Running head: Sound localization after visual prism adaptation

**Effects of prism adaptation on auditory spatial attention in patients
with left unilateral spatial neglect: a non-randomized pilot trial**

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33

Abstract

A short period of adaptation to a prismatic shift of the visual field to the right briefly but significantly improves left unilateral spatial neglect. Additionally, prism adaptation affects multiple modalities, including processes of vision, auditory spatial attention, and sound localization. This non-randomized, single-center, controlled trial aimed to examine the immediate effects of prism adaptation on the sound-localization abilities of patients with left unilateral spatial neglect using a simple source localization test. Subjects were divided by self-allocation into a prism-adaptation group ($n = 11$) and a control group ($n = 12$). At baseline, patients with left unilateral spatial neglect showed a rightward deviation tendency in the left space. This tendency to right-sided bias in the left space was attenuated after prism adaptation. However, no changes were observed in the right space of patients with left unilateral spatial neglect after prism adaptation, or in the control group. Our results suggest that prism adaptation improves not only vision and proprioception but also auditory attention in the left space of patients with left unilateral spatial neglect. Our findings demonstrate that a single session of prism adaptation can significantly improve sound localization in patients with left unilateral spatial neglect. However, in this study, it was not possible to accurately determine whether the mechanism was a chronic change in head orientation or a readjustment of the spatial representation of the brain; thus, further studies need to be considered.

Our findings demonstrate that a single session of prism adaptation can significantly improve sound localization in patients with left unilateral

Keywords: prism adaptation, unilateral spatial neglect, auditory attention, sound localization

1. Introduction

Unilateral spatial neglect (USN) is described as the inability to perceive various stimuli contralateral to a hemispheric cerebral lesion in the presence of a simultaneous, competing ipsilesional stimulus despite the absence of any other sensory or motor disorders (Heilman and Valenstein, 1979). Issues of spatial representation and attention are implicated in USN (Kinsbourne, 1987; Mesulam, 1998; Rizzolatti and Berti, 1990). It is estimated that up to 85% of stroke patients present a left USN in the acute phase following an ischemic event (Azouvi *et al.*, 2002). Moreover, USN can substantially hinder the recovery of physical functions after damage to a cerebral hemisphere (Jehkonen *et al.*, 2006; Mutai *et al.*, 2012).

Although USN is generally regarded as a condition primarily impacting vision, auditory and proprioceptive deficits have also been observed (Mesulam, 1999). Symptoms related to auditory-cue responses include errors in perceiving the origin of vocal communication and difficulties in identifying the sounds of approaching vehicles. Studies investigating auditory spatial attention in patients with brain damage or USN have focused on “sound localization” (Bisiach *et al.*, 1984; Guilbert *et al.*, 2016; Haeske-Dewick *et al.*, 1996; Matsuo *et al.*, 2013a; Matsuo *et al.*, 2013b; Poirier *et al.*, 1981; Shankweiler, 1961; Soroker *et al.*, 1997; Zatorre *et al.*, 1995; Zimmer *et al.*, 2003). Such research has revealed diminished sound-localization abilities in patients with lesions of the right cerebral hemisphere.

Rossetti *et al.* developed goggles equipped with prisms, which can shift visual perception to the right. Wearing such goggles while interacting with the environment is referred to as prism adaptation (PA), and this intervention has been used to treat USN (Rossetti *et al.*, 1998). PA is triggered by the artificial discrepancy between vision and the other

sensory modalities, as in the case of other adaptations to altered sensory environments (Rossetti *et al.*, 1998). Numerous studies have investigated how PA sessions improve visual symptoms and motor function in patients with USN (Jacquin-Courtois *et al.*, 2008; Mizuno *et al.*, 2011; Rode *et al.*, 2001; Rossetti *et al.*, 1998; Shiraishi *et al.*, 2010; Tilikete *et al.*, 2001). The therapeutic effects of a PA session include improved abilities in copying figures/shapes, controlling wheelchairs (Watanabe and Amimoto, 2010), balance (Nijboer *et al.*, 2013), and recalling the names of locations presented on a map. A long-term intervention with PA generally improves the patient's ability to perform activities of daily living (ADLs) (Mizuno *et al.*, 2011; Shiraishi *et al.*, 2010). Additionally, PA is effective for ego-centered neglect (Gossmann *et al.*, 2013). Hence, PA is an important rehabilitative intervention that improves various disorders associated with USN, as well as general ADLs.

PA improves USN in the ipsilesional space (auditory extinction) (Jacquin-Courtois *et al.*, 2013). Pochopien and Fahle found a slight effect on the perceived direction of a sound source in healthy participants (Pochopien and Fahle, 2017). During prism exposure, subconscious head rotation and changes in the proprioception of the arm can lead to the visual adaptation being indirectly generalized to changes in perceived auditory directions. Because PA affects multisensory systems and auditory spatial attention in patients with USN, it might also modulate the sound-localization ability required for auditory spatial perception. We thus aimed to examine the immediate effects of PA on auditory spatial attention in patients with left USN using a simple sound-localization task.

2. Materials and methods

2.1 Study design

This study is registered with the UMIN Clinical Trials Registry (ID: UMIN000031725) and was conducted in accordance with the Ethics Guidelines for medical and health research involving human subjects, as promulgated by the Japanese Ministry of Health, Labor, and Welfare. The study was approved by the local ethics committee of the center where it took place (approval no. 2013/4/1/20075) and participants provided their written, informed consent.

We investigated the effectiveness of a single PA session in the treatment of USN. Following enrolment, patients with USN were asked to select the intervention (PA) or non-intervention (control) group for participation (self-allocation). To minimize potential bias due to the presence or absence of intervention, the patient was informed that the effectiveness of the intervention would be verified in a single session. Because the study was conducted at a single hospital, it was concluded that complete blinding of the intervention was not possible because of the many patient interactions in hospital life. Therefore, a self-selected, non-randomized, controlled-trial design was used.

Participants in both groups underwent simple sound-localization tests before and after the intervention. PA was conducted in a rehabilitation room at the Rehabilitation Hospital between May 1, 2013 and March 31, 2016.

2.2 Participants

We included patients with left USN caused by a right-side stroke or tumor who were admitted to the rehabilitation ward or received outpatient care at our rehabilitation hospital. Written informed consent was obtained from both the patient and a family

member. All experimental procedures were conducted in accordance with the Declaration of Helsinki.

2.3 Inclusion and exclusion criteria

Patient inclusion criteria were: (1) without severe dementia and capable of understanding and completing the sound localization tasks, (2) without hearing loss, (3) without marked cervical movement limitations that could interfere with task execution, (4) without cortical deafness, and (5) with supratentorial lesion(s) in the right hemisphere (stroke or brain tumor). Exclusion criteria were: (1) refusal to participate, (2) severely impaired eyesight, (3) unable to perform PA in the upper right limb, and (4) aphasia.

2.4 USN determination

USN was diagnosed using the conventional subtest of the Behavioral Inattention Test (BIT-C) or the Catherine Bergego Scale (CBS) (Azouvi *et al.*, 2003; Wilson, Cockburn, and Halligan, 1987). The BIT and CBS were conducted by occupational therapists who were not caring for the study patients.

2.5 Prism adaptation

PA was performed as described previously (Watanabe and Amimoto, 2010). Participants were seated in a chair with their heads and trunks secured to maintain an upright posture and wore goggles with prism lenses that deviated images by 10° to the right. Using their right hands, they aimed 100 times in quick succession at a target placed in front of them. The total PA time was approximately 8 min. At the end of prism exposure, the goggles were removed and pointing trials without visual feedback were completed by each

participant to determine the presence of any substantial PA, defined as the experimenter observing a deviation of at least 5° from the target (Jacquin-Courtois *et al.*, 2010).

2.6 Simple sound localization

We employed simple sound-localization tests used previously (Matsuo *et al.*, 2013a; Matsuo *et al.*, 2013b) to investigate the effects of PA on sound-localization abilities in patients with USN. All participants performed two simple sound-localization tasks: one at baseline and the other approximately 8 minutes later (control group) or following PA (PA group), in a sitting position, in a private room fully paneled with sound-absorbing material. The distance between the participant and the central speaker was set as the length of the participant's arm. Speakers were installed at ear-height at seven positions: the center and at 200, 400, and 600 mm to either side of the midline. Participants were fitted with an eye mask and a cap with a laser pointer at its center. The laser pointer was positioned perpendicular to the line between the jaw and the tip of the nose. Complex sounds were played at 0.5-s intervals and the intensity of the sound was set to 60 dB.

As shown in Fig. 1, participants were required to point in the direction from which they believed the vocal stimulus had been emitted with the tip of their noses and signal their answers to the examiner. When the participant answered, the distance in mm between the position of the speaker and that indicated by the laser pointer was measured horizontally.

The localization error was defined as negative (–) if the deviation was to the left and positive (+) if to the right. A possible confound is that the perception of the sound origin may be made more accurate by discrepancies in the time required for sounds to reach the two ears if head movements are not controlled (Perrett and Noble, 1997). Therefore, our localization method required participants to orient their heads to the perceived direction

of the sound stimulus, which equalized the distances of the sound source to the two ears. Sounds were emitted from each source position three times (7×3 design) in random order. The sum of the errors recorded after three playbacks from each source position (excluding the center position) was calculated and used for analysis. The localization tests were conducted by an occupational therapist blinded to the study design.

2.7 Data analysis

Participant baseline characteristics (age, BIT-C, and CBS) were analyzed using independent *t*-tests. Mixed-model (split-plot) analysis of variance (ANOVA) with two within-participant factors (“trial,” baseline versus post-intervention or 8 min later; “position,” L/R200, L/R400, or L/R600) and one between-participants factor (“condition,” PA versus control group) was performed to identify between-group differences. Significant interactions were further assessed using *t*-tests with a post-hoc Bonferroni correction to explore the sound-source positions producing significant interactions. The main effects of trial and condition did not require post-hoc analysis because these factors had only two levels. Effect sizes (η^2) and powers were calculated for each source of variance. Violations of sphericity were corrected with the Greenhouse–Geisser adjustment coefficient. The significance threshold was set to 0.05. All analyses were performed using SPSS v22.0 software (IBM, Armonk, NY, USA).

3. Results

Twenty-eight patients met the inclusion criteria; however, only 23 consented to participate. Of those, 11 (mean age, 59.2 ± 16.5 y) were included in the PA group and 12 (mean age, 62.7 ± 11.9 y) were included in the control group (Fig. 2). All participants

understood the process of the sound source localization test and were able to search for the sound source.

3.1 Baseline characteristics

Table 1 shows the baseline characteristics of both groups. No significant intergroup differences in BIT-C scores ($p = 0.159$), CBS scores ($p = 0.993$), or age ($p = 0.956$) were observed. Therefore, the USN characteristics were similar between the groups at baseline.

3.2 Effects of PA on sound localization

All participants completed the sound-localization task. The mixed-model ANOVA found a significant main effect of position ($F_{[1.319, 27.705]} = 23.660$, $p < 0.0001$, $\eta^2 = 0.53$). All participants showed a tendency for a right shift in the left space and a left shift in the right space. No significant intergroup differences were observed for this tendency. A significant trial $\times$ position interaction was found ($F_{[5, 105]} = 3.278$, $p = 0.027$, $\eta^2 = 0.135$; Table 2). Thus, PA improves sound localization in the left space in patients with left USN. In the control group, within-participant analysis showed no significant differences in localization error from baseline to 8 min at any position of the sound source. However, in the PA group, a significant difference in localization error was observed between baseline and post-intervention at L600 ($p = 0.013$), and the right shift was alleviated after PA. Subsequently, between-groups analysis at each position revealed that the localization errors were significantly lower in the PA than in the control group at the positions L600 ($p = 0.027$) and L400 ($p = 0.029$). Fig. 3 illustrates the left or right localization deviation from each position, demonstrating that both groups of patients with USN mistakenly localized the sound source closer to the center than was actually the case.

4. Discussion

These results suggest that PA causes cross-sensory recalibration. PA has been shown to affect sensory modalities other than direct visual input and proprioception (Jacquin-Courtois *et al.*, 2010; Maravita *et al.*, 2003; Sumitani *et al.*, 2007). For example, improved auditory extinction was observed when six patients with USN with auditory extinction underwent PA therapy (Jacquin-Courtois *et al.*, 2010). PA also improved tactile neglect (Maravita *et al.*, 2003), indicating a therapeutic effect in patients with complex regional pain syndrome (Sumitani *et al.*, 2007). Hence, PA therapy affects the modalities of vision and proprioception, among others. Moreover, PA stimulates brain functions related to the integration of multisensory information necessary for the representation of space. In fact, we showed that a pathological localization shift to the right was mitigated at L400 and L600. Consistent with our findings, changes in visuospatial perception have been found to affect sound-localization ability (Bosen *et al.*, 2017; Callan *et al.*, 2015; Chen and Spence, 2017). PA, which reportedly improves visual symptoms in USN, may therefore do likewise. The deviation toward the center shown in Fig. 3 is similar to previous results (Matsuo *et al.*, 2013a; Matsuo *et al.*, 2013b; Zatorre *et al.*, 1995).

PA-induced changes in proprioceptive receptors may affect auditory attention indirectly. When the sound source is not directly in front of the head, the deviation from the midline will determine the time difference between the arrival of the same sound at the left and right ears. Sound localization exploits this difference as well as differences in loudness between the ears (Hartmann *et al.*, 2016; Middlebrooks and Green, 1991). Moreover, the head axis has been demonstrated to rotate in the direction of the prismatic shift after PA

(Pochopien and Fahle, 2017). Therefore, PA can change sound-source localization indirectly due to a chronic shift in average head orientation.

Our findings demonstrate that PA significantly improves auditory attention to the left space in patients with left USN and that a single session of PA can significantly improve sound localization in patients with left USN. This suggests that PA increases the responsiveness of patients with USN to sounds in the left space.

4.1 Study limitations

This study has several limitations. First, both groups might have included patients with damage in the auditory cortex leading to sound-localization disorders (Krumbholz *et al.*, 2005). Included patients may therefore have experienced diminished sound-localization accuracy due to both brain injury and auditory disorders associated with USN. However, it is also possible that PA affects sound-localization ability similarly in patients with multiple forms of sound-localization impairment. Second, effects of long-term fixed periods of PA, such as 2 weeks (Frassinetti *et al.*, 2002; Mizuno *et al.*, 2011) and 8 weeks (Shiraishi *et al.*, 2010) have been verified. Further studies are needed to investigate the beneficial effects of long-term PA on sound localization and to determine whether a cortical injury is associated with diminished sound localization. Third, this study was conducted at a single medical institution; the experiment has not been validated by repeating it in external institutions. Although all participants completed the localization task, bias is possible. Fourth, in this study, membership in the intervention group was self-selected. However, the effects of PA often occur unconsciously. In other words, the participant cannot decide to adapt. Therefore, we believe that the method of self-selection used in this study had little effect on the results. However, it is highly likely that the

patients who self-selected for the prism group were, on average, relatively highly motivated to achieve rehabilitation progress and proactive in seeking treatments generally. Therefore, the present results require validation in a fully blinded, randomized, controlled trial.

4.2 Conclusions and future directions

This study revealed that in patients with left USN, PA can improve auditory spatial attention (sound localization). However, the study cannot accurately determine whether the mechanism is a chronic change in head orientation or a recalibration of spatial representations in the brain. Therefore, alternate methods such as using language to report perceived locations will need to be explored in future studies.

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Conflicts of interest

AQ6 There are no conflicts of interest.

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424 **Tables**425 **Table 1.** Clinical characteristics of patients in the prism-adaptation and control groups

Sex	Age	Group	Condition	Lesion site (right hemisphere)	BIT-C	CBS
F	58	PA	Cerebral hemorrhage	Putamen	-	3
M	61	PA	Cerebral infarction	Parietal	137	12
F	77	PA	Cerebral infarction	Fronto-parietal	9	22
M	64	PA	Cerebral infarction	Fronto-parietal	-	7
M	51	PA	Cerebral hemorrhage	Putamen	128	9
F	12	PA	Cerebral hemorrhage	Fronto-temporo- parietal	135	7
F	63	PA	Subcortical hemorrhage	Fronto-parietal	113	21
F	69	PA	Cerebral infarction	Fronto-parietal	107	22
M	57	PA	Cerebral hemorrhage	Fronto-parietal	24	20
F	73	PA	Cerebral infarction	Fronto-parietal	-	3
M	66	PA	Cerebral infarction	Parietal	130	14
M	54	Control	Cerebral hemorrhage	Putamen	128	8
F	65	Control	Cerebral infarction	Fronto-parietal	43	27
F	66	Control	Cerebral infarction	Fronto-parietal	63	22
M	51	Control	Cerebral hemorrhage	Putamen	-	5
F	55	Control	Cerebral hemorrhage	Thalamic	137	11
M	56	Control	Brain tumor	Parietal	110	8
M	54	Control	Cerebral hemorrhage	Putamen	-	4
M	82	Control	Cerebral infarction	Temporo-parietal	102	16

M	49	Control	Subcortical hemorrhage	Fronto-parietal	98	17
F	80	Control	Cerebral infarction	Temporo-parietal	129	4
F	83	Control	Subarachnoid hemorrhage, traumatic	Fronto-temporo- parietal	132	17
F	57	Control	Cerebral hemorrhage	Putamen	131	18

426 M = male; F = female; PA = prism adaptation; BIT-C = behavioral inattention test,
427 conventional subtest; CBS = Catherine Bergego scale

428 **Table 2.** Split-plot (mixed-model ANOVA) for sound localization error

Sources	df	<i>F</i>	<i>p</i>	Partial η^2
Between participants				
Condition	1	0	0.995	0
Within participant				
Trial	1	0.495	0.489	0.023
Position	1.319	23.660	0.000*	0.530
Condition $\times$ position	5	1.481	0.202	0.066
Trial $\times$ position	2.955	3.278	0.027*	0.135
Trial $\times$ position $\times$ condition	5	1.798	0.120	0.079

429 df = degrees of freedom; condition = with versus without prism adaptation; trial = baseline
 430 versus post-intervention or 8 min later; position = target position; *, $p < 0.05$
 431

Figure captions

Fig. 1. Method for sound localization measurement

A sound source is installed an arm's length away from and in front of the participant. Participants rotate their heads toward the sound source to indicate the perceived direction. The horizontal distance between the position indicated by a head-mounted laser pointer and the position of the sound source is then measured.

Fig. 2. Recruitment flow diagram

A total of 28 participants met the inclusion criteria. Of these, 5 were excluded. Of those included (23 participants), 12 chose the non-intervention group by self-selection, and 11 chose the intervention group by self-selection.

Fig. 3. Sound source localization errors

Localization errors are expressed as mean $\pm$ SEM for each sound-source position (L/R: 200, 400, and 600 mm) in each group (PA, $n = 11$; control, $n = 12$). Negative and positive errors are defined as deviating to the left and right of the target, respectively. L = left; R = right; PA = prism adaptation; *, $p < .05$

Figure 2