time, too. However, it cannot confirm the automatic activation of a left-to-right representation of temporal intervals in tasks where spatial information is irrelevant. Further investigations are needed to explore the existence of a MTL. As a perspective, future research may take advantage of the broad experiences in the field of number cognition research.

5.2.3. Effects of culture on time perception

As a novel result, the present thesis demonstrates that performance in the TOJ task is co-related to field-dependence; thus accumulating further evidence for the interaction between space and time processing. Nevertheless, although field-dependence has been associated with cross-cultural differences between East Asians and Westerners, I found TOJ to be comparable between Chinese and German subjects, indicating no differences in basic time or space perception.

Current psychological anthropology holds an increasing body of arguments for cross-cultural differences in higher cognitive processes, such as perceptual categorization (Chiu, 1972; Norenzayan et al., 2002; Ji et al., 2004; Kriukova, 2012) or time concepts (Boroditsky, 2001; Núñez & Sweetser, 2006; Fuhrman & Boroditsky, 2007; Boroditsky et al., 2011). Some researchers have indicated that culture even influences attentional and perceptional processes, with Easterners relying more strongly on the background information during visuospatial tasks than Westerners (Ji et al., 2000; Masuda & Nisbett, 2001; Kitayama et al., 2003; Chua et al., 2005; Masuda & Nisbett, 2006). Other authors were not able to replicate the cultural differences during background processing (Gutchess et al., 2006; Rayner et al., 2007; Goh et al., 2007), questioning general cross-cultural distinctions in basic space perception. The present data are in line with this latter notion, suggesting that positive results of sensory stimulation techniques in Western patients with spatial neglect may be generalized across cultures. Nevertheless, the subject might be more complex. Gutchess and Goh revealed that some cross-cultural differences in *central object* processing develop with age, being significantly more pronounced in elderly than younger adults (Gutchess et al., 2006; Goh et al., 2007). The authors propose that in these times, cross-cultural differences are diminishing in young individuals due to rapid changes and internalization of Western values in Asian societies (Goh et al., 2007). As a limitation of the present work, the sample in study 3 was restricted to healthy college students. Hence, as a perspective for future investigations, I strongly suggest repeating the experimental design in a cross-cultural group of *elderly* subjects. Second, I propose to extend the cross-cultural research on perceptual differences to neurological populations and to examine differences in susceptibility to certain treatment techniques. Given cultural differences, these investigations would allow to establish culture-adequate therapy option, leading to a more efficient rehabilitation process in the respective individual.

5.3. Final conclusions

In this dissertation I found clear evidence for time and space interactions in the brain. First, neglect patients with visuospatial deficits showed additional distortions in time reproduction and temporal order judgments. These timing deficits could be ameliorated by Galvanic vestibular stimulation and trunk rotation, which are sensory stimulation techniques that activate brain structures involved in the processing of vestibular and propioceptive information. Sustained effects after repetitive GVS application suggest this method as a promising treatment option in neglect. Second, this work further revealed effects of trunk rotation on time perception in healthy individuals. Their performance was not modulated according to the hypothesis of a MTL, indicating no automatic activation of a left-to-right representation of temporal intervals in task where spatial information is irrelevant. Third, I found that temporal order judgments were influenced by small-field optokinetic stimulation in a healthy cross-cultural sample. Performance between Chinese and German participants was identical, suggesting no cultural differences in space and time perception. The positive effects of OKS on neglect symptoms might thus be comparable across cultures.

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Are time and space linked? The present work examines associations between time and space perception in the brain. Several sensory stimulation techniques known to modulate space perception are applied in time tasks—based on the notion that time processing should be influenced if it interacts with spatial information. As subjects, individuals with distinct space perception are recruited. Study 1 examines the impact of horizontal head and trunk rotation on time reproduction in patients with neglect and healthy individuals. Study 2 investigates the effect of Galvanic vestibular stimulation (GVS) on temporal order judgments in right brain damaged patients. And study 3 analyzes the influence of optokinetic stimulation (OKS) on temporal order judgments in healthy German and Chinese participants, considering possible cross-cultural differences such as field dependence. Based on the present results, the author suggests that time and space processing interact to a certain extent in the brain.

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