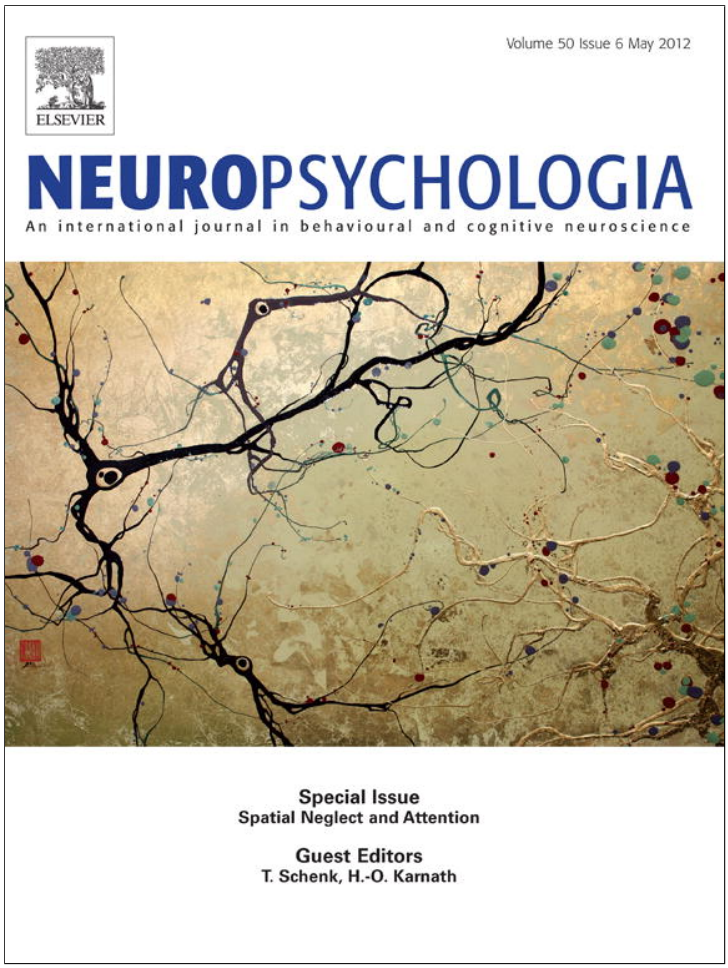

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Recovery from auditory and visual neglect after optokinetic stimulation with pursuit eye movements – Transient modulation and enduring treatment effects

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ABSTRACT

Optokinetic stimulation (OKS) modulates many facets of the neglect syndrome. This sensory stimulation technique is known to activate multiple brain regions (temporo-parietal cortex, basal ganglia, brain stem, cerebellum) some of which are involved in auditory and visual space coding. Here, we evaluated whether OKS modulates auditory neglect *transiently* and induces a sustained effect (Study 1), and whether repetitive OKS *permanently* recovers auditory neglect (Study 2). In Study 1, 20 patients with visuospatial neglect and auditory neglect in an auditory midline task following rightsided stroke were randomly allocated to an experimental and a control group matched for neglect severity and socio-demographic factors. Both groups showed a stable, pathological shift of their auditory subjective median plane (ASMP) in front space to the right side. During leftward OKS the experimental group showed a complete normalization of the shift of the ASMP, which endured until 30 min poststimulation, and returned almost to baseline values 24 h after OKS. In contrast, the control group who viewed the identical but static dot pattern, showed neither change in their ASMP during this condition, nor any significant change at 30 min or 24 h poststimulation. In Study 2, we show in two samples of neglect patients ($N = 3$ each) that repetitive leftward OKS with smooth pursuit eye movements as a therapy induces lasting improvements in auditory (the ASMP) and visual neglect while visual scanning therapy yielded no measurable effects on auditory *and* significantly smaller effects on visual neglect. In conclusion, the experiments show that a single session of OKS induces rapid though transient recovery from auditory neglect including a sustained effect after termination of stimulation, while *repetitive* OKS therapy yields enduring and multimodal recovery from auditory and visual neglect. OKS therapy with pursuit eye movements therefore represents a multimodally effective and easily applicable technique for the treatment of auditory and visual neglect.

1. Introduction

Unilateral lesions of the right cerebral hemisphere often cause a conspicuous neurological syndrome where the patient ignores visual, auditory or tactile stimuli in his contralesional hemispace, termed multimodal neglect (Karnath, Milner, & Vallar, 2002). While this syndrome may affect all modalities the deficits in the visual modality have been investigated most often and in greater detail than in the tactile or auditory modality. In audition, patients often show an ipsilesionally directed error when localizing auditory stimuli in the horizontal (left–right) axis (Bellmann, Meuli, & Clarke, 2001; Bisiach, Cornacchia, Sterzi, & Vallar, 1984; Soroker, Calamaro, Glicksohn, & Myslobodsky, 1997). In particular, patients with right *parietal* lesions show this localization deficit in auditory neglect (Bellmann et al., 2001; Clarke & Bellmann Thiran, 2004). Interestingly, spatial neglect seems to affect selectively the preattentive processing of audiospatial stimuli while that of non-spatial auditory features appears largely preserved (Deoull, Bentin, & Soroker, 2000). In contrast, lesions of the *right basal ganglia* more often tend to cause auditory extinction (Bellmann et al., 2001), although an early study by Heilman and Valenstein (1972) identified lesions of the right inferior parietal lobule in 9/10 patients with auditory extinction. This finding indicates that auditory extinction may result from lesions to different cortical areas. In auditory extinction, patients fail to report stimuli applied to the contralesional ear when simultaneously another auditory stimulus is presented to

Abbreviations: OKS, optokinetic stimulation; ASMP, auditory subjective median plane.

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the ipsilesional ear (De Renzi, Gentilini, & Pattacini, 1984; De Renzi, Gentilini, & Barbieri, 1989; Hugdahl & Wester, 1994; Spierer, Meuli, & Clarke, 2007). With respect to the nature of the underlying deficit, Deoull and Soroker (2000) elegantly showed that spatial localization and reporting the identity of a contralesional auditory stimulus may dissociate. Although 13 out of 14 patients in their study with auditory extinction performed at chance-level when requested to report the left-ear stimulus, the same patients performed clearly above chance when they had to report the identity (not location) of the extinguished stimuli.

As many neglect patients suffer from a poor long-term outcome due to their multiple deficits (Jehkonen et al., 2000), increasing efforts have been made in the last decade to develop novel and more effective treatments (Kerkhoff, 2003; Luauté, Rode, Jacquin-Coutois, & Boisson, 2006b). Several novel treatments based in part on earlier studies using sensory stimulation techniques, i.e. neck-proprioceptive (Schindler, Kerkhoff, Karnath, Keller, & Goldenberg, 2002) or optokinetic stimulation (Kerkhoff, 2003), or techniques for attentional modulation or sensory re-processing using prisms (Sturm, Thimm, & Fink, 2006; Kortte & Hillis, 2011) have shown that neglect phenomena can be reduced significantly by such techniques, both transiently and permanently. However, up to now most of these studies have focused on *visual* neglect phenomena (Kortte & Hillis, 2011), while the question how *auditory* neglect, or audio-spatial deficits in general can be modulated transiently or treated permanently has received little attention.

Clues to the modulation of auditory extinction or auditory neglect may be derived from two relevant studies. (Schüeli, Henn, & Brugger, 1999) assessed word identification (function words) in a dichotic listening test and found the typical right-ear advantage in a baseline condition in healthy subjects. Interestingly, during sinusoidal left-to-right rotation of the subjects in a turning chair with sudden stops this right ear advantage was no longer present because of an increased identification rate of words delivered to the left ear. This result was not due to changes of hearing sensitivitiy during chair rotation. Put differently: vestibular stimulation modulated the right-ear dominance in dichotic listening in healthy subjects. In a similar study (Hiscock, Hampson, Wong, & Kinsbourne, 1985) a diminished right-ear-advantage in dichotic listening was demonstrated due to an increase in left-ear identifications during right-to-left optokinetic stimulation (OKS) with vertical stripes in healthy subjects. Together, both studies show that vestibular or OKS stimulation modulate the left-right pattern in dichotic listening in healthy subjects, and suggest that similar effects might be obtained in patients with auditory neglect or extinction.

In recent studies using OKS we and other groups showed that repetitive optokinetic stimulation eliciting active smooth pursuit eye movements towards the contralesional hemispace leads to a substantial and lasting improvement in patients with *visuospatial* neglect (Kerkhoff, Keller, Ritter, & Marquardt, 2006a; Schröder, Wist, & Hömberg, 2008; Sturm et al., 2006; Thimm et al., 2009). With respect to the mechanisms of OKS it is known that OKS in healthy subjects activates multiple cortical and subcortical regions (temporo-parietal cortex, basal ganglia, brain stem, cerebellum (Bense et al., 2006; Dieterich, Bucher, Seelos, & Brandt, 1998; Konen, Kleiser, Seitz, & Bremmer, 2005), some of which are involved in eye movements and gaze shifts, as well as auditory and visual space coding [parietal, cf. (Schlack, Sterbing-D'Angelo, Hartung, Hoffmann, & Bremmer, 2005). In their study Schlack et al. (2005) showed largely congruent and overlapping receptive fields of neurons in the monkey's ventral intraparietal cortex for visual and auditory spatial stimuli, which enables the integration of visual and auditory information in a modality-invariant representation of external space. This finding is compatible with the multimodal (visual, auditory) deficits frequently found in neglect patients after parieto-temporal lesions (Pavani, Ladavas, & Driver, 2003). Previous studies using OKS in neglect patients have shown significant short-term modulatory effects in visual line bisection (Mattingley, Bradshaw, & Bradshaw, 1994), the subjective visual straight ahead (Karnath, 1996), visual size distortions (Kerkhoff, Schindler, Keller, & Marquardt, 1999b; Kerkhoff, 2000), visual distance judgments (Schindler & Kerkhoff, 2004), tactile extinction (Nico, 1999), tactile search (Keller, Lefin-Rank, Losch, & Kerkhoff, 2009), motor deficits (Vallar, Guariglia, Nico, & Pizzamiglio, 1997a), temporal judgments in healthy subjects (Vicario, Caltagirone, & Oliveri, 2007), and even in the mental number line in neglect (Salillas, Grana, Juncadella, Rico, & Semenza, 2009). Moreover, neurophysiological studies in awake animals indicate a significant optokinetic after-nystagmus after termination of the visual stimulation, which is related to sustained neural activity in brain-stem vestibular nuclei (Waespe & Henn, 1977). This finding indicates a significant sustained effect of OKS after termination of the stimulation and shows that OKS produces modulation effects that clearly outlive the sensory stimulation period. This in turn is a prerequisite for an effective treatment of neglect-related deficits in patients using OKS.

If OKS activates brain regions involved in the visual *and* auditory coding of space, significant modulatory effects of OKS might be expected not only for visual but also for *auditory-spatial* tasks in patients with neglect. In line with this hypothesis, it has been shown recently that auditory motion cues influence visual neglect temporarily (Golay, Hauert, Greber, Schnider, & Ptak, 2005), and that visuomotor prism adaptation reduce leftsided, neglect-related deficits in dichotic listening (Jacquin-Courtois et al., 2010). Together, these studies indicate strong cross-modal (visual–auditory) interactions in spatial neglect and suggest that OKS may modulate auditory neglect, both transiently and permanently.

In the following we describe two studies investigating the effects of OKS on auditory neglect. Study 1 evaluated whether OKS to the contralesional side induces transient recovery from auditory neglect including an early sustained effect (at 30 min) and a later sustained effect (24 h) after stimulation. Study 2 tested whether repetitive OKS as a therapy over a period of 20 sessions improves auditory and visual neglect permanently. Based on the above mentioned mechanisms of OKS we hypothesized that a single sessions of OKS may lead to a rapid though transient improvement of auditory neglect (Study 1), whereas repetitive OKS (Study 2) could lead to enduring improvements of both auditory and visual neglect.

2. Study 1: transient effects of OKS on auditory neglect

2.1. Patients and visual neglect tests

2.1.1. Patients

20 patients (Table 1), all with a single, rightsided, stroke (ischemic infarction in all cases), were recruited on the basis of the results in two visual neglect screening tests (horizontal line bisection and digit cancellation, details see (Reinhart, Keller, & Kerkhoff, 2010) *and* leftsided auditory neglect in a task assessing the auditory subjective median plane (see below) were randomly assigned (by a person not involved in the study who drew lots) to either an experimental group or a control group ($N = 10$ each). Patients in both groups did not differ significantly in neglect severity, chronicity of the brain damage, associated deficits, and socio-demographic variables (see statistics in Table 1). Informed consent was obtained from all subjects prior to inclusion in the study. All experiments performed here were conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki II.

Table 1
Patient data in the two samples of neglect patients (Study 1); OKS: patients receiving OKS-stimulation; control group: patients receiving control stimulation (see text for further details).

	OKS group ($n = 10$)	Control group ($n = 10$)	Statistical comparison
Age, years, mean, range	58.2 (37–74)	59.4 (36–73)	$T = 0.3_{(18)}$, $p > 0.05$, n.s.
Sex (male/female)	7/3	7/3	χ^2, $p > 0.05$, n.s.
Etiology			
Ischemic	10	10	–
Lesion localization[a]			
Frontal	2	3	–
Temporal	9	9	–
Parietal	7	7	–
Occipital	1	0	–
Basal ganglia	1	1	–
Side of neglect	10 leftsided	10 leftsided	–
Months post stroke (MD, range)	3.4 (1–10)	2.6 (1–5)	$T = 0.89$, df = 19, $p > 0.05$, χ^2, $p > 0.05$, n.s.
Left hemiparesis (number of patients)	8/10	10/10	χ^2, $p > 0.05$, n.s.
Left homonymous Visual Field Defect (number of patients)	10/10	9/10	χ^2, $p > 0.05$, n.s.
Number cancellation (omissions left/right, %)	52/20	79/34	Left: $T = 1.9$, df = 19, $p > 0.05$ Right: $T = 1.2$, df = 19, $p > 0.05$
Horizontal line bisection (deviation mm)	19.0 right	21.5 right	$T = 0.37$,df = 19, $p > 0.05$

R and L, right and left; M/F, male/female; MD, median; n.s., not significant. Cancellation test: 20 numerals have to be cancelled from a total of 200 numerals randomly distributed on a sheet of paper (29.7 × 21.9 cm); normal cut-off is 1 omission per hemispace. Line bisection: a horizontal line (200 × 5 mm) has to be transsected manually with the ipsilesional hand, the deviation from the true midline is measured in mm. Normal cut-off is ±5 mm around the true midline. Neglect screening tests according to Kerkhoff, Keller, et al. (2006).

[a] Note that the majority of patients had lesions in multiple lobes within the right cerebral hemisphere, especially in the parietal and temporal lobes.

2.1.2. Visual neglect tests

Patients were assessed with two screening tests of visual neglect: horizontal line bisection and number cancellation. A 200 mm long and 0.4 cm thick, horizontal line was printed in black on a white sheet of paper (size: 29.7 × 21 cm; cf. Reinhart et al., 2010) and shown 3 times to every patient. Patients were instructed to mark the centre of the line with a pencil using their ipsilesional right hand. The deviation (in mm) from the true midpoint was the dependent measure. In number cancellation, subjects were instructed to cross out a specific numeral (i.e. "all number 5") on a 29.7 × 21 cm large sheet of paper, which contained 200 numerals (10 of each numeral from 0 to 9 = 100 numerals in each hemifield). Every numeral occurred 10 times per hemifield so that all numbers (ranging from 0 to 9) occurred with identical frequency on each side of the test sheet. Percent omissions on the left side was the dependent measure reported here.

2.2. Monaural hearing tests

All subjects were screened with a Philips HP 8741/31 or in some cases with a Praecitronic KH-70 puretone audiometer in a sound-shielded testing chamber for the assessment of peripheral hearing functions. None of the patients showed an unilateral hearing loss of >10 dB in any of the frequency ranges tested (0.125, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4.5, 8 and 10 kHz; see Table 2 below).

2.3. Auditory subjective median plane (ASMP)

The task was already described in detail in a recent report (Kerkhoff, Schindler, et al., 2006), therefore only a short description is given here. Subjects heard white-noise, 3 s lasting auditory stimuli (sound pressure level: 75 dB) via headphones (AKG240). Stimuli were presented randomly in the front space at 37 virtual sound source positions along the azimuth plane using binaural simulation techniques (Fig. 1a). This method has been used successfully in previous studies with neglect patients (Tanaka, Hachisuka, & Ogata, 1999). In contrast to free-field auditory stimulation, the delivery of stimuli via headphones may eliminate potential artefacts due to shifts in body orientation (head, trunk) in neglect patients (Tanaka et al., 1999). The stimuli used here contain information about interaural time and intensity differences as well as spectral localization cues provided by the pinna. Thus, the presented sounds had natural quality, and are perceived as coming from the front space and are not perceived as "inside the head". Since "white noise" stimuli are composed of numerous, overlaid single frequencies the potential influences of a monaural sensitivity reduction in a particular frequency range are minimized by this technique. Three trials were presented for each source position, resulting in a total of 111 trials per condition. Half of the trials were presented in left hemispace, the other half in right hemispace. Subjects had to indicate in every trial, whether the up-coming sound was exactly in their subjective median plane, or to the left/right of it. This was

Table 2
Mean peripheral (monaural) hearing acuity (sensitivity loss in dB) in the two neglect patient samples of Study 1 (the standard error of the mean is given in brackets).

Neglect Group	Ear	Frequency (kHz)										
		0.125	0.25	0.5	0.75	1	1.5	2	3	4	6	8
OKS group ($N = 10$)	L	24.7 (2.4)	25.1 (1.5)	25.0 (2.7)	27.5 (2.6)	28.5 (3.0)	30.3 (2.9)	31.2 (2.5)	35.8 (3.9)	39.8 (5.5)	43.6 (4.6)	52.9 (4.4)
OKS group ($N = 10$)	R	25.7 (2.5)	25.3 (1.5)	26.2 (1.7)	27.2 (0.7)	28.1 (1.1)	31.1 (2.1)	34.7 (2.7)	36.4 (3.6)	40.3 (4.6)	46.2 (3.7)	48.6 (4.0)
Control Group ($N = 10$)	L	24.2 (2.6)	22.3 (1.9)	22.1 (1.1)	23.4 (1.8)	24.1 (2.0)	25.0 (2.2)	26.6 (2.4)	29.6 (3.8)	35.8 (4.0)	40.4 (4.6)	50.5 (5.6)
Control Group ($N = 10$)	R	25.3 (1.5)	25.6 (1.8)	24.6 (1.6)	25.4 (1.1)	25.3 (2.01)	25.3 (3.7)	27.2 (3.5)	29.9 (4.0)	36.2 (4.1)	41.8 (5.3)	46.8 (5.3)

L, left; R, right.

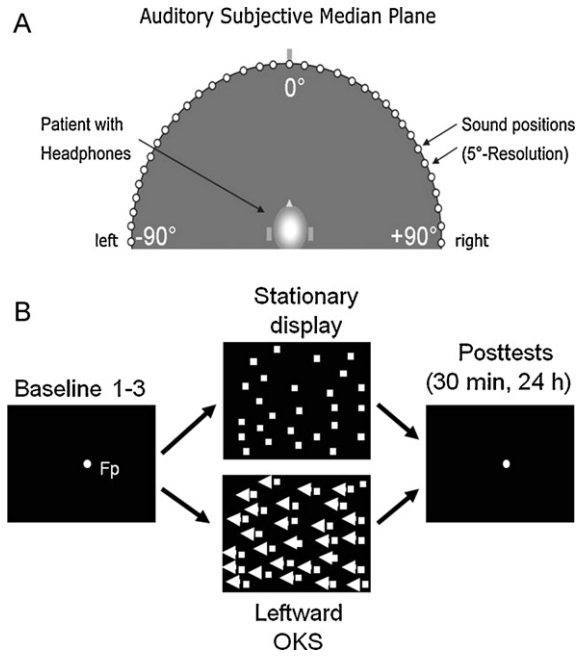

Fig. 1. (A) Layout of the task for determining the auditory subjective median plane (see text for details). (B) Schematic layout of the experimental setup and sequence of conditions in both patient samples; Fp, fixation point. Note that the arrows pointing to the left in the lower figure only serve to indicate the motion direction of all stimuli on the screen, but were not visible during the experiment.

explained to the patients as the position where they considered the auditory stimulus as exactly in the median spatial position in the horizontal (left–right) axis. All subjects were tested with the psychophysical method of limits (Engen, 1971). Hence, if the subject responded with "yes" (="sound was in the ASMP") after initial presentation of the sound this trial was counted as a valid trial. If subjects responded with "no" (="sound was not in the ASMP") after a given trial, the experimenter subsequently presented an auditory stimulus, which was 5° closer to the objective midline position and the psychophysical procedure was repeated again, until the subject responded with "yes" and the trial was finally completed. All subjects were informed beforehand that they would hear auditory stimuli in *front space.* If they perceived a sound as coming from the back (so-called front-back-confusion) they were instructed to respond verbally with "back" and this trial was voided and later in the experiment repeated. No time pressure was present so that subjects could perform the test at a comfortable pace such that no data were lost due to time constraints.

In order to compare the effect of stimulus presentation in hemispace (left and right) we computed the mean deviation from the objective median position (0°; see Fig. 1a) for all valid trials starting in the *left* hemispace and separately for those trials starting in the *right* hemispace. These two scores were used in every subject and every timepoint of measurement in the statistical comparisons reported below in Study 1. Normal cut-off data were available from 22 age-matched subjects (Kerkhoff, Artinger, & Ziegler, 1999a) for this task. Since no motor or pointing response was required by the subjects, auditory impairments in this task cannot be influenced by inaccurate pointing or impaired motor processes (Duhamel, Pinek, & Brouchon, 1986).

2.4. Experimental conditions

Subjects were examined in a dark and quiet room while their head was fixated in a head-and-chin-rest to avoid head shifts during auditory testing. Fig. 1b summarizes the experimental setup. Three baseline measurements of the ASMP were taken on three different days within a period of 7 days to establish stable baseline values for the ASMP task before beginning with the experimental procedures. The day after the third baseline the experimental group (further termed OKS group) received one session (20 min) of leftward optokinetic stimulation. To this purpose, the patients viewed a pattern of 150 yellow squares (size: 2°), which coherently and continuously moved on a black background to the left, neglected side (velocity: 9.4°/s). The subjects in the OKS group were instructed to follow the moving dots with their eyes *while* performing the ASMP task. The control group viewed the identical visual patterns as the OKS group, but these remained stationary on the screen. These patients were instructed to explore the stationary pattern with (saccadic) eye movements while performing the ASMP task, just as neglect patients are instructed during conventional visual scanning training (Kerkhoff, 1998). Two post-tests of the ASMP were performed: one 30 min after cessation of the OKS stimulation respectively stationary dot pattern ("early post-test"), and the other 24 h post stimulation ("late post-test"). During the three baseline and the two post-tests all patients fixated a small yellow fixation dot (0.5° diameter) in the middle of an otherwise black screen. The testing room was kept dark in all conditions (lighting: <50 lx), which effectively prevented the subjects from seeing any visual contours of the testing room or the screen. In the condition during OKS or control stimulation no fixation spot was shown in order to facilitate eye movements of the patients as suggested by the different instructions.

2.5. Statistics

For the analysis of the audiometric data, repeated measures MANOVAs were carried out with the between-subjects factor GROUP (Experimental vs. Control group) and the within-subjects factors EAR (left vs. right) and FREQUENCY (11 frequencies). For the data of the ASMP, repeated measures MANOVAs were carried out with the between-subjects factor GROUP (Experimental vs. Control group) and the within-subjects factors MEASUREMENT POINT (6:3 baseline measurements, 1 test during the experimental manipulation, 2 post-tests, 1 follow up test), and HEMISPACE (2: left vs. right hemispace in which the auditory stimulus was presented). The reported p-values were Greenhouse–Geisser corrected if sphericity was violated. Within-group comparisons were performed with contrasts or dependent t tests.

3. Results

3.1. Monaural hearing tests

Table 2 summarizes the data of the two samples in the monaural (peripheral) hearing tests. Both groups showed comparable hearing sensitivity for both ears. Repeated measures MANOVAs showed neither significant effect of GROUP [$F(1,18) = 1.37$; $p = 0.26$], nor of EAR [$F(1,18) = 0.31$; $p = 0.58$]. A significant effect of FREQUENCY [$F(10,180) = 29.65$; $p < 0.001$] revealed that the auditory sensitivity loss was significantly greater for higher frequencies than for lower frequencies. No significant interactions were noted (largest $F = 1.58$; $p = 0.18$). Hence, both neglect patient groups showed comparable monaural hearing functions without any significant group differences, nor any significant interaural differences, which might interfere with the ASMP task. The only significant result was the expected and well-known sensitivity decline with higher frequencies, which is typical for human subjects at age 60 (Brenninghaus & Lenarz, 2007).

To analyze potential influences of monaural hearing sensitivity on the ASMP we computed Pearson correlation coefficients

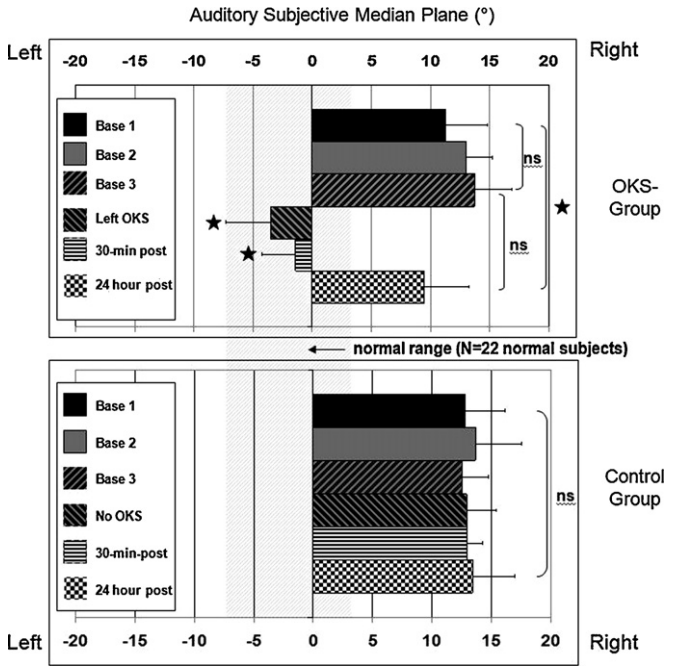

Fig. 2. Mean values (degrees, ±SEM) in the auditory subjective median plane in front space in the two patient samples with auditory neglect as measured three times before stimulation (baseline 1–3), during OKS respectively during no OKS (control) conditions, and at 30 min post-stimulation. Note the significant improvement in the OKS group during OKS and at 30-min-post-stimulation and at 24-h-post-stimulation, whereas the control group showed a stable, pathological deviation of their ASMP towards the right, ipsilesional side over all measurements. The shaded area indicates the complete range of performance in 22 normal subjects for this task (Kerkhoff et al., 1999a). Asteriks indicate significant change with $p < 0.05$. Ns, not significant. Asteriks indicate significant differences with $p < 0.05$; n.s., not significant; OKS, optokinetic stimulation.

(two-tailed, alpha-level 0.05) between the 3 baseline measurements of the ASMP and the results of the monaural hearing tests for both ears and each frequency in the 20 neglect patients. Only one out of 60 correlations reached statistical significance: sensitivity of the right ear at 0.75 Hz correlated with the first baseline of the ASMP ($r = -0.467$, $p < 0.05$), but not with the second baseline of the ASMP ($r = -0.297$, $p > 0.05$, n.s.), nor with the second baseline of the ASMP ($r = -0.252$, $p > 0.05$, n.s.). No other significant correlation was found. Hence, monaural hearing sensitivity had no consistent, measurable influence on the results of the ASMP.

3.2. Auditory subjective median plane (ASMP)

3.2.1. Mean deviation of the ASMP

Fig. 2 summarizes the results graphically. Both groups showed a comparable, pathological shift of their ASMP to the right, ipsilesional side as measured over the three baseline tests. During leftward OKS stimulation the OKS group showed a significant relocation of their initially deviated ASMP into the normal range (−2° to the left), which endured until 30 min post-stimulation (−1° to the left; Fig. 2, upper diagram), and nearly returned to baseline values 24 h later (+9.0° to the right side). In contrast, the control group showed no significant change in the ASMP across all 6 timepoints of measurement (Fig. 2, lower diagram). Notably, no change was observed in the condition where subjects were instructed to make saccadic scanning eye movements when scanning the visual display.

We subjected the results in the ASMP (mean) to a repeated measures MANOVA. This revealed no significant effect for hemispace [$F(1,18) = 0.07$; $p = 0.80$)], nor for the interactions hemispace × group, hemispace × measurement point, hemispace × measurement point × group (largest $F = 0.61$; $p = 0.69$).

There was a significant interaction between group and timepoint of measurement [$F(3,90) = 5.24$; $p = 0.003$]. Planned contrasts revealed no significant change from baseline 1 to 3 (largest $F = 0.54$; $p = 0.47$), thus ruling out spontaneous improvements in auditory neglect. As hemispace showed no significant effect, the ASMP data from the two hemispaces were pooled for all subsequent analyses. The OKS group improved in the ASMP *during* OKS (smallest $t(9) = 2.70$; $p = 0.02$) and at the post-test 30 min *after* OKS (smallest $t(9) = 2.97$; $p = 0.02$), when compared with all baseline measurements. The mean ASMP measured during-OKS and 30-min-after-OKS did not differ significantly from each other ($t(9) = 0.75$; $p = 0.47$), and was not significantly different from the mean performance of 22 normal control subjects (−1.9° to the left; cf. Kerkhoff, Artinger, et al., 1999), one-sample *t*-tests, df = 9; $t = -0.413$; $p > 0.05$ during OKS; and df = 9; $t = 0.177$; $p > 0.05$ tested 30 min after OKS). This indicates full normalization of their initial deviation in the ASMP in the OKS patient group during and 30 min after OKS. There was no significant effect 24 h after OKS (smallest $t(9) = 0.90$; $p = 0.40$).

Post hoc tests showed no significant change in the ASMP in the control group over the 6 timepoints of measurement (largest $t(9) = 0.37$; $p = 0.72$). Their performance was significantly different from the mean performance of 22 normal control subjects in the ASMP in all 6 timepoints of measurement (one-sample *t*-tests, df = 9; smallest $T = 3.999$; largest $p = 0.003$), thus indicating pathological task performance under all conditions.

During baseline measurements all 20 neglect patients showed a pathological, rightsided deviation of the ASMP in terms of a distorted auditory space that lay outside the normal values for this task (cf. Kerkhoff, Artinger, et al., 1999; Kerkhoff, Schindler, et al., 1999). A significant relocation of the initially rightward deviated ASMP towards the left side was seen in all 10 patients in the OKS neglect group during OKS, but in no case (0/10) in the control group. During OKS 4/10 patients scored completely in the normal range, while 6 scored too far to the left side. At 30-min-post-test, 6/10 OKS patients scored in the normal range, 3 scored too far to the left side, and 1 too far to the right side in relation to the normal range (see above). At 24-h-follow-up test, 3/10 neglect patients still scored in the normal range, while 7 scored too far to the right side. In contrast, all 10 patients in the SCAN group scored outside the normal range (too far to the right side) in the ASMP during stimulation, at 30 min follow-up-test, as well as at 24-h-post-test.

In addition, we analyzed our data with respect to alloacusis. Alloacusis implies that a sound source from one hemispace is reported as having originated from the other hemispace in front of the subject. This pattern of results was not found in any of our 20 neglect patients studied in Exp. 1. Auditory extinction to double simultaneous stimulation or dichotic listening was not tested in this study and we therefore cannot report whether our patients also had auditory extinction in such tasks.

3.2.2. Standard deviation of the ASMP

To analyze whether general attentional modulations occurred – potentially induced to a greater extent by the moving display in the OKS group and to a lower extent by the stationary display in the control group – we computed the effects of these two experimental manipulations (leftward OKS vs. stationary display in Exp. 1) on the standard deviation of the 74 trials in the measurements of the ASMP delivered per subject and during every timepoint of measurement in Exp. 1. ANOVA showed no significant effects of Timepoint of Measurement [$F(5,90) = 1.058$; $p = 0.389$], nor of Experimental Group [$F(1, 18) = 0.610$; $p = 0.445$], nor any significant interaction between Timepoint of Measurement × Group [$F(5,$

Table 3
Mean standard deviations in the auditory subjective median plane (ASMP; in°) in the 2 patient groups with leftsided spatial neglect ($N = 10$ neglect patients in the group receiving OKS-stimulation; $N = 10$ neglect patients in the control group). See text for more details.

	Baseline1	Baseline 2	Baseline 3	During Stimulation	30 min after stimulation	24 h post stimulation
OKS group ($N = 10$)	45.5	40.5	42.6	51.9	45.5	34.2
Control group ($N = 10$)	33.5	32.9	32.9	36.8	44.6	38.7

90) = 0.962; $p = 0.445$]. Table 3 summarizes the standard deviations of the ASMP in both groups.

3.3. Relation of auditory neglect to visual neglect measures

Pearson correlation coefficients were computed to evaluate to which extent visual and auditory measures of neglect were correlated. The ASMP correlated significantly with the number of left-sided omissions in the visual cancellation task ($r = 0.44$; $p < 0.05$, two-tailed), and with the rightsided deviation in horizontal line bisection ($r = 0.468$; $p < 0.05$, two-tailed).

3.4. Discussion Study 1

Our study shows that a brief period of OKS stimulation – when subjects are encouraged to perform active tracking eye movements towards the neglected side – leads to a rapid recovery of the pathological mean shift in the ASMP in patients with auditory neglect. Moreover, this sensory stimulation produced a significant sustained effect that outlasted the stimulation period by at least 30 min. During the 30-min and 24-h post-tests no visual stimulation was provided apart from the fixation spot during the ASMP test. Moreover, it is interesting to note that both the *immediate* and the *sustained effect at* 30 min showed a full normalization of the ASMP into the normal range in the neglect group receiving OKS. After OKS the performance of the experimental group lay completely within the normal range (indicated as the shaded area in Fig. 2) and did not differ significantly from the results of 22 normal controls (Kerkhoff, Artinger, et al., 1999) tested with the identical task (as revealed by the one-sample *t*-tests). Individual analyses showed that OKS induced a complete normalization of the ASMP in some neglect patients, which persisted at least for 30 min and in some cases up to 24 h after stimulation. In contrast, no improvement was observed in the control group who otherwise was comparable in all demographic and clinical variables, and importantly showed the same amount of auditory neglect in the ASMP task. As an aside, the repetitive measurements of the ASMP in both neglect groups neatly showed, that this component of auditory neglect can be measured quite reliably for several times without showing task improvements merely by retesting or other unspecific variables.

Interestingly, leftward OKS had no effect on the variability (expressed as the standard deviation) of the ASMP measurements, which were obtained from the same data. If general attentional capacity was better during leftward OKS than during vision of the same but stationary visual pattern – as might be hypothesized because motion might lead to a general increase in attention – this should have also resulted in a less variable performance and therefore smaller standard deviation during leftward OKS. No such effect was found. None of the two experimental modulations affected the standard deviation in the ASMP in any way (see Table 3). We take this as evidence in favor of a specific effect of leftward OKS on the direction of the shift in the ASMP and against an interpretation of our data as resulting merely from increased *generalized* attention induced by leftward motion. In the latter scenario we would have also expected effects of OKS on the standard deviation. We would like to add, that this interpretation by no means excludes an explanation of the OKS-effect in terms of a specific, lateralized effect that facilitates the directing of attention towards the left, neglected hemispace (see Section 4.4, below).

Finally, the degree of auditory neglect in the ASMP task was found to correlate significantly with the degree of *visual* neglect in two conventional visual neglect tests (digit cancellation and line bisection) thus underlining the frequent association of auditory and visual neglect. Put differently, this indicates multimodal neglect in our two patient samples. It is important to keep in mind that auditory neglect was assessed *after* the patients were selected on the basis of visual neglect tests. The reported correlations would have been even higher with the inclusion of a right-brain damaged patient group *without* spatial neglect since this would have increased variance, which in turn increases the correlation coefficients. However, even without such an additional group, the reported correlations show that auditory and visual neglect frequently covary. This significant relationship between visual and auditory neglect corroborates similar findings from earlier studies (Pavani, Husain, Ladavas, & Driver, 2004), and highlights the frequent multimodal (visual and auditory) nature of spatial deficits in patients diagnosed as having visuospatial neglect on the basis of visual neglect tests, as in the present study.

More generally, Study 1 shows an immediate normalization and re-orientation of the initially ipsilesionally shifted ASMP into a more symmetrical midline position. The demonstration of a sustained effect of up to at least 30 min indicates that this modulation effect is not simply due to the subjects' pursuit eye movements during the experimental manipulation, but persists until the post-test where subjects were again requested to fixate a central fixation spot in an otherwise completely dark room. Moreover, the saccadic scanning eye movements performed by the control group when exploring the very same dot pattern on the screen, which was shown dynamically in the OKS group did not induce a comparable normalization of the ASMP in the control group. However, as this group also fixated a central fixation dot in total darkness without any eye movements in the post-test, it appears unlikely that the non-improvement of the control group in the ASMP was simply the result of the scanning eye movements. Since both patient groups did not perform eye movements in the early post test (at 30-min) the clear difference in the ASMP between the groups both during and after the experimental manipulations must result from the leftward moving versus static display of the dot pattern. Finally, given the random and blind allocation of patients to the two patient groups both showing comparable auditory neglect in the ASMP and being well-matched with respect to clinical and socio-demographic variables it appears even more unlikely that the selective improvement of the ASMP in the experimental group was due to any yet unidentified group difference, which potentially may have precluded a comparable improvement of the ASMP in the control group.

In summary, the present study indicates, that OKS not only induces positive effects on visual neglect (Kerkhoff, Keller, et al., 2006), tactile extinction (Nico, 1999) or haptic search (Keller et al., 2009), but also shows *crossmodal* effects on auditory neglect. This leads to the question whether these short-term results can be turned into stable, long-term therapeutic improvements after *repetitive* OKS stimulation in neglect patients. For visual neglect, this long-term stability of repetitive leftward OKS stimulation has been recently shown in several independent studies from four

different groups (Kerkhoff, Keller, et al., 2006; Schröder et al., 2008; Sturm et al., 2006; Thimm et al., 2009). The present results suggest that OKS may be also a successful candidate for the treatment of one important component of auditory neglect, the pathological shift of the ASMP towards the ipsilesional side (Bellmann et al., 2001). As a caveat it must be kept in mind that patients with auditory neglect may also show other auditory deficits such as extinction or impaired *identification* of auditory stimuli in contralesional hemispace, and that we do not yet know whether OKS improves these related auditory deficits as well.

In the subsequent study (Study 2) we therefore explored whether *repetitive* OKS as a therapy applied over a period of 20 sessions (á 50 min) leads to an enduring improvement of auditory and visual neglect. To our knowledge, no published evidence is available, which shows a long-lasting recovery from auditory neglect after therapeutic interventions – hence no cure is currently available to treat auditory neglect and induce lasting improvements.

4. Study 2: Enduring effects of repetitive OKS therapy on auditory and visual neglect

4.1. Patients and methods Study 2

4.1.1. Patient samples

Six patients with leftsided visual and auditory neglect (see Table 4, for details) were recruited based on their performance in four visual neglect screening tests and pathological results in the ASMP task. Inclusion criteria were a single right-hemispheric lesion due to stroke (infarction or hemorrhage) and evidence of leftsided visual neglect in at least 2 out of the 4 screening tests, and a pathological rightward shift in the ASMP. In contrast, lesion size was no criterion for group allocation. Neglect therapy was initiated at the earliest possible moment when the patients were enrolled in our clinic and had completed the baseline period. In most patients this occurred after 2–3 months post-stroke (see Table 3, months since lesion). To our knowledge no specific neglect therapy was initiated in those clinics where the patients were enrolled before they were sent to our rehabilitation clinic. The patients were randomly allocated to either an OKS ($N=3$) or a SCAN ($N=3$) treatment group by having a person neither involved in the study nor associated with the clinic draw concealed papers from an envelope containing 6 sheets of paper stating either "OKS" or "SCAN". All but one patients had suffered from a unilateral, rightsided, ischemic infarction as documented by neuroradiological findings. One patient had suffered from a rightsided, intracerebral hemorrhage. We used CT scans, weighted MRI, or diffusion weighted MRI scans (Roberts & Rowley, 2003) to trace the lesions of the six patients. The brain scans of all patients were inspected and transferred manually onto the standard brain of MRIcro (Version 1.40; Rorden & Brett, 2000). Eight transversal slices in an anterior/posterior commissural orientation were used. The first slice showed inferior temporal gyri and posteriorly the pedunculi cerebelli at the level of the fifth cranial nerve. The last slice was located at the most rostral part of the brain (see Fig. 3, for the lesions of the patients and the position of the transverse sections). The relative lesion load of each patient, defined by the lesion delineated at the eight transversal slices, is shown in Table 3, and it was similar for both patients groups (average OKS group: 17.3 cm^3; average SCAN-group: 18.3 cm^3). All six patients showed medium leftsided visual and auditory neglect (see Table 3). Mann–Whitney tests revealed a slight difference (2.32°) with respect to the mean ASMP averaged over the 3 baselines before treatment between the two groups (OKS group: +18.62° to the right side, Scanning group: +20.92° to the right; $U=21975$; $z=-1.974$; $p=0.048$). Both groups did not differ in their degree of visual neglect as measured by the averaged baseline values before treatment in digit cancellation (%

Table 4
Patient data of 6 patients with right sided stroke and leftsided visual and auditory neglect (study 2). For further details see text.

Patient	Treatment	Age Sex	Etiology MSL	Lesion Localization	Lesion Volume (cm^3)	Visual field, field sparing°	Line bisection, ±deviation (mm)	Copying L/R	Cancel-lation omissions L/R %	Paragraph reading, % errors	Auditory subjective median plane (ASMP)
1	OKS	59/m	ICB, 4	R-par	12	Q, 20°	+7	−/+	3/0	Impaired, 79%	Rightward shift
2	OKS	74/f	MCA, 2	R-par	10,6	HH, 3°	+67	−/+	12/6	impaired, 22%	rightward shift
3	OKS	54/m	MCA, 3 Md = 3	R-par-temp	29,3	Normal	+40	−/+	3/0	slightly Impaired, 4%	rightward shift
Mean	OKS	62.3	3.0	–	17.3	2/3 impaired-	+38	3/3 impaired	6/2	3/3 impaired	3/3 impaired
4	SCAN	57/m	MCA, 9	R-par	16,7	HH, 2°	+8	−/+	3/0	Impaired, 15%	rightward shift
5	SCAN	59/m	MCA, 3	R-par-temp	8,6	Normal	+40	−/+	6/0	Impaired, 13%	rightward shift
6	SCAN	53/m	MCA, 2	R-par, BG	29,5	Normal	+28	+/+	9/1	Impaired, 12%	rightward shift
Mean	SCAN	56.3	4.6 MD = 3	–	18.2	1/3 impaired	25.3	2/3 impaired	6/0.3	3/3 impaired	3/3 impaired

Visual neglect was assessed by the following screening tests: Horizontal Line Bisection, Figure Copying (Copy), Number Cancellation and Paragraph reading. OKS, optokinetic stimulation therapy; SCAN, visual scanning therapy; VF, visual field; MSL, months since lesion; ICB, intracerebral bleeding; MCA, middle cerebral artery infarction; P/T/BG, parietal/temporal/basal ganglia; Q, homonymous, lower quadrantanopia; HH, homonymous, hemianopia; Md, median. The relative lesion load of each patient, defined by the lesion delineated at the eight transversal slices (see Fig. 3) was similar in both patient groups (average OKS: 17.3 cm^3; average SCAN group: 18.3 cm^3).

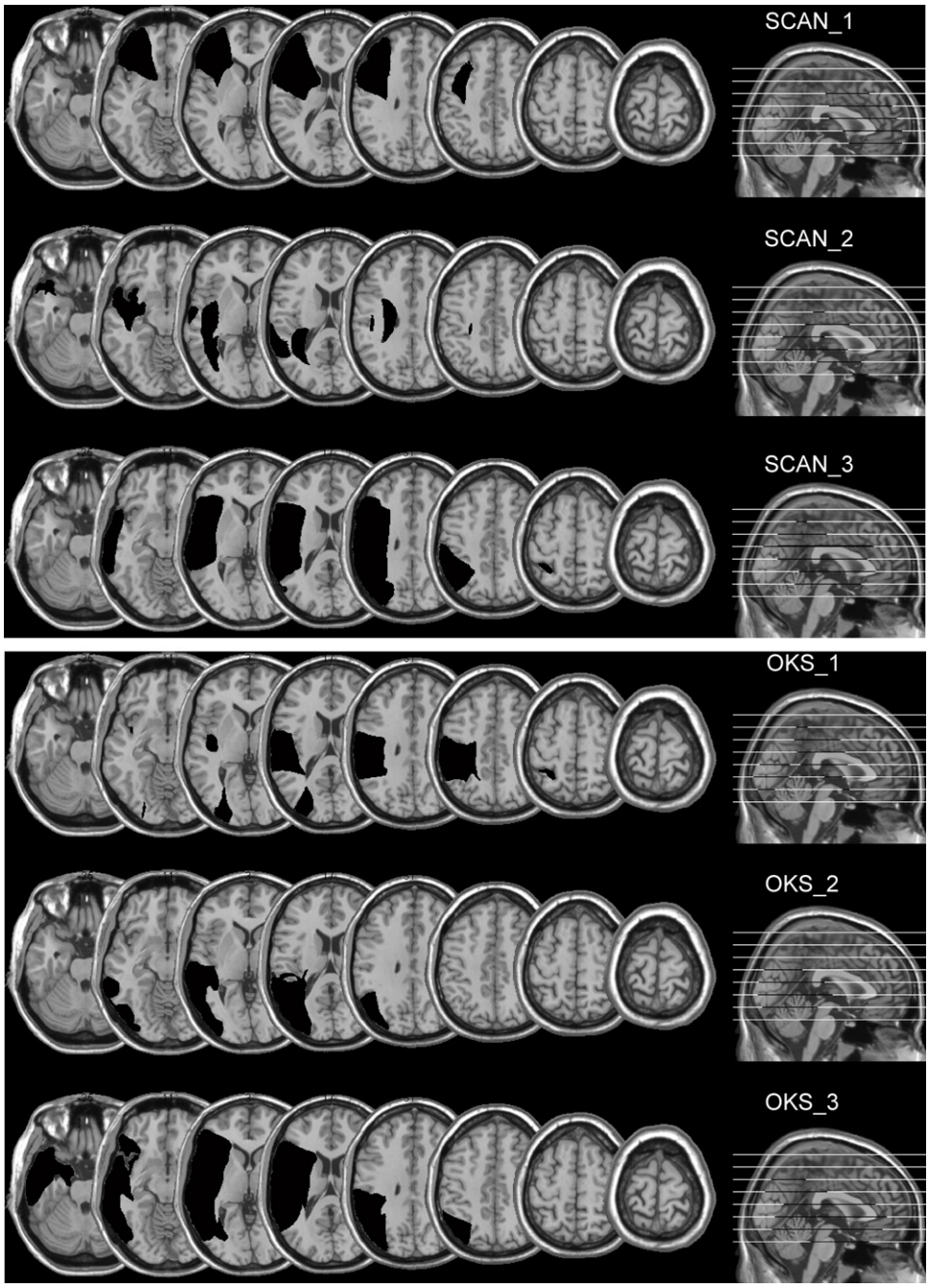

Fig. 3. Lesion mapping in the six neglect patients from study 2. OKS 1–OKS3: patients 1–3 receiving OKS therapy; SCAN1–SCAN3: patients 4–6 receiving visual scanning therapy (see text and Table 4 for further details).

leftsided omissions, $U = 28$; $z = -1.107$; $p > 0.05$), in paragraph reading (% of omitted words, $U = 27$; $z = -1.195$; $p > .05$), nor in horizontal line bisection (mean rightsided deviation from midline, $U = 27$; $z = -1.192$; $p > 0.05$).

In all six patients monaural hearing thresholds (audiometry) were measured as described above (Section 3.1) and revealed age-related normal hearing curves for both ears in all six cases, without showing interaural sensitivity differences of >10 dB.

All six patients were in-patients of a neurological rehabilitation clinic and were enrolled in other therapies (most often occupational and physical therapy, but no specific neglect therapy) during the *total time period* of the study (including baseline and follow-up periods). The amount of these therapies did not differ between the two samples (mean OKS: 12.5 sessions per week; mean SCAN: 13.1 sessions per week).

Auditory and visual neglect tests: Auditory neglect was measured with the same test and experimental setup (ASMP) as in Study 1 (see Section 3.2). Patients fixated a central fixation spot on an otherwise dark screen in a dark room. Their head was fixated in a head-and-chin-rest. Three baselines of the ASMP were obtained before treatment onset over a period of 10 days, one measurement was conducted after completion of 20 treatment sessions (either OKS or visual scanning therapy, see below), and a final follow-up test was performed two months after the last treatment session. 60 trials of the ASMP were performed during each measurement (30 starting from the left

hemispace, 30 starting from the right hemispace). As hemispace of the presentation of the auditory stimulus had no significant effect in the previous group study (see Section 3.2, above), we collapsed the data of the two hemispaces for each timepoint of measurement for statistical analyses.

Visual neglect was measured by the following 3 tests: number cancellation, horizontal line bisection and paragraph reading. The first two tests were already described in detail in the methods section of Study 1, see Section 2.1). As text reading is important in daily life and indented paragraph reading tasks are highly sensitive to reading impairments in neglect (Bachman, Fein, Davenport, & Price, 1993; Towle & Lincoln, 1991), and are not confounded by differences in education (years of schooling, (Bachman et al., 1993), we constructed 45 short reading texts (mean length: 51.7 words, range: 43–65; arranged in 8–10 lines) of different length from two story books. The margins of each text were irregularly indented on both sides in order to facilitate comparisons of errors on the left versus right text side. 8–10 words on every margin (left and right side, when counted over all lines of each text) of each text were filler words and were not necessary for the semantic context of the text. This increased the sensitivity of the test. All texts were matched with respect to length (number of words, letters and lines), spatial arrangement and complexity as judged by the performance of the normal subjects. Each text was displayed sequentially one by one on in blank ink on a white paper (21 × 29.7 cm large) in front of the patient in a distance of 0.5 m. Each patient had to read 3 indented reading tests at each timepoint of measurement. No text was given twice to eliminate memory effects. The mean percent of omissions (averaged over the 3 texts given during each timepoint of measurement) was the dependent measure reported below.

4.1.2. Treatments

Both samples of neglect patients received 20 treatment sessions (à 50 min, 5 sessions per week, one session per work-day). The OKS group received repetitive leftward OKS stimulation with active pursuit eye movements with similar stimulation devices as used in Study 1 and described in more detail in our previous work (Kerkhoff, Keller, et al., 2006). Patients were instructed to look at a computer screen (17″) and make pursuit eye movements to the left (contralesional) side while looking at moving dot displays of 100–200 stimuli (mean velocity: 5–30°). The velocity varied from trial to trial within the indicated range, to keep patients alert and attending the screen. When their eyes had reached the left margin they were instructed to start on the right side again. Head position was fixed in a head- and chin-rest in a central position so that the patients had to perform eye movements without head movements. The visual scanning group viewed the identical visual stimuli on the same computer monitor, but these patterns were always static. These patients were instructed to make systematic scanning eye movements to the left side and explore the visual stimuli on the screen, just as in conventional visual scanning therapy (cf. Kerkhoff, 1998; Pizzamiglio, Guariglia, Antonucci, & Zoccolotti, 2006). They were instructed to look at the symbols on the screen, count them while directing their eyes from left to right, row by row, in a systematic, organized search pattern. The subject's head was fixed as in the OKS group. The patient's distance to the screen was 0.4 m in both therapy settings. Frequent breaks (of 1–2 min) were given during the therapy sessions to the patients in both groups in order to avoid fatigue.

4.1.3. Statistical analyses

The data were analyzed separately for the two groups on the basis of collapsed single raw scores in each of the three visual neglect tests (3 patients × 3 trials = 9 measurements in every session), and on basis of the 60 trials in the ASMP per timepoint of measurement separately in every patient of the two treatment groups. Non-parametric statistics (Friedman-test, Wilcoxon-test) were applied. The alpha-level was set at 0.05 (two-tailed), and corrected for multiple comparisons according to Holm's (1979) procedure, where the fist comparison is computed with alpha, the second with alpha/2, the third with alpha/3, and so on.

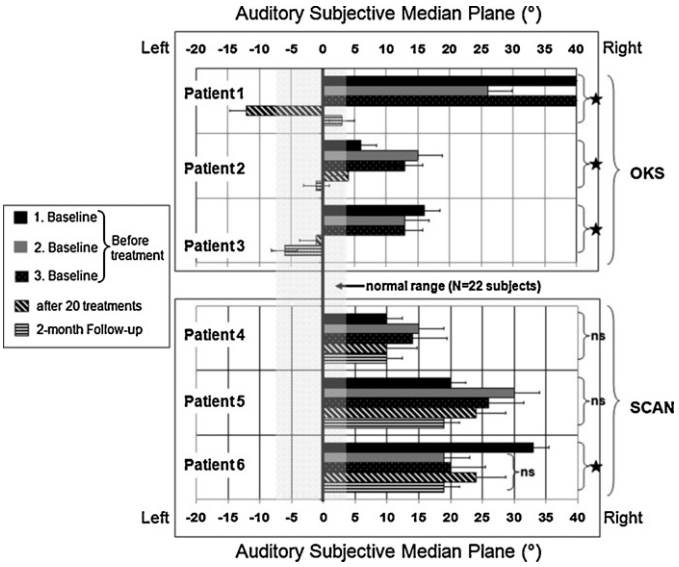

Fig. 4. Mean values (degrees, ±SEM) in the auditory subjective median plane in front space in the six patients with auditory neglect as measured three times before therapy (baseline 1–3), after 20 sessions of optokinetic (OKS) respectively visual scanning therapy (SCAN), and at follow-up 2 months after the end of treatment. Note the significant rightsided shift of the ASMP over the three baseline measurements in all six patients studied. However, all three OKS-patients improved in their ASMP after 20 sessions of leftward OKS, and this improvement remained stable at follow-up. In contrast, none of the 3 patients who had received visual scanning therapy showed any significant change over the 5 measurements, indicating that scanning training had no measurable effect on the ASMP. The shaded area indicates the complete range of performance in 22 normal subjects for this task (Kerkhoff, Artinger, & Ziegler, 1999a). Asteriks indicate significant change with $p < 0.05$. NS, not significant.

4.2. Results Study 2

4.2.1. Auditory subjective median plane (ASMP)

4.2.1.1. OKS-therapy. Non-parametric statistics (Friedman-test) revealed a significant difference between the mean ASMP over the five measurement points in patient 1 ($\chi^2 = 105.537$; df = 4; $p < 0.001$). Subsequent pairwise comparisons (Wilcoxon-test) between successive ASMP measurements in patient 1 revealed no significant improvement from baseline 1 to 2 ($z = -1.776$; $p > .05$), nor from baseline 2 to 3 ($z = -1.775$; $p > .05$), but a highly significant reduction of the rightward shift from baseline 3 to post-treatment ($z = -5.936$; $p < 0.0001$), as well as a significant change from post-treatment to the follow-up-test 2 months later ($z = -4.204$; $p < 0.0001$). All results remained significant after Bonferroni-corrections. Inspection of Fig. 4 shows that patient 1 had a very marked deviation of her ASMP to the right ipsilesional side of about 25–40° before treatment, which was changed into a leftward shift slightly outside the normal range of the ASMP after OKS-therapy. At follow-up this leftward shift had normalized into a slight rightward shift of the ASMP, which however was in the normal range for this task (see shading in Fig. 4).

In patient 2 the Friedman-test revealed a significant difference between the mean ASMP over the 5 timepoints (χ^2: 83.045; df = 4; $p < 0.0001$). Subsequent pairwise comparisons (Wilcoxon-test) between successive measurements of the ASMP in patient OKS2 revealed a significant deterioration (increase of rightward shift) from baseline 1 to 2 ($z = -3.343$; $p < 0.001$), but no further

change from baseline 2 to 3 ($z = -0.826$; $p > .05$). A highly significant reduction of the rightward shift was obtained from baseline 3 to post-treatment ($z = -4.573$; $p < 0.0001$), which remained stable at the follow-up-test ($z = -1.666$; $p > 0.05$). Inspection of Fig. 4 shows that patient 2 had a moderate to severe deviation of the ASMP to the right ipsilesional side of about 7.5–15.4° prior to treatment, which normalized completely after therapy and remained stable at follow-up. Before therapy, all ASMP measurements ranged outside the normal range, after therapy and at follow-up they were in the normal range (see shading in Fig. 4).

In patient 3 the Friedman-test revealed a significant difference between the mean ASMP over the five sessions (χ^2: 123.5; df = 4; $p < 0.0001$). Subsequent Wilcoxon-tests revealed no significant change of the ASMP from baseline 1 to 2 ($z = -1.216$; $p > 0.05$), nor between baseline 2 and 3 ($z = -1.173$; $p > 0.05$), but a significant reduction of the rightward shift from Baseline 3 to post-treatment ($z = -4.494$; $p < 0.0001$), and a significant further change from post-treatment to the follow-up-test ($z = -3.996$; $p < 0.0001$). Fig. 4 shows that patient OKS3 had a stable and significant shift of his ASMP to the right, ipsilesional side of about 14.2–19.2° before therapy, which was normalized after OKS-therapy. At follow-up, the ASMP had shifted slightly but significantly further to the left side, but lay still in the normal range for this task (see shading in Fig. 4).

4.2.1.2. Visual-scanning-therapy. Non-parametric analysis of variance (Friedman-test) revealed no significant difference between the mean deviation in the ASMP over the five different timepoints in patient 4 ($\chi^2 = 5.379$; df = 4; $p > 0.05$), nor in patient 5 ($\chi^2 = 8.457$; df = 4; $p > 0.05$), but in patient 6 ($\chi^2 = 37.216$; $p < 0.001$). Subsequent Wilcoxon tests in patient 6 showed a significant improvement from baseline 1 to 2 ($z = -2.684$; $p < 0.007$), but no further change from baseline 2 to 3 ($z = -0.463$; $p > 0.05$), nor any significant change after Scanning Therapy in contrast to baseline 3 ($z = -0.626$; $p > 0.05$), and no change from post-therapy to follow-up ($z = -1.119$; $p > 0.05$). Put differently: patient 6 showed a significant improvement *before* therapy, but none of the three patients who received visual scanning therapy improved significantly in their ASMP as a result of visual scanning therapy. Moreover, all continued to show a consistent, rightsided shift of their ASMP indicative of auditory neglect. Furthermore, in all three patients the ASMP ranged outside the normal range over all timepoint of measurements of the ASMP (Fig. 4).

The mean reduction of the rightward shift in the ASMP over an averaged baseline (computed over the 3 baseline tests of the ASMP) was −18.6° in the three patients treated with OKS therapy, which contrasted with a mean reduction of only −1.38° in the ASMP in the three neglect patients who had received Visual Scanning Therapy, which was significantly different ($U = 14439$; $p < 0.0001$), when computed over all single trials in each treatment group.

4.2.2. Visual neglect measures

4.2.2.1. OKS-therapy. Although the primary aim of the present study was to evaluate effects of repetitive OKS therapy on *auditory* neglect, we consider it also useful to evaluate potential effects of OKS on *visual* neglect, as this would underline the potential of OKS to induce *multimodal* improvements in spatial neglect and would replicate previous findings. Fig. 5 summarizes the results. In the three OKS-treated neglect patients a significant difference was found between the different timepoints of measurements for the number of leftsided omissions in digit cancellation (Friedman-test, $\chi^2 = 28.651$; df = 4; $p < 0.0001$), leftsided omissions in paragraph reading ($\chi^2 = 32.272$; df = 4; $p < 0.0001$), and the deviation from midline in horizontal line bisection ($\chi^2 = 30.636$; df = 4; $p < 0.0001$).

Subsequent paired comparisons with Wilcoxon-tests revealed no significant change over the three baseline tests in digit cancellation (largest $z = -1.725$; $p > 0.05$), but a significant reduction of leftsided omissions after OKS-therapy as compared to baseline 3 before treatment ($z = -2.668$; $p < 0.008$), and no further change after therapy as compared to the follow-up test ($z = -0.716$; $p > 0.05$). With respect to paragraph reading, a slight but significant deterioration of reading was found from baseline 1 to 3 ($z = -2.060$; $p < 0.039$), a significant reduction of leftsided omissions after OKS-therapy as compared to baseline 3 ($z = -2.675$; $p < 0.007$) and no further change after therapy as compared to the follow-up test ($z = -0.938$; $p > 0.05$). Moreover, the ipsilesional (rightsided) deviation in horizontal line bisection did not change significantly from baseline 1 to 3 ($z = -1.725$; $p > 0.05$), but was significantly reduced after OKS-therapy ($z = -2.668$; $p < 0.0008$). No further change was seen after therapy as compared to the follow-up test in line bisection ($z = -0.716$; $p > 0.05$). Hence, all improvements in visual neglect measures obtained after OKS therapy remained stable at the 2-month-follow-up investigation.

4.2.2.2. Visual-scanning therapy. In the three neglect patients that had received visual scanning therapy a significant difference was found between the different timepoints of measurements for the number of leftsided omissions in digit cancellation (Friedman-test, $\chi^2 = 22.488$; df = 4; $p < 0.0001$), leftsided omissions in paragraphh reading ($\chi^2 = 24.592$; df = 4; $p < 0.0001$), and the deviation from midline in horizontal line bisection ($\chi^2 = 22.126$; df = 4; $p < 0.0001$).

Subsequent paired comparisons with Wilcoxon-tests revealed no significant change from the first to the third baseline test in digit cancellation ($z = -1.706$; $p > 0.05$), no significant reduction of leftsided omissions in digit cancellation after therapy as compared to the third baseline before therapy ($z = -2.025$; $p > 0.05$), and no further change after therapy as compared to the follow-up test ($z = -0.061$; $p > 0.05$). In paragraph reading, there was no significant improvement from baseline 1 to 3 when alpha was corrected ($z = -2.153$; $p > 0.05$), no significant improvement after therapy as compared to the third baseline before therapy ($z = -1.017$; $p > 0.05$), and no further change after therapy as compared to the follow-up test ($z = -1.338$; $p > 0.05$). In horizontal line bisection, a slight but significant *deterioration* from baseline 1 to 3 was found ($z = -2.209$; $p < 0.05$), a significant improvement after therapy as compared to the third baseline before therapy ($z = -2.675$; $p < 0.007$), and no further change after therapy as compared to the follow-up test ($z = -0.477$; $p > 0.05$). Hence, all improvements in visual neglect measures obtained after scanning therapy remained stable at the 2-month-follow-up investigation (Fig. 5).

4.2.2.3. Comparison of OKS versus SCAN therapy. As mentioned above the two groups of patients did not differ significantly in averaged baseline values before treatment (see Section 4.1, above). However, the mean improvement over an averaged baseline was significantly higher after OKS than SCAN therapy in digit cancellation ($U = 6$; $p < 0.001$), reading ($U = 6$; $p < 0.001$) and horizontal line bisection ($U = 3$; $p < 0.0001$). With respect to the stability of the obtained improvements in these 3 tests, both groups did not differ significantly from each other (largest $U = 35.5$; smallest $p = 0.113$) indicating a similar stability of performance from post-test to the follow-up. Inspection of Fig. 5 shows that all six patients showed largely stable performance after cessation of treatments, and the statistical analyses confirmed this impression in both groups.

4.3. Discussion Study 2

Our second study shows that 20 repetitive therapeutic sessions with leftward OKS requiring the patients to actively perform leftward pursuit eye movements leads to an enduring normalization of the ASMP in all three treated neglect patients. In contrast, none of the three patients who received visual scanning therapy

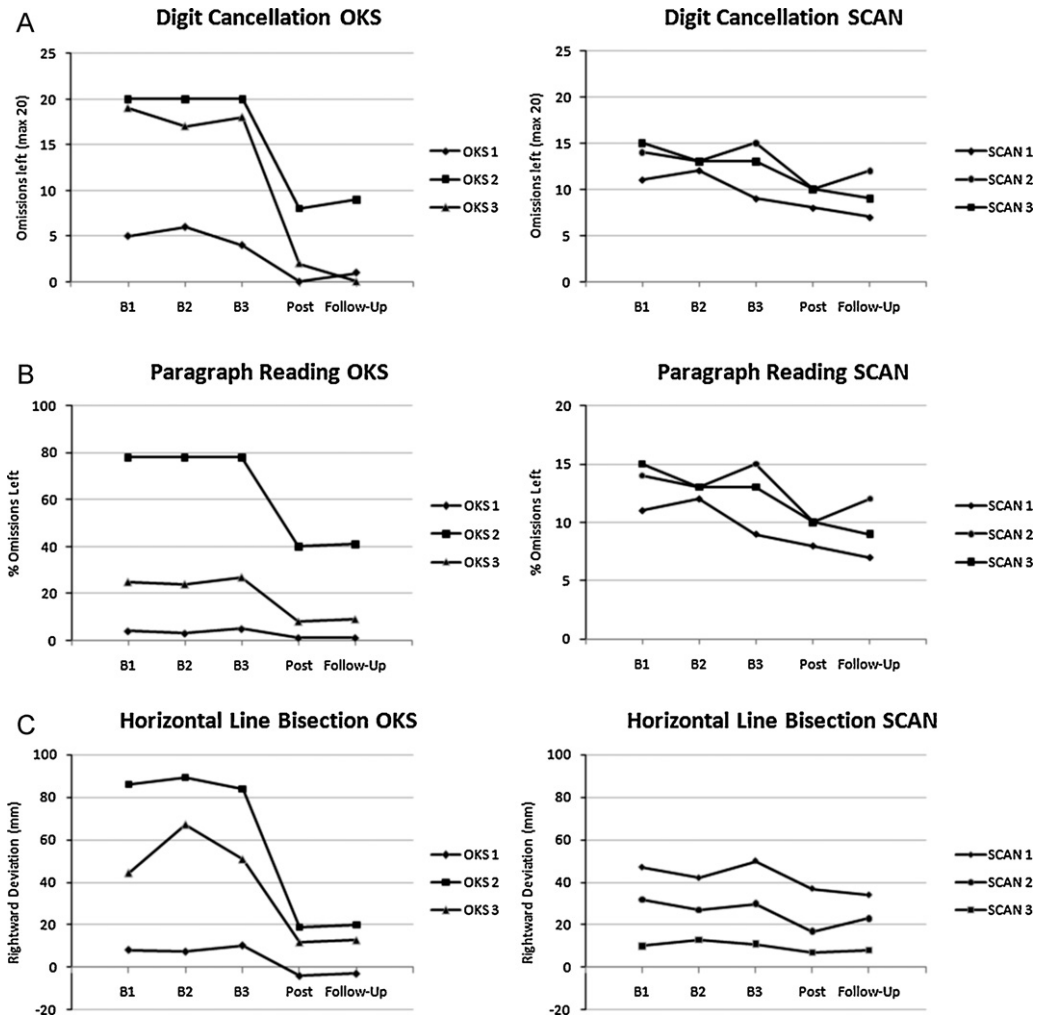

Fig. 5. Mean individual improvements in visual neglect measures in 3 neglect patients who received 20 sessions of OKS therapy (OKS1–OKS3, see left side of tableau) and in 3 neglect patients who received 20 sessions of visual scanning therapy (SCAN1–SCAN3; see right side of tableau). (A) Number cancellation. (B) Paragraph reading. (C) Horizontal line bisection.

improved significantly in their ASMP, which remained pathologically deviated to the ipsilesional (right) side in all three cases. Hence, conventional visual scanning training is unlikely to improve auditory neglect, whereas OKS therapy does so. Furthermore, these results also show that significant *spontaneous* improvements in the ASMP – which might have occurred after or before therapy in both small samples, is unlikely to occur by itself. This implies, that auditory neglect as measured here by the ASMP may persist at least up to 6–7 months post stroke unless treated specifically. As significant spontaneous recovery occurs mostly in the first half year after stroke, it appears that auditory neglect phenomena may be quite persistent.

With respect to the recovery from *visual* neglect by systematic therapy both OKS and scanning treatment led to significant improvements in both samples, although OKS induced greater improvements as scanning training. These findings neatly replicate similar findings from earlier treatment studies (Kerkhoff, Keller, et al., 2006; Schröder et al., 2008; Thimm et al., 2009), which all showed that repetitive OKS with pursuit eye movements to the contralesional side induces lasting and significantly better recovery from *visual* neglect as conventional visual scanning training of the same amount.

Hence, OKS therapy is clearly effective in neglect rehabilitation when it includes *active* smooth-pursuit eye movements to the contralesional side because it induces multimodal and greater improvements as visual scanning therapy. In Section 4.4 we will consider the findings of Study 1 and Study 2 together and address potential mechanisms involved.

4.4. General discussion

Our two studies show a rapid modulation of auditory neglect by OKS as well as enduring treatment effects in auditory and visual neglect after OKS therapy over 20 sessions. How can the short- and long-term effects of OKS in patients with auditory and visual neglect be explained?

4.4.1. Mechanisms of OKS

Functional imaging studies suggest a widespread activation of a cortico-subcortical network during optokinetic stimulation in the blind field of hemianopic patients (Brandt, Bucher, Seelos, & Dieterich, 1998) and in healthy subjects (Dieterich et al., 1998; Lewis, Beauchamp, & DeYoe, 2000). The dynamic stimulation produced significant activations in the occipitotemporal cortex and in the basal ganglia of the patients' damaged hemisphere. In healthy subjects parietal cortex (Konen et al., 2005; Lewis et al., 2000), insular cortex (Lewis et al., 2000), occipital cortex (Lewis et al., 2000) and various cerebellar compartments (Dieterich, Bucher, Seelos, & Brandt, 2000), as well as brain stem regions (Bense et al., 2006) are activated by OKS and pursuit eye movements. In general it is

believed that OKS provides sensory information necessary to compute egocentric spatial information that is required for accurate behaviour in space. Moreover, many of the activated brain regions are involved in gaze and attentional shifts, which were an explicit feature of our OKS therapy. In our patients, OKS may thus have acted on spatial neglect in multiple ways.

First, it may have provided an additional input signal provided by the motion information that allows to correct the pathological, ipsilesional bias in the ASMP or in similar visual midline tasks (i.e. line bisection, straight ahead) towards a more symmetrical midline position. This idea is compatible with findings of a re-orienting of the subjective straight ahead orientation by OKS in neglect patients (Karnath, 1996; Schindler & Kerkhoff, 2004).

Second, we are convinced that active tracking eye movements in response to the presentation of leftward OKS motion is an efficient way to direct attention to the contralesional side. Interestingly, Konen and colleagues showed that OKS *with active tracking* eye movements of their (healthy) subjects yielded significantly higher cortical activations as assessed by functional imaging (fMRI) than *passive viewing* of the same OKS pattern in the same subjects. As a consequence greater modulating effects on the behavioural level would be expected with active tracking and smaller effects with passive viewing of visual motion displays. We therefore hypothesize that OKS plus *active* tracking eye movements is more powerful in the modulation and treatment of neglect-related deficits than passive viewing of dynamical visual patterns even when this is accompanied by nystagmus, as in previous studies (Pizzamiglio et al., 2004). As the visual motion system remains largely functional even after large right hemisphere lesions, because of its many relay stations along striate and extrastriate visual pathways (including MT, MST, parietal lobe) and subcortical visual pathways (Schenk & Zihl, 1997), surviving remnants of this widespread system might be capable of modulating the neuronal activity in the lesioned as well as in the intact cerebral hemisphere of neglect patients. This could be in part responsible for the facilitatory effect of leftward OKS shown here, irrespective of additional left-sided hemianopia, which was present in most of our patients in Study 1 (19 out of 20). Thimm et al. (2009) studied in a recent functional imaging study a group of seven neglect patients who received repetitive OKS therapy as our patients in Study 2. Their study showed – apart from significant behavioural recovery of visual neglect by OKS-therapy – increased cortical activity as measured by functional magnetic resonance imaging (fMRI) in bilateral posterior brain regions, including the left and right parietal cortices, which are involved in spatial attention and gaze shifts (Thimm et al., 2009). We therefore assume further, that OKS acts on the neglect symptomatology in addition to providing a corrective input signal for a more symmetric midline perception also by facilitating pre/attentional mechanisms towards the contralesional hemispace. Compatible with this hypothesis is the finding that slowly moving visual displays such as that used in the present two studies may influence visual neglect phenomena by modulating focal attention towards the neglected hemispace (Mattingley et al., 1994), as well as the recent finding that leftward OKS reduces contralesional omissions in paragraph reading even when the OKS stimulation takes place outside the central visual field where the patients read the text (Reinhart, Schindler, & Kerkhoff, 2011). In summary, OKS may act both via overt shifts of gaze and subjective body orientation *and* via covert attentional shifts.

A few words are to be mentioned with respect to the temporal mechanisms of the OKS effects on auditory neglect. First, OKS seems to act nearly immediate on the ASMP, as there is a clear normalization of the ASMP during the 20 min of OKS in Study 1. Second, this online-effect is maintained after this single stimulation session for at least 30 min and in some cases up to 24 h, which neatly corresponds to sustained effects observed after the termination of OKS stimulation in the brain-stem vestibular nuclei of awake monkeys in a similar time window (Waespe & Henn, 1977). These findings may provide a possible physiological basis for the explanation of the sustained effects of OKS observed in Study 1.

4.4.2. Crossmodal effects of OKS

Our present experiments extend previous findings according to which OKS not only modulates visual line bisection (Mattingley et al., 1994), the subjective visual straight ahead (Karnath, 1996), visual size distortions (Kerkhoff, 2000; Kerkhoff et al., 1999b), visual distance judgments (Schindler & Kerkhoff, 2004), tactile extinction (Nico, 1999), tactile search (Keller et al., 2009), motor deficits (Vallar et al., 1997a), temporal judgments (Vicario et al., 2007) and the mental number line in neglect (Salillas et al., 2009), but also shows clear cross-modal, visual–auditory modulation effects in the auditory neglect modality. The crossmodal (visual–auditory) modulation effect that OKS induced on the auditory midline task extends the findings by Schüeli et al. (1999) and (Hiscock et al., 1985) who showed that sensory stimulation modulates auditory performance in healthy subjects by showing that even larger effects are achieved with such techniques in multimodal neglect. Moreover, the present findings are in accordance with numerous sensory stimulation studies showing that OKS (Kerkhoff, 2000; Karnath, 1996), neck-muscle vibration (Schindler et al., 2002) and caloric-vestibular stimulation (Karnath, 1994) all have a significant modulatory effect on different components of the neglect syndrome (for reviews see, Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Kerkhoff, 2003; Vallar, Guariglia, & Rusconi, 1997b). This cross-modal effect on visual and auditory neglect may be related to congruent, multimodal representations of auditory and visual space (Knudsen & Brainard, 1995), which have been found in the monkey's ventral intraparietal cortex (Schlack et al., 2005). As the parietal cortex is also involved in auditory spatial attention shifts (Shomstein & Yantis, 2006), and leftward OKS therapy activates this cortex region (Thimm et al., 2009) it appears likely that leftward OKS facilitates also such auditory-spatial attention shifts. This hypothesis has to be tested in subsequent experiments. By all these mechanisms, leftward OKS may restore the multiple visual and auditory mis-representations of horizontal space in spatial neglect. This crossmodal efficacy of OKS therapy makes it an effective – and because of its easy application – attractive technique in neglect rehabilitation that should promote subsequent studies in this field.

Despite our encouraging results in Exp. 2 a few caveats are appropriate. First, we cannot completely exclude the possibility that our two small treatment samples may have differed in other, yet unknown aspects and therefore performed differently during the 2 therapies. Such factors could be additional deficits, which we may have overlooked in our patients. Moreover, we do not know whether these findings can be generalized to all severity levels of neglect, i.e. patients with very severe, acute neglect. Second, although we found greater and crossmodal effects of OKS therapy in contrast to visual scanning therapy it is not our intention to say that visual scanning therapy is no longer useful for neglect patients. In fact, scanning therapy had some effect in our patients (Exp. 2) as well, and it is currently regarded as the best evaluated treatment for visuospatial neglect (Lincoln & Bowen, 2006). Moreover, it has a fixed place in clinical routine therapy for neglect. Nevertheless, it also seems clear that visual scanning training induces few if any improvements on *non-visual* neglect (haptic search cf. (Schindler et al., 2002); auditory neglect: current study), and requires many more therapeutic sessions than OKS therapy until improvements occur (for review see Kerkhoff & Schenk, in press). Therefore, the search for more effective therapies that address these nonvisual deficits and lead to a quicker recovery from multimodal neglect is

necessary. Finally, of course our results from exp. 2 require replication in larger, randomized patient samples.

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