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CROSS-MODAL NEUROPLASTICITY : Auditory spatial recalibration following visuo-motor adaptation

Tissieres Isabel

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CROSS-MODAL NEUROPLASTICITY :
Auditory spatial recalibration following visuo-motor adaptation

Thèse de doctorat en Neurosciences (PhD)

présentée à la

Faculté de biologie et de médecine
de l'Université de Lausanne

par

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Auditory spatial recalibration following visuo-motor adaptation

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Prof. Jean-Pierre Hornung

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« C'est dans l'étude approfondie des détails que l'on surprend les secrets de la nature, et c'est à ceux qui ont le courage de tout entreprendre qu'il est permis de croire que l'on peut tout expliquer. »

Félix Vicq d'Azyr

LIST OF ABBREVIATIONS

AC	auditory cortex
AG	angular gyrus
ALA	antero-lateral auditory area
ANOVA	analysis of variance
BG	basal ganglia
BOLD	blood oxygen level dependent
CN	cochlear nucleus
DAS	dorsal attentional system
dHb	deoxygenated hemoglobin
DNLL	dorsal nucleus of the lateral lemniscus
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
GLM	general linear model
Hb	oxygenated hemoglobin
IC	inferior colliculus
IFC	inferior frontal cortex
IFG	inferior frontal gyrus
IID	interaural intensity difference
IPL	inferior parietal lobule
ITD	interaural time difference
LA	lateral auditory area
LNTB	lateral nucleus of the trapezoidal body
L-PA	leftward prism adaptation

LSO	lateral superior olive
MGB	medial geniculate body
MNI	Montreal neurological institute
MNTB	medial nucleus of the trapezoidal body
MSO	medial superior olive
MTG	middle temporal gyrus
PA	prism adaptation
PAC	primary auditory cortex
PC	parietal cortex
PET	positron emission tomography
PMC	premotor cortex
PPC	posterior parietal cortex
pP	planum polare
pT	planum temporale
SC	superior colliculus
SHD-VAS	shift of hemispheric dominance within the VAS
SMG	supramarginal gyrus
SRM	spatial release from masking
STG	superior temporal gyrus
STS	superior temporal sulcus
R-PA	rightward prism adaptation
USN	unilateral spatial neglect
VAS	ventral attentional system
VLSM	voxel-lesion symptom-mapping

ABSTRACT (ENGLISH)

"I think I heard a child screaming in this room full of smoke! Or, maybe, could it be a piece of metal that fell on the ground? No, I heard it again. I am sure now. It is a child and it comes from 20 meters ahead, slightly on the left. Call for backup I will enter first!"

Mapping the auditory space requires paying attention to several auditory cues as the ones illustrated in the example above: identity, location and direction of sounds. In the absence of visual information, it will be even more important to rely on these cues to be able to navigate properly. The visual input can be reduced following visual loss or decrease of conscious visual perception, a condition called unilateral spatial neglect; or in particular conditions such as in the example above, when firefighters have to rescue a child from a house full of smoke. When the visual input is reduced, the other sensory modalities will have to adjust their responses in order to maintain an adaptative behavior. The neuroplasticity induced by the modulation of a sensory modality on another sensory modality is referred as cross-modal plasticity.

This thesis is composed of two major parts and includes five studies. The first part, involving two studies, is dedicated to the investigation of the neural substrates of sound lateralization and auditory neglect in patients with brain lesions. The second part, involving three studies, is dedicated to the investigation of cross-modal plasticity and focuses on prism adaptation.

Two studies investigated auditory spatial deficits using an anatomo-clinical imaging approach on patients with a first unilateral stroke. Results showed that contralateral auditory extinction was associated with similar temporo-parieto-frontal regions on either hemisphere; that ipsilateral auditory extinction in patients with left hemispheric damage was associated with lesions involving intrahemispheric white matter connections; and that auditory sound segregation deficits linked to the inability to correctly use implicit spatial cues were predominantly induced by lesions including a large left temporo-parietal network. Three studies investigated the plasticity in sound localization induced by prism adaptation, a visuo-motor training used in the rehabilitation of neglect deficits. Two of them focused on the neural correlates modulated by prism adaptation during visual and auditory detection tasks. The last study investigated the effect of this adaptation on the alleviation of auditory spatial deficits occurring after a brain lesion. The results of these studies showed that the inferior parietal lobule is similarly modulated by the adaptation during a visual or auditory task, suggesting a supramodal role of this region. Moreover, the results of these studies allowed specifying for which patients this adaptation is efficient to alleviate auditory spatial deficits.

Overall, these studies contributed to a better understanding of the nature of auditory spatial deficits in patients with brain damages. They showed the intrinsic ability of the healthy and damaged adult brain to adapt and improve. These findings illustrate how we can use the visual modality to help recover auditory spatial deficits. These results could potentially allow the development of new neurorehabilitation strategies.

Key-words: Sound localization, cross-modal plasticity, unilateral spatial neglect, IRMf, VLSM

RESUME (FRENCH)

"Je crois que j'ai entendu un cri d'enfant provenant de cette pièce pleine de fumée! Ou bien était-ce un objet en métal tombé sur le sol? Non, je l'ai entendu à nouveau. J'en suis sûr maintenant. C'est un enfant et ça vient de 20 mètres devant, légèrement sur la gauche. Appelle du renfort, je rentre en premier. "

Pour se représenter l'espace auditif, il faut tenir compte de nombreux indices tels que ceux illustrés dans l'exemple précédent : l'identité d'un son, sa localisation dans l'espace et son mouvement. En l'absence d'information visuelle, ces indices sont encore plus importants pour pouvoir s'orienter correctement. L'information visuelle peut se retrouver réduite pour plusieurs raisons : suite à une perte de la capacité visuelle, suite à une diminution de la conscience de l'espace visuel liée à un syndrome que l'on nomme héminégligence, ou dans des conditions particulières comme celle de l'exemple cité au début : lorsque des sapeurs-pompiers doivent sauver un enfant pris au piège dans une maison pleine de fumée. Lorsque l'information visuelle est réduite, les autres modalités sensorielles doivent s'ajuster afin que l'individu puisse conserver un comportement adaptatif. Cette neuroplasticité induite par la modulation d'un sens en réponse à un autre sens, s'appelle plasticité cross-modale.

Cette thèse s'articule autour de deux axes principaux et inclut cinq études. Le premier axe est dédié à l'étude des corrélats anatomiques des déficits spatiaux auditifs et comporte deux études focalisées sur les déficits spatiaux auditifs de patients cérébrolésés. Le deuxième axe est dédié à l'étude de la plasticité cross-modale et comporte trois études focalisant sur l'adaptation prismatique.

Les deux premières recherches ont permis d'étudier les déficits spatiaux auditifs en utilisant une méthode d'analyse permettant les corrélations anatomo-cliniques. Les résultats ont démontré que l'extinction auditive contralatérale est provoquée par des lésions dans des régions temporo-fronto-pariétales similaires de chaque hémisphère ; que l'extinction auditive ipsilatérale à la suite de lésions impliquant l'hémisphère gauche pouvait être liée à des déconnections calleuses intra-hémisphériques ; et que les déficits de ségrégation liés à l'incapacité d'utiliser les indices spatiaux implicites étaient provoqués principalement par des lésions situées au sein d'un large réseau temporo-pariétal dans l'hémisphère gauche. Les trois études suivantes ont permis d'étudier la plasticité induite par l'adaptation prismatique, un protocole de réhabilitation utilisé pour diminuer les déficits spatiaux des patients héminégligents. Ces études ont permis de confirmer le rôle supramodal du lobule pariétal inférieur, qui est modulé de façon similaire par l'adaptation dans chacune des modalités sensorielles (vision, audition); et de préciser pour quels patients cette adaptation est utile pour diminuer les déficits spatiaux auditifs.

En résumé, ces études ont contribué à une meilleure compréhension de la nature des déficits spatiaux auditifs que les patients peuvent présenter suite à une lésion cérébrale. Elles ont également permis de dévoiler la capacité du cerveau adulte sain ou cérébrolésé à s'adapter et ont aussi démontré que l'on peut utiliser la vision pour aider la réhabilitation des déficits spatiaux auditifs. Ces résultats pourraient potentiellement permettre le développement de nouvelles stratégies thérapeutiques en neuroréhabilitation.

Mots-clefs: Localisation auditive, plasticité cross-modale, héminégligence, neuroimagerie

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CHAPTER 1 INTRODUCTION

Processing of auditory spatial representations is done hierarchically beginning with the computation of monaural and binaural spatial cues by the cochlea and brainstem, then the processing of unimodal spatial inputs and finally the cross-modal integration in multimodal brain regions. Final objectives are to give to the individual the ability to be entirely oriented in his environment, to navigate properly and to be able to physically interact with it. To be completely adapted with this multisensory environment, the brain needs to constantly learn how to adapt – i.e. **recalibrate** – its responses. This intrinsic ability of the brain to learn and adjust in relation to the changing environment is coined as **neuroplasticity**. The objects that we find in our environment, even auditory objects, elicit multiple sensory representations. For example, the sound of a phone ringing elicits semantic representations, motor representations and visual representations. If the capacity of the nervous system to integrate all this information is altered following the loss or reduction of a sense, it will give to the brain a conflicting information. **Cross-modal recalibration** would then take place in order to allow the restoration of functional auditory spatial representations.

The aims of the present thesis were to investigate changes of auditory spatial representations induced by the modulation of visual inputs and to understand if these interventions could be useful means for the alleviation of auditory spatial deficits following brain lesions. In order to achieve these goals, the work of the present thesis was divided around two main axes. The first axis was dedicated to the study of auditory spatial deficits and their neural substrate in patients following a first unilateral stroke. These deficits were investigated using an anatomo-clinical approach in two studies, one focusing on auditory extinction (Tissieres et al., In Revision) and the other focusing on the use of implicit spatial cues for sound object segregation (Tissieres et al., In Preparation). The second axis was dedicated to the study of the auditory space modulation by interventions targeting visual capacities. This axis was explored in three studies focusing on prism adaptation in healthy participants using fMRI (Crottaz-Herbette et al., 2017; Tissieres et al., 2017b) and in patients using anatomo-clinical correlations (Tissieres et al., 2017a).

This introduction will start with a review of the mechanisms and neural underpinnings of human auditory spatial processing. Then, a second part will explain and define the main auditory spatial deficits occurring following a brain lesion. The following parts will be dedicated to the definition of the cross-modal recalibration and more precisely, of two specific situations in which auditory spatial processing is modulated by interventions on the visual modality: following prism adaptation and following visual deprivation.

1.1 Human auditory spatial representations

1.1.1 Auditory spatial processing

To localize sound sources, humans mostly use monaural spectral and binaural disparity cues. Binaural cues are used principally for localization in the horizontal plane (azimuth) and are obtained because of the geometry of the head and of the external ears (Fig.1A & B). Sound waves coming from a specific source lead to two types of disparities when arriving at the two ears: the interaural time difference (ITD) and the interaural intensity difference (IID) (Blauert, 1997; Grothe et al., 2010). An interaural time difference means that sounds arriving from the left side will reach the left ear first and vice-versa for sounds arriving from the right side. The difference in time of sound arrival at each ear will allow determining the angle of the sound source. For low frequency sounds, the auditory system evaluates ITD from phase delays, while for high frequency sounds it does it through group delays. ITDs variations with frequency - they become smaller at high frequency - are due to the frequency dispersion of the diffracted waves. To know the sound source using ITDs one must know the spectral content of the sound. About the other binaural cue, the magnitude of IIDs is dependent of the wavelength of the sound. With a low-frequency sound the IIDs will be very small, above 3 kHz IIDs will become larger and then reliable. The physicist Lord Rayleigh (1907) discovered that ITDs are mostly used to determine the location of low-frequency tones and IIDs to high-frequency tones: this is called the "**duplex theory**". In the studies of the present thesis, the sounds used for the auditory spatial tasks are complex tones (environmental sound objects and broadband noises) created with ITDs. Complex tones are random and therefore do not imply the same difficulties for sound localization than pure tones (Blauert, 1997).

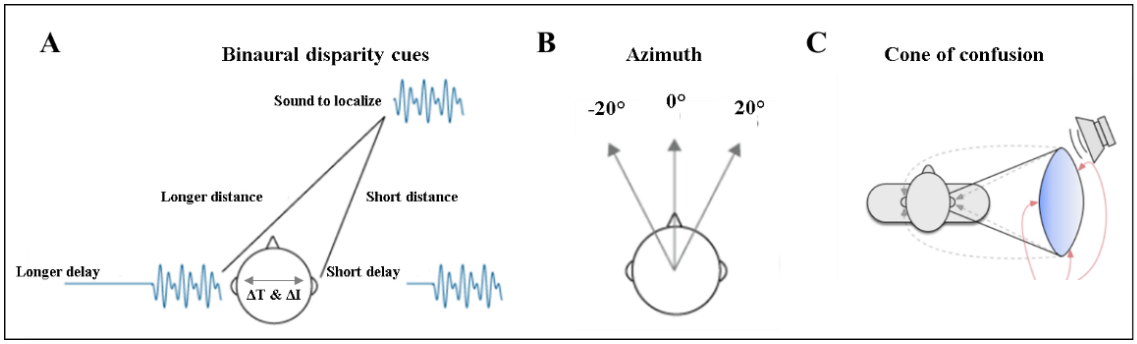

Figure 1. Human spatial cues. In (A.) are represented the binaural disparity cues used for sound localization in the azimuth: interaural time differences (ΔT) and interaural intensity differences (ΔI). In (B.) are represented the angle values in the azimuth: 0° corresponding to the median plane, negative values to the left of the median plane and positive values to the right of the median plane.

The region of space in which we have the greatest spatial acuity is around the midline (i.e. in front). There, humans can detect changes in the sound location as little as 1°, which corresponds to an ITD of 10 to 15 µs or an IID of 0.5 to 0.8 dB, depending on the frequency of the sound. Monaural cues used for sound localization are produced by the pinna, which modulates the spectral shape of acoustic signals before they reach the tympani. Furthermore, at some locations along the interaural axis (Fig. 1C.), sounds will have similar binaural disparity cues (ITDs and IIDs) and this will induce localization errors, the so-called "**cone of confusion"**. These localization errors can be reduced using monaural spectral cues through head movements. Finally, the properties of a sound will have an impact on its localization. Results on the effect of the complexity of a sound on human auditory localization performances are scarce, however one study has demonstrated that humans are more precise for broadband noises than for narrowband noises indicating that greater neuronal recruitment will help further with sound localization (Middlebrooks, 1992).

Binaural processing is also required for **sound segregation** (Blauert, 1997). Sound segregation refers to the ability to extract one sound from the surrounding noise. It is also known as the 'Cocktail party effect'. In presence of a continuous sound stream, some characteristics of the sounds will allow grouping elements of the sounds in time and frequency as pertaining to the same source (an auditory stream or object) and allow also segregating the sounds in different units when they belong to different sources. Hearing in a context of multiple sound sources is referred as 'Auditory scene analysis' (Bregman, 1990).

Thresholds for signal detection are measured, either in free-field or with headphones, when signal and mask are spatially separated from various distances. The variable of interest is the level of unmasking, i.e. the increase in performance linked to an increased distance between the sounds. This contribution of spatial cues to sound object segregation is implicit and can be measured with the Spatial Release from Masking paradigm (SRM). How different the use of implicit and explicit spatial cues are, either in their mechanism or neural correlates, is still unclear. Evidence coming from lesions studies showing double dissociations in patients' deficits (further developed in section 1.1.3) suggest distinct neural correlates for the processing of implicit and explicit spatial cues (Duffour-Nikolov et al., 2012). This assumption was further explored in our study focusing on the neural substrate of implicit and explicit spatial deficits in stroke patients (Tissieres et al., In Preparation).

1.1.2 Neural correlates of auditory spatial processing

1.1.2.a Hierarchical processing of auditory spatial cues

The coding of ITD and IID begins in the superior olivary complex in the brainstem where the outputs coming from the cochlea arrive (Fig. 2). The medial superior olive receives monosynaptic excitatory input and disynaptic inhibitory input from both ears and calculates ITD and IID. Then the lateral superior olive receives monosynaptic excitatory input from the ipsilateral cochlear nucleus and disynaptic inhibitory input from the other side. In other words, neurons in one cochlear nucleus respond stronger when sounds hit the ipsilateral ear than the contralateral ear. Then, the inferior colliculus of one side receives information about binaural disparities of the contralateral auditory field via the projections from the medial and lateral superior olivary nuclei. In the lateral nucleus of the inferior colliculus, contralateral azimuth angles of 0-180° are mapped along the rostrocaudal axis. This rostrocaudal map signifies that neurons in the inferior colliculus have receptive fields that are spatially tuned, and that when shifting from rostrally to caudally neurons representing sounds sources are arranged from midline positions to contralateral caudal positions (in azimuth).

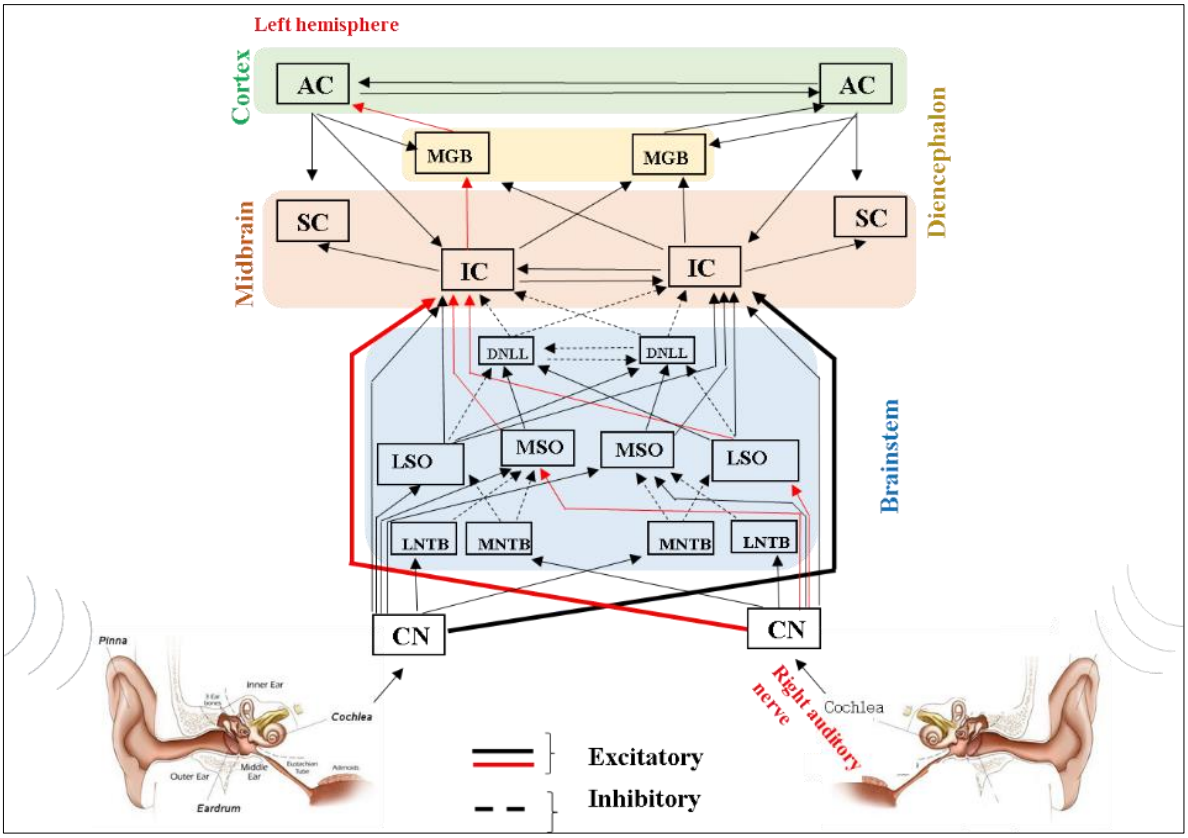

Figure 2. Ascending auditory pathway. Schematic representation adapted from (Künzel and Wagner, 2017) of the ascending auditory pathway from the cochlea, through the brainstem and the midbrain to the auditory cortex. Black and red lines represent excitatory connections. Dotted lines represent inhibitory connections. Red lines are illustrating the contralateral pathway from the right auditory nerve to the left auditory cortex.

In the inferior colliculus, some projections will converge like the inputs from the lateral superior olive and from the dorsal cochlear nucleus meaning a combination of IIDs and spectral cues, but some other will remain separated like the projections from the lateral and medial superior olive.

Neurons arriving from the inferior colliculus in the auditory cortex conserve their functional specificities. Cortical neurons processing low-frequency sounds will be still sensitive to ITDs, while cortical neurons processing high-frequency sounds will be more sensitive to IIDs. Spectral cues that are generated by the filter properties of the ear are important here too. Finally, even if cortical regions process auditory spatial information, it is impossible to draw a map of auditory space similar to the ones observed in visual or somatosensory cortices. An hypothesis suggested by Stecker and colleagues proposes that sound localization could be done by the comparison between the activity of groups of contralateral and ipsilateral neurons within each hemisphere (Stecker et al., 2005).

Finally, at a cortical level, a functional network is processing auditory spatial information. This network is the dorsal 'Where' stream from the dual-stream model and is thoroughly explained in the next section (1.1.2.b The dual-stream model).

1.1.2.b The dual-stream model

Cortical regions are also involved in sound source localization. Evidences coming from animal studies (Rauschecker and Tian, 2000; Romanski et al., 1999a; Romanski et al., 1999b) as well as from human studies (Barrett and Hall, 2006; Clarke et al., 2002; Clarke and Thiran, 2004; Murray et al., 2006; Rauschecker and Tian, 2000; Retsa et al., 2018) suggest that, as for the visual system, the auditory system is divided in two anatomo-functionally segregated processing streams (Fig. 3A & B): **the "What" and "Where" streams** (Bachevalier, J. and Mishkin, M., 1986.; Kaas and Hackett, 1999; Ungerleider and Haxby, 1994; Ungerleider and Mishkin, M, 1982). The first one, the 'What' stream, is dedicated to the recognition of sound identity and relies on anterior parts of the temporal lobe and on the inferior frontal gyrus. The second one, the 'Where' stream, is dedicated to sound localization and relies on posterior parts of the superior temporal gyrus, the inferior parietal lobule and the superior frontal sulcus. The planum temporale is considered a shared auditory area necessary for sound localization as well as sound identification processes (Arnott et al., 2004; Arnott and Alain, 2011; Recanzone and Cohen, 2010).

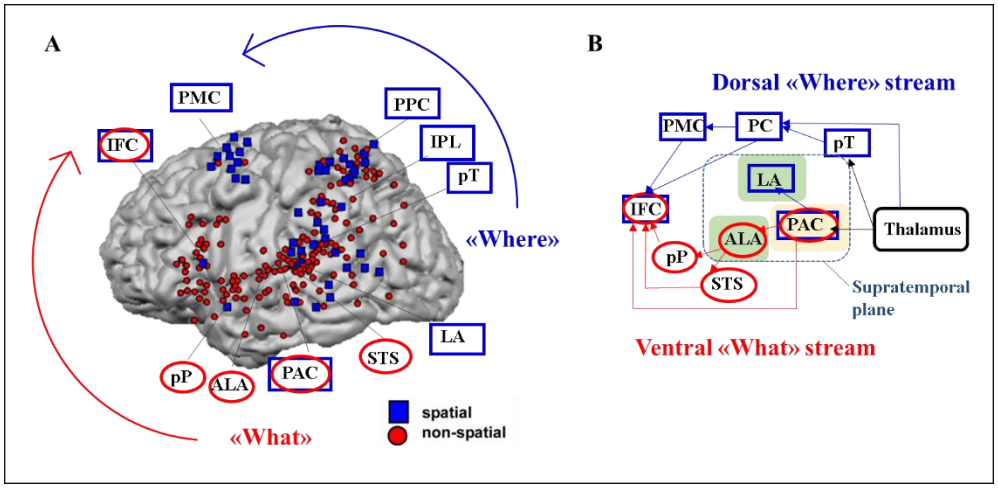

Figure 3. The dual-stream model. In (A.) are represented the 'What' and 'Where' processing streams (adapted from (Leavitt et al., 2011)). In (B.) are represented the connections between the main regions of the dorsal 'Where' and the ventral 'What'. In orange is outlined the core (PAC) and in green is outlined the belt (ALA, LA). Regions marked with a blue square were shown to process mainly spatial information and regions marked with a red circle were shown to process mainly non-spatial information.

Moreover, a subcortical and cortical asymmetry was reported in the processing of auditory spatial representations (Kaiser and Lutzenberger, 2001; Salminen et al., 2010; Schönwiesner et al., 2007; Spierer et al., 2009; Zatorre and Penhune, 2001). A right hemispheric dominance for auditory localization was demonstrated by several studies, including the one from Spierer and colleagues, who investigated the hemispheric competence for auditory spatial representations in patients with unilateral brain lesions (Spierer et al., 2009). Results showed that the left hemisphere computes for the contralateral spatial hemispace while the right hemisphere is processing the whole space analysis. Their results also highlighted the role of the right temporo-parietal cortices.

1.1.3 Auditory spatial and attentional deficits following unilateral brain damage

Clinical studies helped to understand the mechanisms of auditory spatial processing by studying auditory spatial deficits following brain lesions (Adriani et al., 2003; Haeske-Dewick et al., 1996; Rey et al., 2007; Sanchez-Longo and Forster, 1958; Sonoda et al., 2001; Tanaka et al., 1999; Zatorre and Penhune, 2001).

1.1.3.a Auditory neglect

Unilateral spatial neglect (USN) is a relatively common syndrome that patients with brain damage can experience. Symptoms will manifest by a lack of attention to the hemispace contralesional. Deficits can affect one or several sensory modalities depending on the lesion site; and very different patterns of deficits are observed across patients (Heilman et al., 2000; Mesulam, 1999).

The implication of the ventral attentional system in USN deficits has been demonstrated over the past years. Indeed, USN has been linked to lesions including the right IPL or STG (Corbetta and Shulman, 2011; Karnath et al., 2001; Mort et al., 2003; Vallar and Perani, 1986), to regions of the VAS (Fig. 4A & C) or to lesions of the fiber tracts connecting them (Fig. 4B) (Bartolomeo et al., 2007; Schotten et al., 2014; Verdon et al., 2010). Neglect patients have difficulties in disengaging their attention from stimuli presented to the ipsilesional side and have a strong attentional bias toward contralesional stimuli (Bartolomeo and Chokron, 2002).

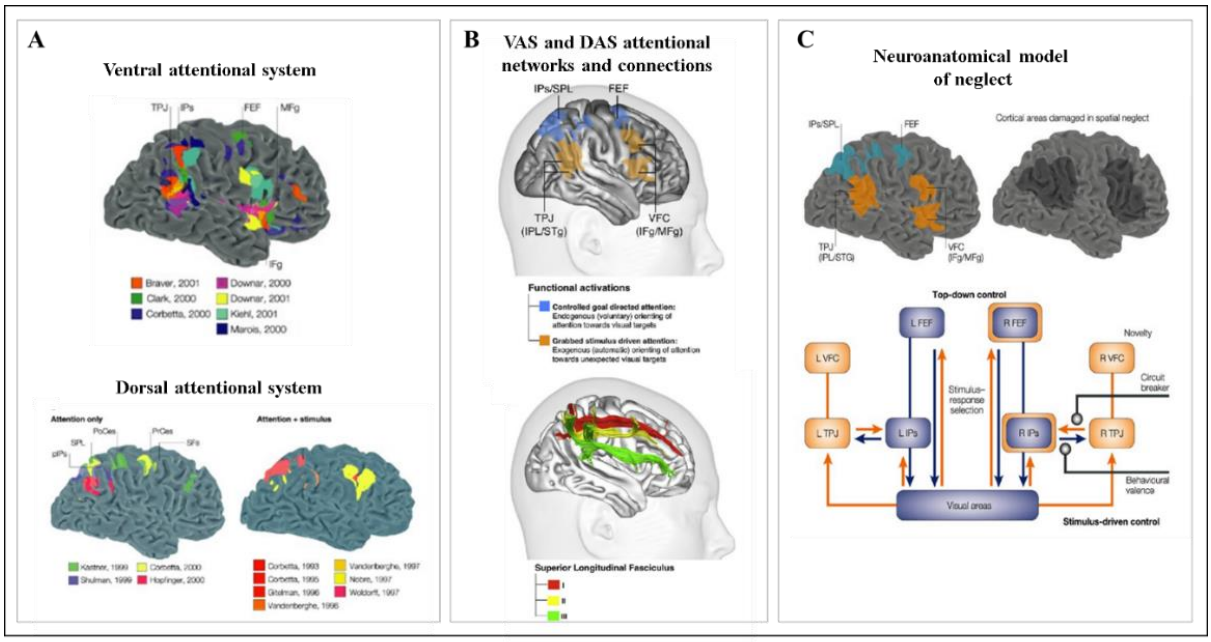

Figure 4. Attentional systems. In (A.) are represented the brain regions shown to be involved in the ventral attentional system (VAS, upper part) and in the dorsal attentional system (DAS, lower part). In (B.) are represented the VAS and DAS and the branches of the superior longitudinal fasciculus that were shown to functionally connect these regions. In (C.) are represented the VAS and DAS, along with the main lesion sites inducing neglect deficits (upper part) and a neuroanatomical model explaining the interactions between the regions involved in these two networks (lower part). Illustrations were adapted from (Chica, A. et al., 2012; Corbetta, M., 2005; Corbetta and Shulman, 2002a).

The multimodal spatial deficits and the fact that all symptoms occur without any impairment of primary sensory abilities (Bisiach, 1993; Di Pellegrino et al., 1997; Farah et al., 1989; Mesulam, 1999; Rorden et al., 1997) raised the hypothesis that unilateral neglect is linked to the dysfunction of multimodal attentional regions by direct lesions or by disconnections between them through a lesion of white matter tracts (Bartolomeo et al., 2007; Bisiach et al., 1984, 2004; Bueti et al., 2004). Different subtypes of neglect have been reported in the literature. Indeed, neglect deficits can involve the intentional-motor or sensory-inattention processing, they can be related to the personal or extra-personal space and the symptoms can manifest through unilateral or bilateral stimulation; (Heilman et al., 2000). The specific case of a neglected hemispace when two stimuli are presented simultaneously is called extinction (Parton et al., 2004).

Due to the complexity of the auditory system, auditory neglect can provoke very different deficits (Gokhale et al., 2013). Auditory neglect deficits can involve a difficulty in localizing sounds in the contralesional hemispace (Pinek et al., 1989; Pinek and Brouchon, 1992). Second type of auditory neglect deficits is related to a difficulty in localizing sounds in the entire space with specific impairments as alloacusis, i.e. mislocalization of sound sources to the ipsilesional hemifield (Altman et al., 1979; Ruff et al., 1981; Soroker et al., 1997). Investigation of the neural substrate of these deficits showed that impairments in localization in the contralesional hemispace can occur after right or left brain hemispheric lesions (Efron et al., 1983; Haeske-Dewick et al., 1996; Klingon and Bontecou, 1964; Lessard et al., 2000; Pinek and Brouchon, 1992; Sanchez-Longo and Forster, 1958; Wortis and Pfeffer, 1948; Zatorre et al., 1995). Studies that investigated impairments in localization in the entire space found either a right or left hemispheric dominance (Bisiach et al., 1984; Pinek et al., 1989; Ruff et al., 1981).

The paradigms that have been developed and used to assess auditory neglect deficits are the dichotic listening test (Kimura, 1967), the diotic listening test (Bellmann et al., 2001; Clarke and Thiran, 2004) and auditory lateralization paradigms. The dichotic listening test is a task that involves simultaneous presentation of two different words, one to each ear, and allows investigating auditory extinction. This task does not allow distinguishing extinction deficits due to attentional impairments or due to perceptual impairments (Beaton and McCarthy, 1995; Hugdahl and Wester, 1994). The diotic listening test is

therefore complementary as it involves bilateral presentation of both words with lateralization of each with interaural time differences (ITD).

Using these three paradigms: auditory lateralization, dichotic and diotic listening; previous study from our group on four neglect patients identified two types of auditory neglect following a right brain lesion (Bellmann et al., 2001). First type of auditory neglect is linked to lesions in subcortical regions, including the basal ganglia, which lead to an imbalance in the allocation of attentional resources to the left hemispace. Patients with these lesions show an asymmetry at the dichotic and diotic listening tasks but not at the auditory lateralization task. Second type of neglect is linked to lesions including regions in the fronto-parietal network, which lead to a distortion of the auditory space and to an auditory extinction. Patients with these lesions show an asymmetry at the dichotic listening task, a preserved performance at the diotic listening task and an impaired sound localization at the auditory lateralization task. However, no quantitative study has been conducted so far to compare the neural substrate underlying extinction at either task. For this reason, we conducted an anatomo-clinical study including these three paradigms and two groups of patients who suffered from either left or right hemispheric damages (Tissieres et al., In Revision).

1.1.3.b Deficits in the use of explicit and implicit spatial cues

Spatial abilities can be impaired in two different ways following brain damage: either explicitly or implicitly. Patients can experience difficulties in explicitly pointing to the source of an oncoming sound (Makous & Middlebrooks, 1990; Clarke et al., 2002; Pavani et al., 2001; Zatorre and Penhune, 2001) and/or have troubles in sound-object segregation (Carlyon, 2004; Carlyon et al., 2001; Darwin, 1997; Litovsky et al., 2002; Thiran and Clarke, 2003), an ability that requires to implicitly localize the competing oncoming sounds in order to separate and identify them (Roman et al., 2002). Double dissociations between deficits in sound localization and stream segregation observed in stroke patients (Duffour-Nikolov et al., 2012) suggest that the implicit and explicit use of spatial cues might rely on distinct neural correlates and might be related to distinct mechanisms. Paradigms developed to test the explicit use of spatial cues are auditory lateralization tasks and to test implicit spatial cues the Spatial

Release from Masking (SRM) (Carhart et al., 1967; Culling et al., 2004; Hawley et al., 2004; Saupe et al., 2010; Thiran and Clarke, 2003). Using these two paradigms and an anatomo-clinical approach, we investigated the deficits following a left or right hemispheric stroke and their underlying neural substrate (Tissieres et al., In Preparation).

1.2 Cross-modal neuroplasticity

Perception of space and navigation in a coordinated environment is possible through the integration of spatial information coming simultaneously from all the senses. Therefore, there are multimodal systems that compute this information allowing the development of a unified construct. Indeed, in everyday situations, when an object is encountered it will be perceived by several modalities and not by only one. For example, a 'fire' can be seen, heard, smelt and can even provoke some emotion to the subject. Each perception will be processed in parallel by its sensory system and then spatial treatment will be computed by areas that treat modality-specific information and by multimodal – heteromodal – areas that combine and integrate the information. These mechanisms allow orienting attention, directing the movement and navigating in a multisensory environment (Bavelier and Neville, 2002; Kujala et al., 2000; Merabet and Pascual-Leone, 2010). Therefore, **cross-modal representations** are perceptions built on the interaction between two or more sensory modalities.

Our environment is very rich and comports many distractors, noise, what makes auditory sound localization more difficult. Cross-modal representations allow enhancing the performance by decreasing the uncertainty and increasing the signal-to-noise ratio (Alais and Burr, 2004; Ernst and Banks, 2002). Moreover, our environment is constantly changing and the brain needs to be able to adapt to these changes (sound intensity, luminance, reverberations) as well as to changes emanating from its own body. These changes could impact the way the sensory modalities interact. So, in order to keep a correct spatial representation of the environment, there is a constant alignment between the different modality-specific representations through **cross-modal recalibration** (Bergan, J. et al., 2005; Recanzone, 1998; Wallace, M. and Stein, B., 2007; Wozny and Shams, 2011). The use of this specific neuroplastic capacity of the brain in order to alleviate auditory spatial deficits was explored in the present thesis using two different

visual interventions, i.e. prism adaptation and visual deprivation. These two interventions elicit cross-modal spatial processing and could potentially allow recalibration of auditory spatial representations, which would be useful in the neurorehabilitation of auditory deficits following stroke.

1.2.1 Audio-visual spatial recalibration

Importance of vision in the construction and calibration of auditory spatial representations was first demonstrated in animal studies (Feldman, D. and Knusden, E., 1997; Keuroghlian and Knudsen, 2007) Additionally, a study in the barn owl manipulated the alignment of visual and auditory maps, by putting on the animals prism goggles that shifted the entire visual field of 20 degrees (Keuroghlian and Knudsen, 2007). The animals were raised with these prisms and their auditory spatial abilities adjusted to the deviated visual input. This study demonstrated that there is a critical period for an accurate adjustment between the auditory and visual maps. Young owls can adapt to 20 degrees of displacement, but adult owls can only adapt to small visual shifts.

In humans, changes in auditory spatial representations induced by an altered visual input were investigated mainly in the following three domains: following brief or permanent visual deprivation, with the ventriloquism illusion and with prism adaptation.

Visual deprivation can occur following partial or total visual loss. Impact of visual deprivation on sound localization abilities has been investigated in blind patients as well as in blindfolded healthy controls. The ventriloquism illusion is a good example of the inter-dependency between visual and auditory information. A ventriloquist is a performer who tries to make the audience feel that his own voice appears from elsewhere, from a puppet for example. In the ventriloquism illusion, the localization of a sound is biased towards a spatially disparate visual stimulus simultaneously presented (Recanzone, 1998). Prism adaptation is a sensori-motor adaptation in which participants perform a perceptual-motor task while wearing prismatic googles that deviate the visual field laterally. Realignment of spatial coordinates through cross-modal recalibration is used in the neurorehabilitation of unilateral spatial neglect deficits. This thesis focuses on visual deprivation and prism adaptation.

1.2.2 Prism adaptation

Prism adaptation (PA) is a perceptual adaptation induced by sensory discrepancy. During PA participants wear goggles mounted with prisms that shift the entire visual field laterally (Fig. 4A). PA is a sensori-motor adaptation; therefore, it involves vision, movement and proprioception (Fig. 4B). In the 10-15 first trials participants show pointing errors, i.e. errors in the direction of the prism's deviation (Fig 4C), then they adapt their movement and point to the target correctly (Held et al., 1966).

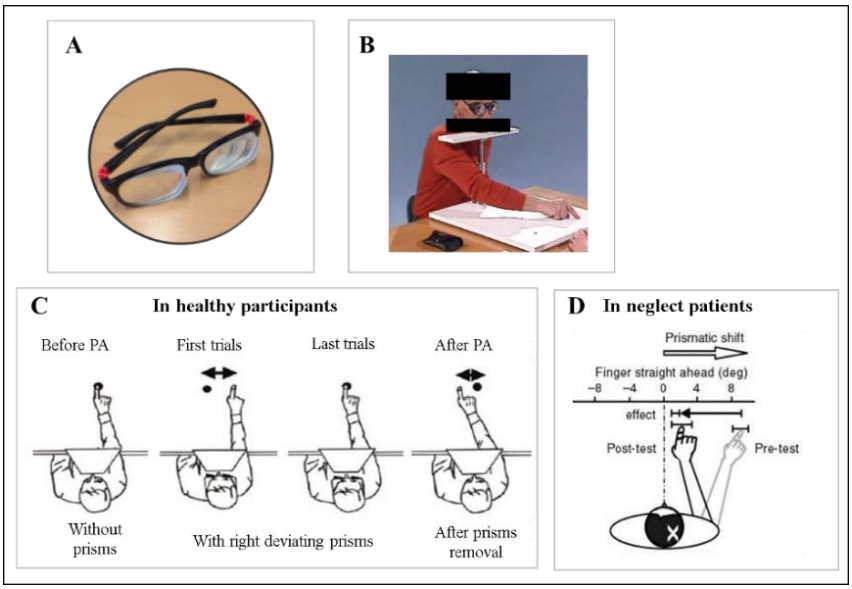

Figure 5. Prism adaptation procedure. In (A.) are represented the prismatic goggles we designed and developed for our studies: deviation of 10 degrees, light, leg of glasses can be replaced by an elastic, MR-compatible. In (B.) is represented the experimental apparatus: the participant/patient is sitting with the head positioned on a chinrest, two black dots are placed at a distance of 57 cm 14 degrees to the left and to the right of his body midline. In (C. & D.) are represented the four stages of the experimental procedure: before the adaptation phase the participant/patient does several trials without the prisms. Healthy participants will be able to touch the target without errors, whereas patients will touch the right side of the point due to their neglect deficits. Then they have to do 150 pointing movements while wearing the prismatic goggles. Once the goggles removed, they are asked to point again without the prisms. They will point more to the left than before PA, this measure is the aftereffect and is due to the sensori-motor recalibration (adapted from Jacquin-Courtois et al., 2013; Rossetti et al., 1998).

PA has been used to investigate visuo-motor plasticity in healthy subjects and to alleviate spatial deficits in patients with USN (Fig. 4D). USN is a multimodal syndrome usually encountered following a right hemispheric lesion and can involve deficits in one or several sensory modalities. Many studies have highlighted the benefits of PA in improving visuo-spatial deficits (Barrett et al., 2012; Rossetti et al., 1998; Striemer and Danckert, 2010). A systematic review of the main therapeutic approaches in the

rehabilitation of USN deficits showed that PA is the most effective neurorehabilitation protocol (Yang et al., 2013). In USN, PA was shown to improve behavior for the left side of space in non-visual modalities as well. These last years, several studies have shown benefits of PA on neglect deficits for example, in visual performance (i.e. the line bisection (Rossetti et al., 1998)); in mental imagery (Rode et al., 1998); in wheel chair driving (Jacquin-Courtois et al., 2008) and in neglect dysgraphia (Rode et al., 2006). Using a dichotic listening task, a paradigm allowing the investigation of auditory extinction, Jacquin-Courtois and colleagues showed improvements of left auditory neglect deficits after PA (Jacquin-Courtois et al., 2010). With a different design involving a dual task and allowing the study of visual and auditory spatial gradients, another group showed no effect of PA on auditory deficits (Eramudugolla et al., 2010). Through which mechanism the modulation of auditory spatial representations could take place is therefore still unclear. It remains for example to determine if PA modulates the auditory space through the same neural mechanisms as it does for the visual space; which auditory spatial capacities could be modulated by PA and for which patients it allows reducing some auditory USN deficits. To answer those questions two studies were conducted. The first study using an event-related fMRI paradigm aimed at investigating if the brain regions underlying auditory-spatial processing are modulated similarly than the regions underlying visuo-spatial processing by PA. The second study used anatomo-clinical correlations to determine for which auditory USN deficits and which patients PA could be beneficial.

1.2.2.a Neural bases of prism adaptation

Prism adaptation involves three main calibration mechanisms: i) postural adjustments; ii) recalibration of target position and strategic control; and iii) spatial realignment of the different reference frames involved (Redding and Wallace, 2006). In normal subjects several studies revealed the involvement of the right posterior parietal cortex and right cerebellum during the successive stages of this visuo-motor adaptation (Chapman et al., 2010; Clower et al., 1996; Danckert et al., 2008; Küper et al., 2014; Luauté et al., 2009). During the initial phase of adaptation, participants show pointing errors due to the misalignment induced by the prismatic goggles. Neuroimaging studies have demonstrated that the brain

regions involved in error correction include the left anterior intraparietal sulcus, anterior cingulate and primary motor cortex (Clower et al., 1996; Danckert et al., 2008). Recalibration was shown to be related to activity in the posterior parietal cortex and occipital sulcus (Luauté et al., 2009), regions underlying the adjustment of movement plans. Spatial realignment, also investigated in Luauté's study, involves the cerebellum. Chapman and colleagues, using a blocked-design fMRI paradigm, compared the initial adaptation phase (error correction) to the last phase (spatial realignment) of adaptation (Chapman et al., 2010). Their results confirmed the involvement of the cerebellum in spatial realignment and showed additionally that the inferior parietal cortex is also involved. Panico and colleagues were able to demonstrate the causal implication of the cerebellum in spatial realignment with a paradigm involving a multiple-step adaptation, i.e. exposure to a progressive visual shift from 2 to 10 degrees of displacement, and inhibitory transcranial direct current stimulation (Panico et al., 2018). Their results support the hypothesis that the cerebellum, through its anatomical parieto-ponto-cerebellar connections, contributes to the adjustment of the motor behavior via an automatic online correction.

In a study investigating the modulations, after PA, Crottaz-Herbette and colleagues compared task-related brain activations before and after rightward PA (Crottaz-Herbette et al., 2014). They showed that PA modulates visuo-spatial representations bilaterally in the inferior parietal lobules (IPL) by increasing the representation of the left, center and right visual field in the left and decreasing the representation of the right visual field in the right IPL . These findings suggest that rightward PA shifts the hemispheric dominance within the ventral attentional system from the right to the left hemisphere (Clarke and Crottaz-Herbette, 2016).

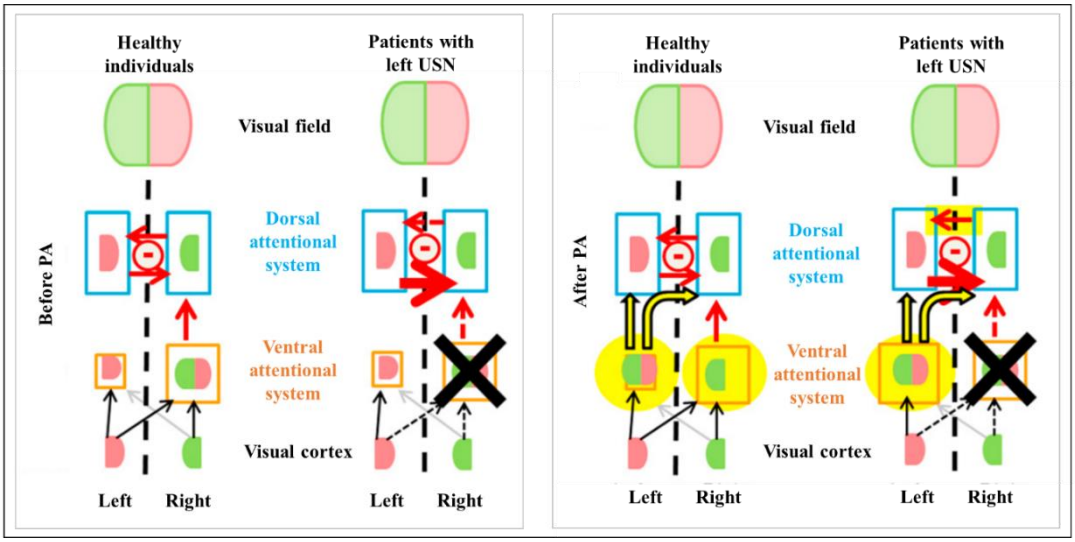

Figure 6. Modulation of the dorsal (DAS) and ventral (VAS) attentional systems in healthy and brain damaged individuals by prism adaptation (PA). On the left are represented the DAS and VAS before PA. On the right are represented the DAS and VAS after PA. This illustration is adapted from (Clarke and Crottaz-Herbette, 2016).

Figure 6 is a schematic representation of the 'shift of hemispheric dominance through the VAS' (SHD-VAS) model, which explains the interaction between the VAS and DAS and how PA, by modulating the VAS allows the restoration of the input to the DAS. The alleviation of neglect deficits by PA would rely on such modulation of the VAS (Clarke and Crottaz-Herbette, 2016). To determine if this model could explain the pseudo-neglect experienced by healthy participants following a leftward PA, we conducted a study using an event-related fMRI paradigm before and after a session of PA with leftward deviating goggles (Crottaz-Herbette et al., 2017). Our results using a leftward adaptation were compared to the results of a rightward adaptation by using a between-subjects design.

1.2.3 Visual deprivation

In the past decades, several studies demonstrated increased sound localization performances following visual deprivation (Abel and Shelly Paik, 2004; Lessard et al., 1998; Röder et al., 1999). Neuroimaging studies have highlighted the role of the visual cortex in the enhanced auditory-spatial processing of blind patients (Gougoux et al., 2005; Kujala et al., 1995; Poirier et al., 2006; Voss et al., 2008) as well as a more efficient auditory processing within the tonotopic primary auditory cortex (Stevens and Weaver, 2009). These two neural mechanisms indicate that there are cross-modal and intramodal changes

induced by the visual deprivation that allow the compensation of visual deficits by enhancing the capacities of the remaining senses.

Lessard and colleagues investigated early-blind patients, i.e. patients with congenital deficits affecting the visual system, with or without residual vision (in the periphery) and compared their performances in sound localization to those of healthy controls blindfolded or not (Lessard et al., 1998). All participants were tested under binaural and monaural conditions, meaning that each condition had a specific set of spatial cues. Their results showed that in the binaural condition, healthy controls (blindfolded and sighted controls) performed as well as blind participants. According to the authors, this result shows that blind patients do have a three-dimensional auditory space representation similarly to healthy individuals. Interestingly, blind patients with residual vision were less accurate than the other groups for peripheral sound positions and had similar performances than the other groups for central sound positions. The authors were expecting opposite results, indeed as the residual vision is in the periphery they made the hypothesis that auditory-spatial recalibration would take place where vision is lacking, i.e. in the midline. They made three hypotheses to explain these surprising results. First, some confusion could be created by the fact that these blind patients with residual vision in the periphery have to develop an auditory map partially supported by vision. Second, these patients have orienting behaviors that are not always adequate and head position is sometimes in positions that can negatively impact their ability to correctly localize the sounds. Third, the deafferented sensory regions can not be used for the auditory-spatial recalibration because they are not stimulated anymore. Results for the monaural condition (one ear was blocked during stimulus presentation) showed that healthy controls (blindfolded and sighted controls) performed similarly, with a positional bias in direction of the unobstructed ear when a sound was presented to the obstructed ear. Blind patients with residual vision were less accurate than the other groups and showed a positional bias too. Blind patients without residual vision showed surprising results: half of the patients showed similar results than controls, but with more response variability for sounds presented to the obstructed ear and reporting that those sounds seemed qualitatively different. The other half showed normal performances, very similar to the performances in the binaural condition. The authors conclude that the qualitative differences observed in some patients

for sounds presented to the obstructed ear indicate that blind patients use more efficiently monaural cues than healthy controls for auditory processing.

Abel and colleagues conducted a study to investigate if healthy subjects are able to adapt to a visual deprivation that would allow the correct localization of sound sources without vision (Abel and Shelly Paik, 2004). To do so they studied two groups: one group was blindfolded and the other was not blindfolded. Subjects were tested five consecutive days. Results showed that blindfolded subjects made more errors than the other group and had larger reaction times. Both groups performed better for broadband noise stimuli than for other stimuli. Over the five training sessions, both groups showed an improvement, but the blindfolded group showed a larger improvement in reaction times than the other group and this was due to the improvements in using spectral cues. The authors argued that the ability to adapt to situations with sudden and/or temporarily obscured vision and to use auditory cues appropriately can be extremely important. They give the examples of firefighters and military services who have to operate in environments where smoke or fog obstructs the vision and for which an error could result in fatalities.

Indeed, firefighters are frequently evolving in poor visual environments, e.g. dark or full of smoke. When they navigate in these environments, they need to be extremely vigilant to auditory inputs that could be related to individuals to rescue or to potential dangers to avoid. One interesting question is if his learning and intensive training leads to permanent changes in auditory-spatial abilities. We intend to test his assumption in a behavioral study using auditory and visuo-spatial tasks and if the hypothesis would be verified, to further investigate the underlying neural correlates of this cross-modal recalibration using a neuroimaging paradigm.

1.2.3.a Neural bases of auditory-spatial recalibration following visual deprivation

Over the past decades, numerous neuroimaging studies have reported plastic changes following visual loss related to auditory processing (Gougoux et al., 2005; Kujala et al., 1992, 1995; Liotti et al., 1998; Muchnik et al., 1991; Niemeyer and Starlinger, 1981; Röder et al., 1999; Zwiers et al., 2001).

Röder and colleagues conducted a study on congenitally blind individuals aiming at understanding the behavioral and electrophysiological indices of spatial tuning within the central and peripheral auditory space (Röder et al., 1999). Behavioral results showed that blind participants have better performances at sound localization compared to healthy controls, when attending to sounds presented in the periphery. Electrophysiological results showed a significant difference in the gradient of N1 amplitude, when sounds were presented on the periphery, with steeper N1 gradient for the blind group. This compensatory reorganization was further investigated by comparing the scalp distributions of N1 for the two groups. For the healthy group, the enhanced N1 was anteriorly located over the anterior scalp, while for the blind group it was more posteriorly located. In a subsequent study, the same group of authors compared these results from congenitally blind individuals to the ones from blind individuals with late onset, i.e. individuals who have lost their sight as older children or adults (Fieger et al., 2006). They report similar behavioral results for late-onset blind patients than for early-blind patients. The late-onset blind patients also demonstrate better sound localization performances for sounds presented in the periphery, as do the congenitally blind patients. However, late-onset blind patients use a different mechanism to do so, by showing sharper spatial tuning at a later stage of auditory processing as the significant difference in P3 highlighted.

Using positron emission tomography, a functional neuroimaging method, Gougoux and colleagues investigated sound localization in early-blind individuals (Gougoux et al., 2005). First, they evaluated sound localization performance of early-blind patients in an anechoic chamber. Next, they divided the participants in three groups according to their performance: i) early-blind patients who could localize sounds more accurately than healthy controls; ii) early-blind patients who were unable to localize sounds more accurately than healthy controls; iii) healthy controls. Then, the three groups performed the same task in the scanner. Imaging results showed that the early-blind patients who were more accurate than controls recruited their right striate and extrastriate cortices to do so. Furthermore, they showed a significant correlation between these occipital activations and behavioral performances. This correlation was driven by patients who showed better sound localization showing larger occipital activations.

Three main mechanisms have been suggested to explain cross-modal neuroplasticity (for a review, see: Bavelier and Neville, 2002): i) subcortical connectivity: changes in connections between the inferior colliculi and thalamus that will result in modulations of the input arriving to the primary sensory area; ii) cortico-cortical feedback: changes in connections between modality-specific and multimodal areas; iii) long-range connections between sensory cortices: changes in feedforward connections between primary sensory areas (Fig. 7).

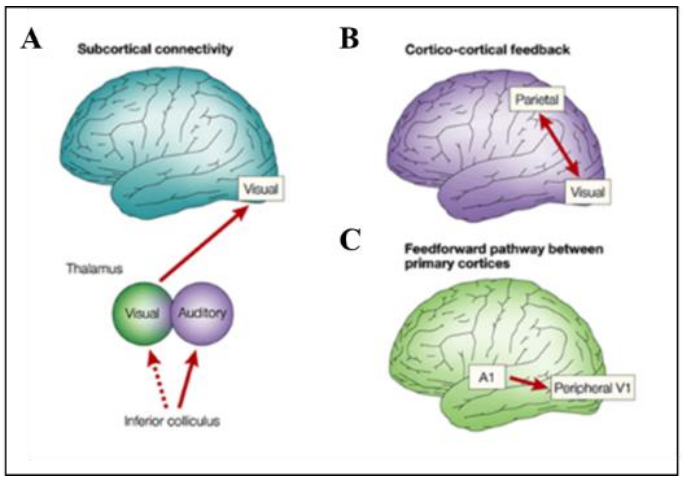

Figure 7. Mechanisms underlying cross-modal plasticity. This figure, adapted from (Bavelier and Neville, 2002), is proposing three main mechanisms for cross-modal plasticity. (A) the first mechanism involves changes in the subcortical connectivity, (B) the second mechanism relying on changes in cortico-cortical connections between modality-specific and multimodal areas, and (C) the third mechanism that relates to changes in feedforward connections between primary sensory cortices.

The three main mechanisms illustrated in Figure 7 are related to distinct types of cross-modal plasticity. Changes related to an altered subcortical connectivity have been most often observed in young animals and are rather rare in adults (Cooper Howard M. et al., 1993; Hyde and Knudsen, 2002). Changes related to cortico-cortical feedbacks can occur following trainings or following sensory loss (Bavelier et al., 2000; Bullier et al., 2001) and can be observed in adults. Changes related to feedforward pathways between primary cortices have been observed following sensory loss, for example with the recruitment of the primary cortex V1 for auditory processing and have been reported in adults too (Gougoux et al., 2005; Kujala et al., 1995; Poirier et al., 2006; Voss et al., 2008).

1.3 Aim of the thesis

The aims of this thesis were to investigate: i) the neural correlates of explicit and implicit auditory spatial cues processing; ii) the neural correlates of auditory neglect deficits; and iii) the impact of cross-modal recalibration as a strategy to improve auditory spatial capacities. The ultimate objective underlying the studies included in the present work was to determine the patients' needs and the neuroplastic abilities of the auditory spatial system in order to define better neurorehabilitation strategies in the future.

To do so, the first part of this thesis includes two neuroimaging studies analyzing the relations between lesions' anatomy and deficits in auditory spatial processing. Using a combined neuropsychological and neuroanatomical approach it is possible to determine which brain regions are necessary for a given function allowing a better understanding of the fundamental auditory spatial processing. The aims of these studies were to determine the neural substrate of auditory extinction and of the deficits in using implicit spatial cues for sound object segregation. The second part involved three studies using a sensori-motor recalibration protocol, i.e. prism adaptation, used to lessen unilateral spatial neglect deficits and that was shown to have an effect on various sensory modalities: vision, motor, proprioception. Goal was to investigate if this visuo-motor adaptation would have an effect on auditory neglect deficits and if the neural changes induced by this adaptation would be similar during a visual or an auditory detection task, which would be suggesting that the spatial recalibration done by prism adaptation is supported by brain regions performing a supramodal computation of the spatial representations.

CHAPTER 2 METHODOLOGY

2.1 Voxel-Lesion Symptom Mapping

Voxel-Lesion Symptom-Mapping (VLSM) is a mass-univariate statistical method used to assess the necessary contribution of patients brain lesions on their deficits at a behavioral task on a voxel-by-voxel basis (Bates et al., 2003). If a patient with a focal stroke has a specific deficit, we could infer that the territory affected by the stroke is essential for this cognitive function (Sperber and Karnath, 2017). So far, VLSM has been used to study the impact of a brain lesion on various cognitive functions such as motion detection (Saygin, 2007), attention (Molenberghs et al., 2009; Verdon et al., 2010), language (Bates et al., 2003; Saygın et al., 2004; Walker et al., 2011) or sound localization (Spierer et al., 2009). By testing each voxel independently, this method allows determining its specific importance for the cognitive function of interest. Neuroimaging methods, such as fMRI, EEG or PET show regions that are involved in a task or a given cognitive function. However, VLSM allows causal inferences as it specifies which regions are essential to the task or cognitive function (Sperber and Karnath, 2017).

Figure 8 explains the different steps involved in the VSLM. This method works on a voxel-by-voxel level: for each voxel two groups of patients are created, one group with the patients that have this voxel damaged and one group with the patients that have this voxel spared. Then it does a statistical test between these two groups' behavioral performances. If there is a significant result, it would indicate that when this voxel is damaged the patients present deficits at this task. Usually, the lesions of the patients are drawn manually from MRI or CT scans on axial slices using a specific software and then normalized on the Montreal Neurological Institute's (MNI) brain atlas. VLSM analyses are finally performed using a specific statistical software allowing non-parametrical analyses (Rorden et al., 2007) on the data acquired from the behavioral tasks and on the normalized brain images. In order to increase statistical power, the minimal group-size for statistical analyses is usually set to 15%. Depending on the group-size, different statistical tests are possible. For groups with more than 10 patients, the Brunner-Munzel test is appropriate (Medina et al., 2010). In order to avoid risks of false positives linked to multiple comparisons, a False Discovery Rate (FDR) correction is applied (Benjamini, Y. and Hochberg, Y., 1995).

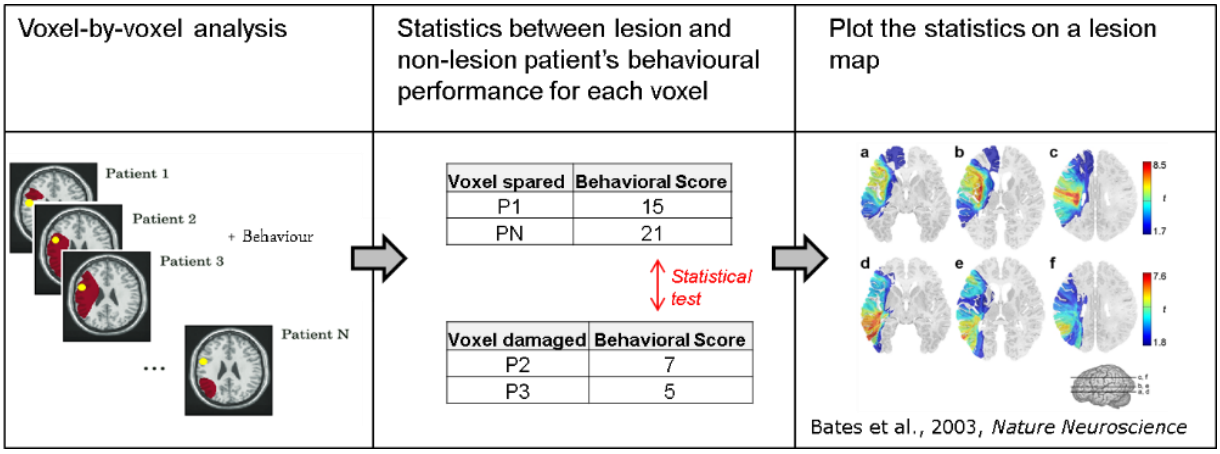

Figure 8. Voxel-lesion Symptom-Mapping procedure. Illustration adapted from (Bates et al., 2003), of the steps involved in the anatomo-clinical correlations used in the VLSM. The first step requires to draw manually patients' lesions to allow voxel-by-voxel analysis. The second step concerns the statistical analysis between the groups (voxel spared, voxel damaged) on the behavioral data. This is done for each voxel (P1, P2, P3 and PN corresponds to the patients from the first step). Final step is the plotting of the statistics on a lesion map after the correction of the statistical threshold.

VLSM has advantages and limitations. First of all, the vascular architecture of the brain is of specific importance because more than 50% of ischemic strokes involves the middle cerebral artery (Arboix et al., 2008; Muir et al., 2006), therefore most of the patients will have brain lesions involving territories around this artery. If the cognitive function of interest is not supported by the brain regions around the middle cerebral artery, it will be more difficult to find patients with a lesion including the regions important for this cognitive function. Second, for valid VLSM analyses, several criteria in the patients selection and examination must be fulfilled (Sperber and Karnath, 2017). These criteria include the delay post-stroke (acute, subacute, chronic), the neuropsychological comorbidity, the patients' age, the stroke etiology and the time point of imaging. All these factors can have detrimental effect on the VSLM results if not taken correctly into account. Indeed, these criteria can themselves explain most of the variability of the deficits. Third, VLSM is a method that assumes a statistical independence of all the voxels that are tested, but a stroke can induce distributed damages over the entire brain (Lee et al., 2009; Phan et al., 2005). However, multivariate methods are showing promising results to overcome this limitation. Finally, VLSM has the advantage to be data-driven and does not involve the a priori selection of regions of interest or cut-off scores for behavioral performance. Indeed, with their method Bates and colleagues (2003) allow including continuous behavioral data as well as brain lesions including either part of the

brain. Another advantage of VLSM is the causality it allows. Indeed, results of VLSM analyses allow determining the impact of each voxel on the performance.

VLSM and fMRI are different tools, but they can be complementary. For example, VLSM involves one brain image per subject, whereas fMRI involves autocorrelated time series of images from each subject. In VLSM the behavior is the dependent variable whereas in fMRI the behavior is the independent variable. In VLSM the spatial map is the independent variable used to predict the behavior, whereas in fMRI the spatial map is the dependent variable we want to predict by manipulating variables in our task. However, Bates and colleagues comparing results from fMRI to results from VLSM concluded that both methods are correlated up to r = .55 (Bates et al., 2003). In another study, the convergence of results coming from healthy subjects in a fMRI paradigm and of VLSM findings in stroke patients has been investigated and permitted to show that attentional effects, i.e. selection between competing stimuli, can be attributed to the middle segment of the lower bank of the right inferior parietal sulcus (Molenberghs et al., 2008). The strongest overlap between both neuroimaging methods was shown when stimuli were positioned along the horizontal axis. This study is a good example of the complementarity of VLSM and fMRI methods in the validation of cognitive models.

2.2 Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive imaging method (Ogawa et al., 1992) used to measure brain activity by detecting changes in the local oxygenation of blood in areas of the brain, which will reflect the amount of underlying cognitive activity (Logothetis et al., 2001).

The signal measured by fMRI is the change in oxygenation, i.e the blood oxygenation level dependent (BOLD) signal. When neurons become more active, they need more oxygen, therefore the amount of blood flow to that area will be increased. Deoxygenated (dHb) and oxygenated (Hb) hemoglobin have different magnetic properties. The former is more magnetic, i.e. paramagnetic, and the latter is resistant to the magnetic field, i.e. diamagnetic. This difference leads to an improved MR signal because the

diamagnetic Hb does not interfere as much with the magnetic signal. The hemodynamic response is the increase in blood flow that we see following a brief period of neuronal activity. The oxygenated blood displaces deoxygenated blood around 2 seconds later. The peak will arrive approximately 4 to 6 seconds after, with a slight undershoot afterwards before returning to the baseline level 15 to 20 seconds after (Fig. 9).

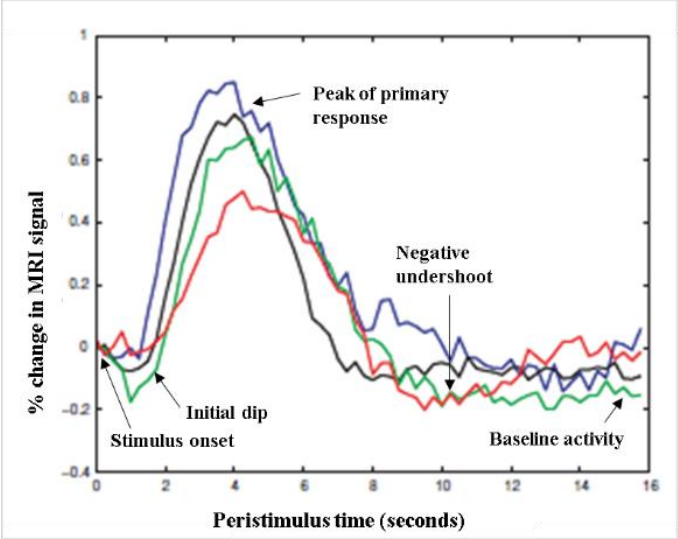

Figure 9. Hemodynamic response. Figure adapted from (Poldrack et al., 2011) illustrating the different stages of the hemodynamic response: stimulus onset at 0 sec; initial dip between 0 and 2 seconds; peak of primary response approximatively 4 to 6 seconds after stimulus onset; negative undershoot approximatively 10 seconds after stimulus onset; and return to baseline activity 14 to 16 seconds after stimulus onset.

The hemodynamic response follows a certain linearity that allows creating statistical models. Indeed, event-related fMRI paradigms, i.e. designs using rapid intermixed trials with short – 2 to 5 seconds – intertrial intervals, showed that the BOLD response behaves as a linear time invariant system (Boynton et al., 1996; Dale and Buckner, 1997; Vazquez and Noll, 1998). The usual approach in analyzing fMRI data is through the General Linear Model (GLM) (Fig. 10). The GLM works by considering that at each time point, the hemodynamic response is equal to the events active at that point. To specify the model, we have to create a design matrix (X in the Fig. 10) determining which events are active at each time point. Each column of the matrix will correspond to an event and each row to a time point. The assumption is that the specific shape of the hemodynamic response will change in amplitude in active voxels. Therefore, this assumption is used mathematically, by a procedure coined as convolution, to

predict the hemodynamic response of a voxel at a certain time point. To minimize residual errors (Ɛ in the Fig. 10), available parameters that could explain some part of the brain activity are included (ß in the Fig. 10) in the prediction model. These parameters can be motion correction parameters, age or heart beat rate for example.

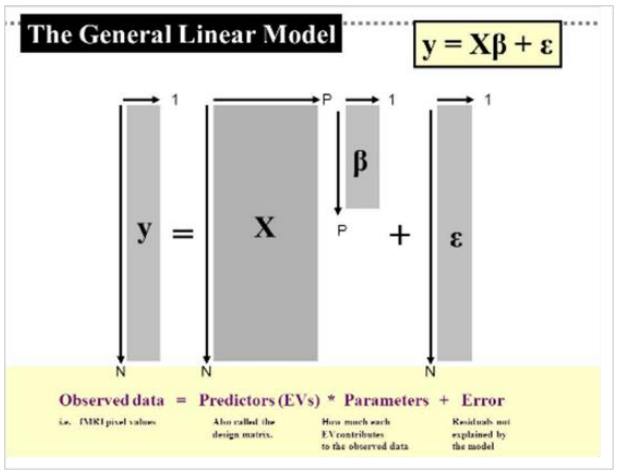

Figure 10. The General Linear Model (GLM). Illustration of the GLM adapted from (Poldrack et al., 2011), where y is referring to the observed data; X to the predictors, ß to the parameters and Ɛ to the residual error.

Usually, analysis of fMRI data follows these major processing steps: correction for spatial distortion of the fMRI images (distortion correction); realignment of the scans across the time to correct for participant's motion (motion correction); correction of differences in timing across the slices in each image (slice timing correction); alignment of each participant's data into o common spatial template (spatial normalization); blurring of the images to improve the signal-to-noise ratio (spatial smoothing); removing or attenuating the low-frequency in order to improve the signal-to-noise ratio (temporal filtering); fitting a statistical model to the data (statistical modeling); correction for multiple comparisons (statistical inference); and visualization of results (visualization).

The GLM statistical method is an univariate approach in which each voxel is analyzed independently. Therefore, in order to minimize Type I errors, i.e. false positive errors, a correction for multiple comparisons is required. Different methods to correct for multiple comparisons exist. The Bonferroni correction has been shown to be too conservative by reducing to much the estimated number of degrees

of freedom. Another approach is the family-wise error rate that is based on the assumption of random Gaussian field and works by applying a Gaussian smoothing filter. Whereas this approach is interesting to reduce Type I errors, it can significantly increase Type II errors, i.e. false negative errors. Finally, the false discovery rate is an interesting stepwise algorithm that controls for about 5% of false positive activation (incorrect rejections of null-hypotheses) by sorting the p-values and sequentially rejecting the hypotheses starting from the smallest p-values.

fMRI, such as other neuroimaging methods, has advantages and limitations as well. The big advantage of fMRI is that it is non-invasive and allows investigating the activity of brain regions or brain networks in animals, humans, either healthy or patients populations, in non-harmful ways. With the increasing popularity of fMRI these last decades, methods have been developed, such as Resting State fMRI, allowing investigating populations that cannot be in an active task, such as infants, comatose patients or patients following a stroke. This method allows to determine if some brain networks are functionally disturbed by examining the brain activity when it is at rest. Another advantage is that fMRI has a good spatial resolution. Depending on the scanner parameters the spatial resolution can be as good as having voxels of 1 x 1 x 1 mm with a 3 Tesla machine, or even less with a ultra high field 7 Tesla machine. This resolution allows studying the activity of small structures such as subcortical regions, but one has to take into account that the increase of spatial resolution increases the signal-to-noise ratio as well. Limitations of fMRI paradigms concern the temporal resolution weakness. Indeed, the hemodynamic response is much slower than the underlying neuronal activity. For example, the peak of activity of the hemodynamic response following the presentation of a visual stimulus in V1 will arrive around 5 seconds later, while it takes around 200 ms to the neurons in V1 to process the visual stimulus. Furthermore, fMRI is an indirect method and it only permits to determine correlational relations. Finally, not everyone can be included in fMRI studies. There are exclusion criteria based on magnetic resonance safety and on health issues. These exclusion criteria are for example: have a pacemaker, an insulin pump, a piece of metal in the body (piercing or projectile), be pregnant, be claustrophobic, diabetic or subject to panic attacks.

CHAPTER 3 SUMMARY OF THE RESULTS

3.1 STUDY A - Exploring auditory neglect: anatomo-clinical correlations of auditory extinction

Isabel Tissieres, Sonia Crottaz-Herbette and Stephanie Clarke

This article is in revision in the Journal 'Annals of Physical and Rehabilitation Medicine'.

Contribution

The candidate contributed decisively in the analyses, writing of the paper and partly on data acquisition.

Abstract

Background: The key symptoms of auditory neglect include left extinction on tasks of dichotic and/or diotic listening and rightward shift in locating sounds. Whereas the anatomical correlates of the latter are relatively well understood, there are no systematic studies on auditory extinction.

Methods: We examined 20 patients with right (RDH) and 19 with left hemispheric damage (LHD) using dichotic and diotic listening tests. Either test consists of simultaneous presentation of word pairs; in the dichotic test one word is presented to each ear, in the diotic test each word is lateralized by means of interaural time differences and presented to one side.

Results and Conclusion: RHD was associated with exclusively contralesional extinction in dichotic or diotic listening, whereas LHD led in selected cases to contra- or ipsilesional extinction. Bilateral symmetrical extinction occurred in RHD or LHD, in dichotic or diotic listening. The anatomical correlates of these extinction profiles offer an insight into the organisation of the auditory and attentional systems. First, left extinction in dichotic vs. diotic tests involves different parts of the right hemisphere, which explains the double dissociation between these two neglect symptoms. Second, contralesional extinction in the dichotic test relies on homologous regions in either hemisphere. Third, ipsilesional extinction in the dichotic test following LHD was associated with lesions of the intrahemispheric white matter, interrupting callosal fibres outside their midsagittal or periventricular trajectory. Fourth, bilateral symmetrical extinction was associated with large parieto-fronto-temporal LHD or with smaller parieto-temporal RHD, suggesting thus that divided attention, supported by the right hemisphere, and auditory streaming, supported by the left, are likely to play a critical role.

3.2 STUDY B – Left and right hemispheric lesions impair implicit use of spatial cues in auditory streaming

Isabel Tissieres, Sonia Crottaz-Herbette and Stephanie Clarke

This article is in preparation for submission (Final stage).

Contribution

The candidate contributed decisively in the analyses, writing of the paper and partly on data acquisition.

Abstract

Previous studies reported a double dissociation between deficits in explicit sound localization and in sound object segregation on the basis of implicit use of spatial cues, suggesting the existence of a position-linked representation of sound objects that is distinct from the position-independent representation within the ventral auditory stream and from the explicit sound localization processing within the dorsal stream. Here we provide evidence for the anatomical substrate of spatial-cue based sound object segregation.

Fifty-seven participants (17 controls; 20 patients with left and 20 with right hemispheric damage) were assessed for explicit sound localization and for the effect of spatial release from masking (SRM). The latter used two simultaneous environmental sounds; the position of the masker varied (a central and 2 positions within each hemispace, simulated with interaural time differences) whereas the target remained central. Voxel-based Lesion-Symptom Mapping (VLSM) was applied to either task.

Performance in the explicit localization task depended critically on the right parietal cortex, confirming the role of the right dorsal auditory pathway in explicit localization.

For the SRM task, separate VLSM analysis was performed for each of the 5 masker positions. It highlighted the critical role of a large temporo-parieto-frontal region within the left hemisphere, independently of the position of the masker. In addition, a smaller parieto-temporal region was highlighted, more specifically when the masker was central or to the right.

Thus, explicit and implicit use of spatial cues depend on at least partially distinct neural networks. The involvement of a left temporo-parieto-frontal network in the SRM effect is in agreement with the role of a left temporo-frontal network in position-linked representation of sound objects, which was reported in a previous EEG study.

3.3 STUDY C - Supramodal effect of rightward prismatic adaptation on spatial representations within the ventral attentional system

Isabel Tissieres, Eleonora Fornari, Stephanie Clarke and Sonia Crottaz-Herbette

This article was published in the Journal 'Brain Structure and Function' in 2017.

Contribution

The candidate contributed decisively in the elaboration of the experimental design, the recruitment of participants, the analyses and writing of the paper.

Abstract

Rightward prismatic adaptation (R-PA) was shown to alleviate not only visuo-spatial but also auditory symptoms in neglect. The neural mechanisms underlying the effect of R-PA have been previously investigated in visual tasks, demonstrating a shift of hemispheric dominance for visuo-spatial attention from the right to the left hemisphere. We have investigated whether the same neural mechanisms underlie the supramodal effect of R-PA on auditory attention. Normal subjects underwent a brief session of R-PA, which was preceded and followed by an fMRI evaluation during which subjects detected targets within the left, central and right space in the auditory or visual modality. R-PA-related changes in activation patterns were found bilaterally in the inferior parietal lobule. In either modality the representation of the left, central and right space increased in the left IPL, whereas the representation of the right space decreased in the right IPL. Thus, a brief exposure to R-PA modulated the representation of the auditory and visual space within the ventral attentional system. This shift in hemispheric dominance for auditory-spatial attention offers a parsimonious explanation for the previously reported effects of R-PA on auditory symptoms in neglect.

3.4 STUDY D - For better or worse: The effect of prismatic adaptation on auditory neglect

Isabel Tissieres, Mona Elamly, Stephanie Clarke and Sonia Crottaz-Herbette

This article was published in the Journal 'Neural Plasticity' in 2017.

Contribution

The candidate contributed decisively in the elaboration of the experimental design, the recruitment of participants, the analyses and writing of the paper.

Abstract

Patients with auditory neglect attend less to auditory stimuli on their left and/or make systematic directional errors when indicating sound positions. Rightward prismatic adaptation (R-PA) was repeatedly shown to alleviate symptoms of visuo-spatial neglect and once to restore partially spatial bias in dichotic listening. It is currently unknown whether R-PA affects only this ear-related symptom or also other aspects of auditory neglect. We have investigated the effect of R-PA on left-ear extinction in dichotic listening, space-related inattention assessed by diotic listening, and directional errors in auditory localization in 10 neglect patients. The most striking effect of R-PA was the alleviation of left ear extinction in dichotic listening, which occurred in half of the patients with initial deficit. In contrast to the non-responders, their lesions spared the right dorsal attentional system and posterior temporal cortex. The beneficial effect of R-PA on ear-related performance contrasted with detrimental effects on diotic listening and auditory localization. The former can be parsimoniously explained by the SHD-VAS model, which is based on the R-PA-induced shift of the right-dominant ventral attentional system to the left hemisphere. The negative effects in space-related tasks may be due to the complex nature of auditory space encoding at cortical level.

3.5 STUDY E – A brief exposure to leftward prismatic adaptation enhances the representation of the ipsilateral, right visual field in the right inferior parietal lobule.

Sonia Crottaz-Herbette, Eleonora Fornari, Isabel Tissieres and Stephanie Clarke

This article was published in the Journal 'eNeuro' in 2017.

Contribution

The candidate contributed to the recruitment of participants and data acquisition.

Abstract

A brief exposure to rightward prismatic adaptation (PA) was shown to shift visual field representation within the inferior parietal lobule from the right to the left hemisphere. This change in hemispheric dominance could be interpreted as i) a general effect of discrepancy in visuo-motor alignment caused by PA or ii) a direction-specific effect of rightward PA. To test these hypotheses, we compared the effects of rightward and leftward PA on visual representation. Three groups of normal subjects underwent an fMRI evaluation using a simple visual detection task before and after brief PA exposure using leftward- or rightward-deviating prisms or no prisms (L-PA, R-PA, Neutral groups). A two-way ANOVA Group x Session revealed a significant interaction, suggesting that PA-induced modulation is direction-specific. Post hoc analysis showed that L-PA enhanced the representation of the right visual field within the right inferior parietal lobule. Thus, a brief exposure to L-PA enhanced right hemispheric dominance within the ventral attentional system, which is the opposite effect of the previously described shift in hemispheric dominance following R-PA. The direction-specific effects suggest that the underlying neural mechanisms involve the fine-tuning of specific visuo-motor networks. The enhancement of right hemispheric dominance following L-PA offers a parsimonious explanation for neglect-like symptoms described previously in normal subjects.

CHAPTER 4 GENERAL DISCUSSION

The specific aims of the present thesis were to investigate auditory-spatial deficits following brain lesions and the neuroplasticity of auditory space representations with the broader goal to allow designing more successful rehabilitation protocols in the future. Therefore, in this chapter the results of the five studies composing the present work will be discussed regarding their impact on the understanding of auditory spatial processing and deficits, the plasticity of auditory space representations and their neural correlates.

First, we will review the results from the studies on auditory neglect deficits and on the insight they offer into the neural organization of auditory spatial processing. Second, we will explore the cross-modal plasticity induced by prism adaptation on auditory spatial processing and we will propose putative mechanisms underlying this cross-modal recalibration. Third, results from the five studies will be debated regarding the auditory attentional networks in order to highlight their support for an additional pathway suggested by previous results, integrating spatial and non-spatial information for sound object processing. Finally, future directions will be proposed regarding fundamental as well as clinical perspectives.

4.1 Correlates of auditory neglect

Auditory neglect can lead to three types of deficits. The first type of deficits concerns sound lateralization tasks with patients presenting systematic directional errors (Altman et al., 1979; Bellmann et al., 2001; Bisiach et al., 1984; Haeske-Dewick et al., 1996; Soroker et al., 1997). The second type of deficits is an extinction of contralesional items when simultaneously presented to the patient (Heilman and Valenstein, 1972; Hugdahl and Wester, 1994). The failure to report stimuli on the left side was shown using tasks of dichotic listening, in which simultaneous auditory stimuli are presented to each ear (Deouell and Soroker, 2000; Heilman and Valenstein, 1972; Hugdahl et al., 1991). The third type of

deficit is an extinction of left-sided stimuli, so related to space and not to the ear of entry, as demonstrated by tests of diotic listening (Bellmann et al., 2001; Spierer et al., 2007; Thiran and Clarke, 2003). In this latter test, sounds are lateralized by means of interaural time differences: two stimuli are presented simultaneously to both ears.

These three key symptoms of auditory neglect can occur in a given patient together or in separation. A double dissociation has been initially described between extinction on diotic listening and rightward shift in sound localization (Bellmann et al. 2001). In this study, four patients with neglect characterized by extinction on dichotic listening were investigated; two had extinction on diotic listening and normal performance in sound localization that were attributed to lesions on the basal ganglia, whereas the other two patients presented rightward shifts on sound localization and normal performance on diotic listening that were attributed to lesions of parieto-fronto-temporal brain regions. A later study reported a double dissociation between extinction on dichotic vs. diotic (Spierer et al., 2007). This study included 15 patients with auditory neglect. Five out of 15 patients presented a significant asymmetry on diotic listening, due to a decrease of reporting stimuli presented on the left side, and normal performance on dichotic listening. Six other patients presented significant asymmetry on dichotic listening and normal performance on diotic listening. Only one patient out of the 15 did not present deficits in sound localization too. Spierer's study did not investigate the underlying anatomical substrate of each patient's profiles.

Double dissociations among auditory neglect deficits suggest that the three types of deficits should depend on distinct neural correlates. Sound localization was attributed to the right parietal cortex, as established in a series of studies (Spierer et al., 2009; Tanaka et al., 1999). The dichotomy of rightward shift in auditory localization vs. left spatial extinction was shown to rely on damage centred on the prefrontal, superior temporal and inferior parietal cortex vs. lesions of basal ganglia, respectively (Bellmann et al. 2001), suggesting indeed different neural networks. So far, there was no systematic quantitative study of the neural correlates of auditory extinction.

Using anatomo-clinical correlations to investigate the different types of auditory extinction we were able to go further in the understanding of auditory attentional networks and auditory neglect deficits (Tissieres et al., In Revision). The first result of this study concerns the difference in the neural substrate of left extinction in dichotic vs. diotic tasks. Dichotic and diotic listening deficits for the contralesional left hemispace were linked to different brain regions of the right hemisphere. This difference explains the previously described double dissociation between these symptoms of auditory neglect, i.e. extinction related to the ear of entry or to the side of entry. Additionally, results showed that contralesional extinction in dichotic listening relies on a similar neural substrate in either hemisphere; thus, both right and left auditory cortices are involved, each one critically for information provided by the contralesional ear. Third, ipsilesional extinction in dichotic listening following LHD was linked to lesions involving intra-hemispheric white matter; thus, the callosal disconnection which is believed to cause this deficit can also occur in cases of intrahemispheric and not only midsagittal or periventricular interruptions of the callosal pathway. Fourth, bilateral symmetrical extinction was linked to LHD in a large parieto-fronto-temporal region, and with RHD in a smaller parieto-temporal region, indicating a role of divided attention, supported by the right hemisphere, and of auditory streaming, supported by the left hemisphere.

In an independent study, we investigated the neural correlates of the implicit and explicit use of spatial cues (Tissieres et al., In Preparation). We were able to show the hemispheric asymmetry in the computation of either cues explaining the double dissociation reported in previous studies. Results clearly demonstrated that sound object segregation involves bilateral regions but relies predominantly in left fronto-temporo-parietal areas, while the explicit use of spatial cues involved in sound object localization relies on the right dorsal attentional pathway. Moreover, results also permitted to see the impact of left unilateral neglect on the implicit use of spatial cues. Indeed, RHD patients showed a performance asymmetry driven by a globally lower performance than the one of the LHD group for all positions, but more so for positions on the right hemispace. This performance asymmetry is explained by the fact that when the masker sound is presented on the left hemispace, it is neglected by the patient and therefore has less impact on the detection of the central target.

These results highlighting the role of left hemispheric structures for the spatial processing involved in sound object segregation offer new insights for therapeutical approaches. By strengthening the auditory attentional systems, as for example using prism adaptation, deficits in using implicit spatial cues could be potentially alleviated. However, no study so far has investigated this hypothesis.

In summary, these two studies allowed understanding the organization of auditory spatial processing showing that either left or right hemispheric damage can lead to auditory spatial deficits.

4.2 Multimodal changes induced by prism adaptation

In an experiment using an fMRI event-related paradigm we studied the neural plasticity induced by prism adaptation using visual or auditory detection tasks and we were able to show that the inferior parietal lobule is similarly modulated by PA in each modality, unraveling its supramodal role in the realignment of the spatial coordinates (Tissieres et al., 2017b). Results showed that rightward PA enhances the involvement of the left angular gyrus in the detection of the targets presented on the left, center and right auditory space and decreases the involvement of the right supramarginal gyrus for the targets presented on the right auditory space. Thus, rightward PA shifts the hemispheric dominance for auditory-spatial attention from the right to the left IPL. This effect of PA is in line with previously results and is in keeping with the SHD-VAS model (Clarke and Crottaz-Herbette, 2016; Crottaz-Herbette et al., 2014). In addition to the previous results and to the model, present results highlight the fact that the IPL is the multimodal brain region subserving the supramodal spatial processing induced by PA and therefore this region might be related to the positive effects of PA on multimodal symptoms of neglect. Furthermore, another fMRI study was conducted aiming at understanding the directional effect of PA (Crottaz-Herbette et al., 2017). In this study, neural mechanisms involved in rightward PA and leftward PA were compared. Results showed that the inferior parietal lobule underlies the realignment of spatial coordinates for both adaptations in opposite ways. Indeed, following the rightward adaptation, the left visual field was enhanced within the left IPL, whereas following the leftward adaptation, it is the right

visual field that was enhanced within the right IPL. This enhancement of the right IPL enhances regions involved in the right ventral attentional system and by this way strengthen the right attentional bias, which explains the pseudo-neglect reported following leftward PA in healthy participants and which adds supporting evidence for the SHD-VAS model.

As the IPL is dedicated to the multimodal realignment of spatial coordinates, it should be involved in the latter stage of the adaptation. Petitet and colleagues, used a mathematical modelling and proposed a neuro-computational model (Fig. 11) explaining the different steps involved in prism adaptation. In their Bayesian model composed of eight steps, the multimodal integration is indeed taking place at the last stage (Petitet et al., 2017). The eight steps of the model are: i) the entry of the sensory input to the eyes; ii) the visual inverse model calculating the visual displacement; iii) the decision maker in charge of the alignment between the actual and perceived target location; iv) the motor inverse model in charge of determining the motor commands based on the direction determined by the decision maker; v) the feedback information about the reaching endpoint is sent to visual and proprioceptive models allowing the adjustment of the future motor command; vi) the feedback information about the movements are sent to visual and proprioceptive models; vii) the Bayesian integration of all the precedent forward predictions coming from each modality; and viii) the multimodal integration.

However, the specific assumption that the multimodal integration occurring at the last step of the prism adaptation relies on the inferior parietal lobules remains to be empirically demonstrated. To answer this question, a high-density electrophysiological approach, which would allow investigating the temporal aspects of the different steps involved in PA as well as their neural correlates, should be used.

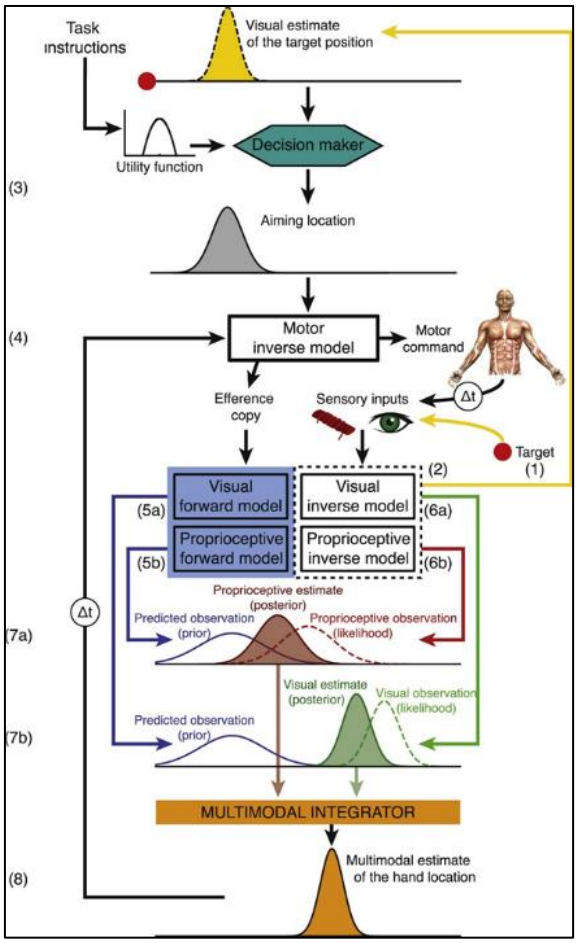

Figure 11. Neuro-computational model of prism adaptation. Illustration adapted from (Petitet et al., 2017) showing the proposed Bayesian model of the different steps underlying the visuo-motor recalibration induced by prism adaptation. In (1) is represented the sensory input (light) entering to the eyes through the deviating prism lens. In (2) is represented the visual inverse model computing the visual displacement. In (3) is represented the decision maker, which will allow aligning the reaching endpoint with the target location. In (4) is the motor inverse model, which allows the transformation of the goal (aiming direction) into an action plan (motor command). In (5) is represented the efference copy of this action plan sent to visual and proprioceptive models in order to generate predictions about the next motor command (due to the ballistic movements, this prediction is restricted to the reaching endpoint and not to the entire movement). In (6) is represented the sensory feedbacks (visual and proprioceptive) generated by the movements. These sensory feedbacks are integrated in modality-specific sensory inverse models that include the location of the hand. In (7) is the Bayesian integration of the modality-specific forward predictions. In (8) is represented the latter stage involving the multimodal integration of the different spatial estimates.

In another experiment, the alleviation of auditory neglect deficits using PA was investigated in ten patients following a first right hemispheric stroke (Tissieres et al., 2017a). Results showed a beneficial effect of rightward PA on auditory neglect limited to the alleviation of left-ear extinction in dichotic listening. This particular effect can be explained by the SHD-VAS model (Clarke and Crottaz-Herbette, 2016.; Crottaz-Herbette et al., 2014). The ventral attentional system is known to be involved in the

detection of unexpected stimuli and therefore, in the reorienting of attention (Corbetta and Shulman, 2002; Igelström and Graziano, 2017.; Shulman et al., 2010, 2003; Todd et al., 2005). In neglect patients it is often damaged preventing the detection of targets (Corbetta and Shulman, 2002). The shift of the ventral attentional system to left IPL allows restoring the alerting input to the dorsal attentional system on either side, both for auditory and visual targets. The results from this study showing that for the alleviation of the left extinction to occur, the right dorsal attentional system needs to be intact, are in line with the model. The effect of rightward PA on deficits at the diotic listening task was not consistent and it even worsened deficits for several patients. Our results showed that in specific conditions rightward PA can enhance the rightward spatial bias and by doing so amplify neglect symptoms. When it happened in diotic listening, the initial condition of the patients involved scores that where extremely low or within lower normal range on both sides. Rightward PA increased the reporting on the right but not on the left side. The beneficial effect on the right side can be explained by the SHD-VAS model and the ensuing activation of the left dorsal attentional system. Both patients who presented this effect suffered from damages involving brain regions on the right dorsal attentional system, which consequence was to prevent the re-orienting of attention to the left.

The results of this study confirmed the previous results reporting a beneficial effect of PA on auditory extinction as tested with the dichotic listening paradigm (Jacquin-Courtois et al., 2010). Moreover, the present results reporting detrimental or no effects on the space-related measures also allow understanding the results of Eramudugolla and colleagues, that showed no effect of PA on the auditory spatial gradients (Eramudugolla et al., 2010).

In summary, the results from our studies investigating PA allowed demonstrating the supramodal role of the IPL, suggesting its involvement in the realignment of the spatial coordinates. The recruitment of multimodal brain regions allows this protocol to be efficient at alleviating auditory neglect deficits, when

the neural structures damaged do not prevent the shift of spatial representations from the right to the left hemisphere.

4.3 Attentional systems

The auditory attentional system was shown to be organized as the visual attentional system around two main streams: the dorsal 'Where' stream and the ventral 'What' stream (Fig. 12). The dual-stream model implies that the semantic representations of sound objects in the brain regions along the ventral 'What' stream are position-independent, i.e. do not involve spatial information about the sound object. Whereas in the dorsal 'Where' stream sound objects are coded about their position, but not their semantic category. These two pathways are independent and dedicated to different mechanisms, but they were shown to communicate and in specific tasks, results showed involvement of dorsal regions in semantic tasks and ventral regions in spatial tasks.

In a repetition priming electrophysiological study, the mechanisms of the combined information about the meaning and the position of a specific sound object and how it is represented in the brain were investigated (Bourquin et al., 2013). Their results identified position-independent representations of sound objects within the right temporo-frontal region and left temporo-parietal region supporting the dual-stream model. Additionally, a position-linked representation was found within the ventral stream of the left hemisphere including the posterior parts of the superior and middle temporal gyri. This result suggests that some regions of the ventral stream on the left hemisphere process both semantic and spatial information including the binding of these two types of information. The spatial information arriving to the ventral stream regions in the left hemisphere could be provided either by early-stage auditory area: the ALA, or by input from the dorsal stream (Budd et al., 2003; Rivier and Clarke, 1997; van der Zwaag et al., 2011; Viceic et al., 2006; Wallace et al., 2002). Current results suggest that combined coding for semantic and spatial representations takes place in the supratemporal plane. Further results supporting that the binding of semantic and spatial information occurs at the level of early-stage auditory areas

come from a study conducted by Cammoun and colleagues that investigated the intrahemispheric connectivity of the human auditory cortex using a neuroimaging method coined as Diffusion Spectrum Imaging (DSI) (Cammoun et al., 2015). DSI is a non-invasive in vivo approach that allows the study of the structural connectivity through the use of specific MRI sequences. Results showed that several streams are originating from the PAC, while there are only a few connections between the dorsal and ventral streams outside the supratemporal plane. Recent ultra-high field fMRI study from our group confirmed the involvement of early-stage areas in the combining of spatial and non-spatial information (Da Costa et al., 2018).

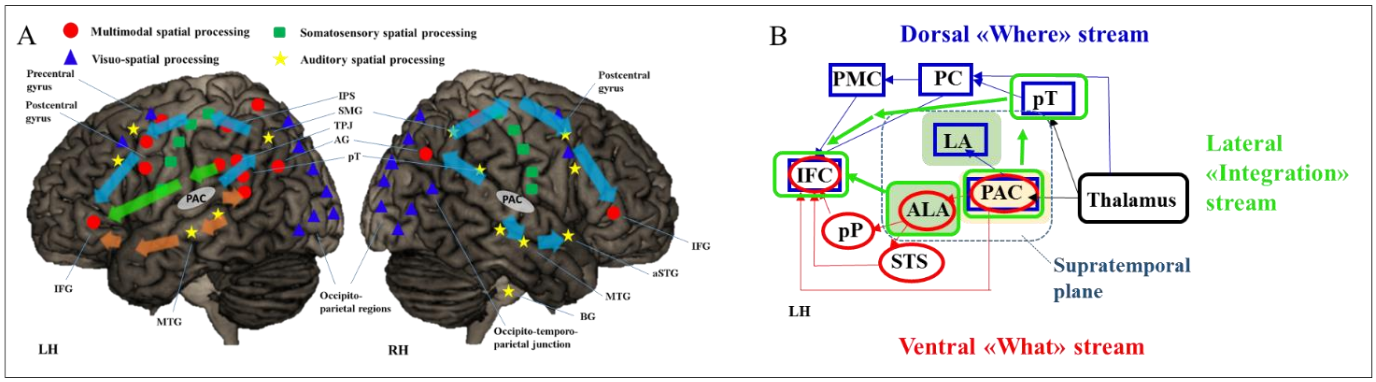

Figure 12. Attentional streams for auditory processing. Schematic representations of our findings combined with the results coming from the existing literature. In A. Illustration of the brain regions shown by the literature and the present studies to be involved in unimodal and multimodal spatial processing. Attentional auditory pathways are represented with the colored arrows: dorsal 'Where' stream (blue), ventral 'What' stream (orange) and the lateral 'Integration' stream (green). B. Schematic representation of the brain regions involved in each processing stream.

Evidence coming from the studies conducted here on the neural correlates of sound segregation (Tissieres et al., In Preparation), on the neural mechanisms of prism adaptation (Crottaz-Herbette et al., 2017; Tissieres et al., 2017a, 2017b) are supporting the existence of left hemispheric structures dedicated to the spatial processing of sound objects.

Results from the studies presented above strongly support the right hemispheric dominance for auditory spatial processing and auditory attention. These abilities depend on a right-dominant parieto-frontal network. However, these results indicate that the left hemisphere also computes spatial representations, in particular of the ipsilateral auditory space, which might be important for sound object segregation and might be a useful pathway for rehabilitation of auditory neglect using PA.

4.4 Conclusions

Auditory spatial deficits can occur following brain damage and severely impair patient's quality of life. In some cases, it can even prevent the patients to start working again. Rehabilitation strategies targeting specifically these deficits are still scarce nowadays. The aims of the present thesis were to better determine auditory neglect by investigating the neural substrate underlying each deficits and to evaluate the impact of prism adaptation, a visuo-motor training protocol, on the alleviation of these deficits.

Cross-modal recalibration can be a useful way to target auditory spatial deficits when the modulation of the unimodal brain regions' activities is not possible due to lesions involving the auditory system. A better understanding of which brain regions are performing multimodal spatial treatment allows selecting the good trainings, i.e. trainings that recruit these brain regions.

The results from the studies composing the present work demonstrate the auditory spatial recalibration following prism adaptation, which is a visuo-motor training protocol. By showing that the inferior parietal lobule is the supramodal brain region underlying the multimodal benefits of prism adaptation and by determining for which patients this training could be efficient, we provided strong evidence that this visuo-motor adaptation is a promising therapy for the rehabilitation of auditory-spatial deficits.

4.5 Future directions

The effect of PA on auditory-spatial deficits was investigated using an auditory lateralization task and two tasks evaluating auditory extinction. The impact of prism adaptation on the alleviation of deficits in the implicit use of spatial cues remains however to be evaluated.

Based on our findings showing that prism adaptation has selective beneficial effects, it will be important to conduct a large clinical trial to determine statistically which patients are good responders. Then, to

conduct clinical trials including only the good responders to assess to which extent auditory neglect deficits can be improved using prism adaptation. Another line of research should focus on determining the optimal duration, intensity and number of sessions of prism adaptation to obtain a successful, long-term, improvement of auditory spatial deficits.

Moreover, the multisensory processing of the inferior parietal lobule remains to be demonstrated, as well as the temporal aspects of the prism adaptation to understand when the multimodal integration takes place. A high-field electrophysiological study would be a useful way to answer both questions as it allows a precise temporal investigation and gives insight about the brain regions involved in each mechanism.

Finally, our results add strong evidence for the existence of a third auditory processing stream dedicated to the integration of position-dependent and position-independent representations of sound objects. Additional studies are needed to address the exact neural correlates of this lateral 'Integration' stream, their temporal aspects and the functional connectivity between this stream and the other two, i.e. the dorsal 'Where' and the ventral 'What' streams.

CHAPTER 5 BIBLIOGRAPHY

Abel, S.M., Shelly Paik, J.E., 2004. The benefit of practice for sound localization without sight. Applied Acoustics 65, 229–241. https://doi.org/10.1016/j.apacoust.2003.10.003

Adriani, M., Maeder, P., Meuli, R., Thiran, A.B., Frischknecht, R., Villemure, J.-G., Mayer, J., Annoni, J.-M., Bogousslavsky, J., Fornari, E., Thiran, J.-P., Clarke, S., 2003. Sound recognition and localization in man: specialized cortical networks and effects of acute circumscribed lesions. Exp Brain Res 153, 591–604. https://doi.org/10.1007/s00221-003-1616-0

Altman, J.A., Balonov, L.J., Deglin, V.L., 1979. Effects of unilateral disorder of the brain hemisphere function in man on directional hearing. Neuropsychologia 17, 295–301.

Arboix, A., Cendrós, V., Besa, M., García-Eroles, L., Oliveres, M., Targa, C., Balcells, M., Comes, E., Massons, J., 2008. Trends in Risk Factors, Stroke Subtypes and Outcome. CED 26, 509–516. https://doi.org/10.1159/000155989

Arnott, S.R., Alain, C., 2011. The auditory dorsal pathway: Orienting vision. Neuroscience & Biobehavioral Reviews, Wired for Sound 35, 2162–2173. https://doi.org/10.1016/j.neubiorev.2011.04.005

Arnott, S.R., Binns, M.A., Grady, C.L., Alain, C., 2004. Assessing the auditory dual-pathway model in humans. NeuroImage 22, 401–408. https://doi.org/10.1016/j.neuroimage.2004.01.014

Bachevalier, J., Mishkin, M., 1986. Visual recognition impairment follows ventromedial but not dorsolateral prefrontal lesions in monkeys - ScienceDirect. URL https://www.sciencedirect.com/science/article/pii/0166432886902251.

Barrett, A.M., Goedert, K.M., Basso, J.C., 2012. Prism adaptation for spatial neglect after stroke: translational practice gaps. Nature Reviews Neurology 8, 567–577. https://doi.org/10.1038/nrneurol.2012.170

Barrett, D.J.K., Hall, D.A., 2006. Response preferences for "what" and "where" in human non-primary auditory cortex. NeuroImage 32, 968–977. https://doi.org/10.1016/j.neuroimage.2006.03.050

Bartolomeo, P., Chokron, S., 2002. Orienting of attention in left unilateral neglect. Neurosci Biobehav Rev 26, 217–234.

Bartolomeo, P., Thiebaut de Schotten, M., Doricchi, F., 2007. Left Unilateral Neglect as a Disconnection Syndrome. Cereb Cortex 17, 2479–2490. https://doi.org/10.1093/cercor/bhl181

Bates, E., Wilson, S.M., Saygin, A.P., Dick, F., Sereno, M.I., Knight, R.T., Dronkers, N.F., 2003. Voxel-based lesion–symptom mapping. Nature Neuroscience 6, 448–450. https://doi.org/10.1038/nn1050

Bavelier, D., Neville, H.J., 2002. Cross-modal plasticity: where and how? Nat. Rev. Neurosci. 3, 443–452. https://doi.org/10.1038/nrn848

Bavelier, D., Tomann, A., Hutton, C., Mitchell, T., Corina, D., Liu, G., Neville, H., 2000. Visual attention to the periphery is enhanced in congenitally deaf individuals. Journal of neuroscience 20, RC93–RC93.

Beaton, A., McCarthy, M., 1995. On the nature of auditory neglect: a reply to Hugdahl and Wester. Brain Lang 48, 351–358. https://doi.org/10.1006/brln.1995.1017

Bellmann, A., Meuli, R., Clarke, S., 2001. Two types of auditory neglect. Brain 124, 676–687.

Benjamini, Y., Hochberg, Y., 1995. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing on JSTOR. URL http://www.jstor.org/stable/2346101.

Bergan, J., Ro, P., Ro, D., Knusden, E., 2005. Hunting Increases Adaptive Auditory Map Plasticity in Adult Barn Owls | Journal of Neuroscience. URL http://www.jneurosci.org/content/25/42/9816?utm_source=TrendMD&utm_medium=cpc&utm_campaign=JNeurosci_TrendMD_0.

Bisiach, E., 1993. Mental representation in unilateral neglect and related disorders: the twentieth Bartlett Memorial Lecture. Q J Exp Psychol A 46, 435–461.

Bisiach, E., Cornacchia, L., Sterzi, R., Vallar, G., 1984. Disorders of perceived auditory lateralization after lesions of the right hemisphere. Brain 107 (Pt 1), 37–52.

Bisiach, E., McIntosh, R.D., Dijkerman, H.C., McClements, K.I., Colombo, M., Milner, A.D., 2004. Visual and tactile length matching in spatial neglect. Cortex 40, 651–657.

Blauert, J., 1997. Spatial Hearing: The Psychophysics of Human Sound Localization. MIT Press.

Bourquin, N.M.-P., Murray, M.M., Clarke, S., 2013. Location-independent and location-linked representations of sound objects. NeuroImage 73, 40–49. https://doi.org/10.1016/j.neuroimage.2013.01.026

Boynton, G.M., Engel, S.A., Glover, G.H., Heeger, D.J., 1996. Linear systems analysis of functional magnetic resonance imaging in human V1. J. Neurosci. 16, 4207–4221.

Bregman, A.S., 1994. Auditory Scene Analysis: The Perceptual Organization of Sound. MIT Press.

Budd, T.W., Hall, D.A., Gonçalves, M.S., Akeroyd, M.A., Foster, J.R., Palmer, A.R., Head, K., Summerfield, A.Q., 2003. Binaural specialisation in human auditory cortex: an fMRI investigation of interaural correlation sensitivity. NeuroImage 20, 1783–1794. https://doi.org/10.1016/j.neuroimage.2003.07.026

Bueti, D., Costantini, M., Forster, B., Aglioti, S.M., 2004. Uni- and cross-modal temporal modulation of tactile extinction in right brain damaged patients. Neuropsychologia 42, 1689–1696. https://doi.org/10.1016/j.neuropsychologia.2004.04.005

Bullier, J., Hupé, J.-M., James, A.C., Girard, P., 2001. Chapter 13 The role of feedback connections in shaping the responses of visual cortical neurons, in: Progress in Brain Research, Vision: From Neurons to Cognition. Elsevier, pp. 193–204. https://doi.org/10.1016/S0079-6123(01)34014-1

Cammoun, L., Thiran, J.P., Griffa, A., Meuli, R., Hagmann, P., Clarke, S., 2015. Intrahemispheric cortico-cortical connections of the human auditory cortex. Brain Struct Funct 220, 3537–3553. https://doi.org/10.1007/s00429-014-0872-z

Carhart, R., Tillman, T.W., Johnson, K.R., 1967. Release of masking for speech through interaural time delay. J. Acoust. Soc. Am. 42, 124–138.

Chapman, Heidi L, Eramudugolla, R., Gavrilescu, M., Strudwick, M.W., Loftus, A., Cunnington, R., Mattingley, J.B., 2010. Neural mechanisms underlying spatial realignment during adaptation to optical wedge prisms. Neuropsychologia 48, 2595–2601. https://doi.org/10.1016/j.neuropsychologia.2010.05.006

Chapman, Heidi L., Eramudugolla, R., Gavrilescu, M., Strudwick, M.W., Loftus, A., Cunnington, R., Mattingley, J.B., 2010. Neural mechanisms underlying spatial realignment during adaptation to optical wedge prisms. Neuropsychologia 48, 2595–2601. https://doi.org/10.1016/j.neuropsychologia.2010.05.006

Chica, A., Bartolomeo, P., Lupianez, J., 2012. Two cognitive systems for endogenous and exogenous spatial attention. URL https://www.researchgate.net/publication/257002420_Two_cognitive_systems_for_endogenous_and_exogenous_spatial_attention.

Clarke, S., Crottaz-Herbette, S., 2016a. Modulation of visual attention by prismatic adaptation. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2016.06.022

Clarke, S., Crottaz-Herbette, S., 2016b. Modulation of visual attention by prismatic adaptation. Neuropsychologia 92, 31–41. https://doi.org/10.1016/j.neuropsychologia.2016.06.022

Clarke, S., Crottaz-Herbette, S., n.d. Modulation of visual attention by prismatic adaptation. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2016.06.022

Clarke, S., Thiran, A.B., 2004. Auditory neglect: what and where in auditory space. Cortex 40, 291–300.

Clarke, S., Thiran, A.B., Maeder, P., Adriani, M., Vernet, O., Regli, L., Cuisenaire, O., Thiran, J.-P., 2002. What and Where in human audition: selective deficits following focal hemispheric lesions. Exp Brain Res 147, 8–15. https://doi.org/10.1007/s00221-002-1203-9

Clower, D.M., Hoffman, J.M., Votaw, J.R., Faber, T.L., Woods, R.P., Alexander, G.E., 1996. Role of posterior parietal cortex in the recalibration of visually guided reaching. Nature 383, 618–621. https://doi.org/10.1038/383618a0

Cooper Howard M., Herbin Marc, Nevo Eviatar, 2004. Visual system of a naturally microphthalmic mammal: The blind mole rat, Spalax ehrenbergi. Journal of Comparative Neurology 328, 313–350. https://doi.org/10.1002/cne.903280302

Corbetta, M., 2005. (13) Neural basis of recovery of spatial attention deficits in spatial neglect. ResearchGate. URL https://www.researchgate.net/publication/7531262_Neural_basis_of_recovery_of_spatial_attention_deficits_in_spatial_neglect.

Corbetta, M., Shulman, G.L., 2011. Spatial neglect and attention networks. Annu. Rev. Neurosci. 34, 569–599. https://doi.org/10.1146/annurev-neuro-061010-113731

Corbetta, M., Shulman, G.L., 2002a. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3, 201–215. https://doi.org/10.1038/nrn755

Corbetta, M., Shulman, G.L., 2002b. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3, 201–215. https://doi.org/10.1038/nrn755

Crottaz-Herbette, S., Fornari, E., Clarke, S., 2014. Prismatic Adaptation Changes Visuospatial Representation in the Inferior Parietal Lobule. Journal of Neuroscience 34, 11803–11811. https://doi.org/10.1523/JNEUROSCI.3184-13.2014

Crottaz-Herbette, S., Fornari, E., Tissieres, I., Clarke, S., 2017. A Brief Exposure to Leftward Prismatic Adaptation Enhances the Representation of the Ipsilateral, Right Visual Field in the Right Inferior Parietal Lobule. eNeuro 4. https://doi.org/10.1523/ENEURO.0310-17.2017

Culling, J.F., Hawley, M.L., Litovsky, R.Y., 2004. The role of head-induced interaural time and level differences in the speech reception threshold for multiple interfering sound sources. J. Acoust. Soc. Am. 116, 1057–1065.

Da Costa, S., Clarke, S., Crottaz-Herbette, S., 2018. Keeping track of sound objects in space: The contribution of early-stage auditory areas. Hearing Research. https://doi.org/10.1016/j.heares.2018.03.027

Dale, A.M., Buckner, R.L., 1997. Selective averaging of rapidly presented individual trials using fMRI. Hum Brain Mapp 5, 329–340. https://doi.org/10.1002/(SICI)1097-0193(1997)5:5<329::AID-HBM1>3.0.CO;2-5

Danckert, J., Ferber, S., Goodale, M.A., 2008. Direct effects of prismatic lenses on visuomotor control: an event-related functional MRI study. Eur. J. Neurosci 28, 1696–1704. https://doi.org/10.1111/j.1460-9568.2008.06460.x

Deouell, L.Y., Soroker, N., 2000. What is extinguished in auditory extinction?

Di Pellegrino, G., Basso, G., Frassinetti, F., 1997. Spatial extinction on double asynchronous stimulation. Neuropsychologia 35, 1215–1223.

Duffour-Nikolov, C., Tardif, E., Maeder, P., Thiran, A.B., Bloch, J., Frischknecht, R., Clarke, S., 2012. Auditory spatial deficits following hemispheric lesions: Dissociation of explicit and implicit processing. Neuropsychological Rehabilitation 22, 674–696. https://doi.org/10.1080/09602011.2012.686818

Efron, R., Crandall, P.H., Koss, B., Divenyi, P.L., Yund, E.W., 1983. Central auditory processing. III. The “cocktail party” effect and anterior temporal lobectomy. Brain Lang 19, 254–263.

Eramudugolla, R., Boyce, A., Irvine, D.R.F., Mattingley, J.B., 2010. Effects of prismatic adaptation on spatial gradients in unilateral neglect: A comparison of visual and auditory target detection with central attentional load. Neuropsychologia 48, 2681–2692. https://doi.org/10.1016/j.neuropsychologia.2010.05.015

Farah, M.J., Wong, A.B., Monheit, M.A., Morrow, L.A., 1989. Parietal lobe mechanisms of spatial attention: Modality-specific or supramodal? Neuropsychologia 27, 461–470. https://doi.org/10.1016/0028-3932(89)90051-1

Feldman, D., Knusden, E., 1997. An Anatomical Basis for Visual Calibration of the Auditory Space Map in the Barn Owl’s Midbrain | Journal of Neuroscience. URL http://www.jneurosci.org/content/17/17/6820.short (accessed 3.21.18).

Fieger, A., Röder, B., Teder-Sälejärvi, W., Hillyard, S.A., Neville, H.J., 2006. Auditory spatial tuning in late-onset blindness in humans. J Cogn Neurosci 18, 149–157. https://doi.org/10.1162/089892906775783697

Gokhale, S., Lahoti, S., Caplan, L.R., 2013. The Neglected Neglect: Auditory Neglect. JAMA Neurol 70, 1065–1069. https://doi.org/10.1001/jamaneurol.2013.155

Gougoux, F., Zatorre, R.J., Lassonde, M., Voss, P., Lepore, F., 2005. A Functional Neuroimaging Study of Sound Localization: Visual Cortex Activity Predicts Performance in Early-Blind Individuals. PLOS Biology 3, e27. https://doi.org/10.1371/journal.pbio.0030027

Grothe, B., Pecka, M., McAlpine, D., 2010. Mechanisms of Sound Localization in Mammals. Physiological Reviews 90, 983–1012. https://doi.org/10.1152/physrev.00026.2009

Haeske-Dewick, H., Canavan, A.G.M., Hömberg, V., 1996. Sound localization in egocentric space following hemispheric lesions. Neuropsychologia 34, 937–942. https://doi.org/10.1016/0028-3932(95)00167-0

Hawley, M.L., Litovsky, R.Y., Culling, J.F., 2004. The benefit of binaural hearing in a cocktail party: effect of location and type of interferer. J. Acoust. Soc. Am. 115, 833–843.

Heilman, K.M., Valenstein, E., 1972. Auditory Neglect in Man. Arch Neurol 26, 32–35. https://doi.org/10.1001/archneur.1972.00490070050007

Heilman, K.M., Valenstein, E., Watson, R.T., 2000. Neglect and related disorders. Semin Neurol 20, 463–470. https://doi.org/10.1055/s-2000-13179

Held, R., Efstathiou, A., Greene, M., 1966. Adaptation to displaced and delayed visual feedback from the hand. Journal of Experimental Psychology 72, 887.

Hugdahl, K., Wester, K., 1994. Auditory neglect and the ear extinction effect in dichotic listening: a reply to Beaton and McCarthy (1993). Brain Lang 46, 166–173. https://doi.org/10.1006/brln.1994.1009

Hugdahl, K., Wester, K., Asbjørnsen, A., 1991. Auditory neglect after right frontal lobe and right pulvinar thalamic lesions. Brain and Language 41, 465–473. https://doi.org/10.1016/0093-934X(91)90167-Y

Hyde, P.S., Knudsen, E.I., 2002. The optic tectum controls visually guided adaptive plasticity in the owl's auditory space map. Nature 415, 73–76. https://doi.org/10.1038/415073a

Igelström, K.M., Graziano, M.S.A., n.d. The inferior parietal lobule and temporoparietal junction: A network perspective. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2017.01.001

Jacquin-Courtois, S., O'Shea, J., Luauté, J., Pisella, L., Revol, P., Mizuno, K., Rode, G., Rossetti, Y., 2013. Rehabilitation of spatial neglect by prism adaptation: A peculiar expansion of sensorimotor after-effects to spatial cognition. Neuroscience & Biobehavioral Reviews 37, 594–609. https://doi.org/10.1016/j.neubiorev.2013.02.007

Jacquin-Courtois, S., Rode, G., Pavani, F., O'Shea, J., Giard, M.H., Boisson, D., Rossetti, Y., 2010. Effect of prism adaptation on left dichotic listening deficit in neglect patients: glasses to hear better? Brain 133, 895–908. https://doi.org/10.1093/brain/awp327

Jacquin-Courtois, S., Rode, G., Pisella, L., Boisson, D., Rossetti, Y., 2008. Wheel-chair driving improvement following visuo-manual prism adaptation. Cortex 44, 90–96. https://doi.org/10.1016/j.cortex.2006.06.003

Kaas, J.H., Hackett, T.A., 1999. "What" and "where" processing in auditory cortex. Nature Neuroscience 2, 1045–1047. https://doi.org/10.1038/15967

Kaiser, J., Lutzenberger, W., 2001. Location changes enhance hemispheric asymmetry of magnetic fields evoked by lateralized sounds in humans. Neuroscience Letters 314, 17–20. https://doi.org/10.1016/S0304-3940(01)02248-0

Karnath, H.-O., Ferber, S., Himmelbach, M., 2001. Spatial awareness is a function of the temporal not the posterior parietal lobe. Nature 411, 950–953. https://doi.org/10.1038/35082075

Keuroghlian, A.S., Knudsen, E.I., 2007. Adaptive auditory plasticity in developing and adult animals. Progress in Neurobiology 82, 109–121. https://doi.org/10.1016/j.pneurobio.2007.03.005

Kimura, D., 1967. Functional Asymmetry of the Brain in Dichotic Listening. Cortex 3, 163–178. https://doi.org/10.1016/S0010-9452(67)80010-8

Klingon, G.H., Bontecou, D.C., 1964. Auditory field localization. Trans Am Neurol Assoc 89, 210–211.

Kujala, T., Alho, K., Näätänen, R., 2000. Cross-modal reorganization of human cortical functions. Trends Neurosci. 23, 115–120.

Kujala, T., Alho, K., Paavilainen, P., Summala, H., Näätänen, R., 1992. Neural plasticity in processing of sound location by the early blind: an event-related potential study. Electroencephalogr Clin Neurophysiol 84, 469–472.

Kujala, T., Huotilainen, M., Sinkkonen, J., Ahonen, A.I., Alho, K., Hämäläinen, M.S., Ilmoniemi, R.J., Kajola, M., Knuutila, J.E., Lavikainen, J., 1995. Visual cortex activation in blind humans during sound discrimination. Neurosci. Lett. 183, 143–146.

Künzel, T., Wagner, H., 2017. Cholinergic top-down influences on the auditory brainstem. e-Neuroforum 23, 35–44. https://doi.org/10.1515/nf-2016-A107

Küper, M., Wünnemann, M.J.S., Thürling, M., Stefanescu, R.M., Maderwald, S., Elles, H.G., Göricke, S., Ladd, M.E., Timmann, D., 2014. Activation of the cerebellar cortex and the dentate nucleus in a prism adaptation fMRI study. Hum. Brain Mapp. 35, 1574–1586. https://doi.org/10.1002/hbm.22274

Leavitt, V.M., Molholm, S., Gomez-Ramirez, M., Foxe, J.J., 2011. "What" and "Where" in Auditory Sensory Processing: A High-Density Electrical Mapping Study of Distinct Neural Processes Underlying Sound Object Recognition and Sound Localization. Front Integr Neurosci 5. https://doi.org/10.3389/fnint.2011.00023

Lee, E., Kang, D.-W., Kwon, S.U., Kim, J.S., 2009. Posterior Cerebral Artery Infarction: Diffusion-Weighted MRI Analysis of 205 Patients. CED 28, 298–305. https://doi.org/10.1159/000229016

Lessard, N., Lepore, F., Poirier, P., Villemagne, J., Lassonde, M., 2000. Sound localization in hemispherectomized subjects: the contribution of crossed and uncrossed cortical afferents. Exp Brain Res 134, 344–352. https://doi.org/10.1007/s002210000463

Lessard, N., Paré, M., Lepore, F., Lassonde, M., 1998. Early-blind human subjects localize sound sources better than sighted subjects. Nature 395, 278–280. https://doi.org/10.1038/26228

Liotti, M., Ryder, K., Woldorff, M.G., 1998. Auditory attention in the congenitally blind: where, when and what gets reorganized? Neuroreport 9, 1007–1012.

Logothetis, N.K., Pauls, J., Augath, M., Trinath, T., Oeltermann, A., 2001. Neurophysiological investigation of the basis of the fMRI signal. Nature 412, 150–157. https://doi.org/10.1038/35084005

Luauté, J., Schwartz, S., Rossetti, Y., Spiridon, M., Rode, G., Boisson, D., Vuilleumier, P., 2009a. Dynamic changes in brain activity during prism adaptation. J. Neurosci 29, 169–178. https://doi.org/10.1523/JNEUROSCI.3054-08.2009

Luauté, J., Schwartz, S., Rossetti, Y., Spiridon, M., Rode, G., Boisson, D., Vuilleumier, P., 2009b. Dynamic changes in brain activity during prism adaptation. J. Neurosci. 29, 169–178. https://doi.org/10.1523/JNEUROSCI.3054-08.2009

Medina, J., Kimberg, D.Y., Chatterjee, A., Coslett, H.B., 2010. Inappropriate usage of the Brunner–Munzel test in recent voxel-based lesion-symptom mapping studies. Neuropsychologia 48, 341–343. https://doi.org/10.1016/j.neuropsychologia.2009.09.016

Merabet, L.B., Pascual-Leone, A., 2010. Neural reorganization following sensory loss: the opportunity of change. Nature Reviews Neuroscience 11, 44–52. https://doi.org/10.1038/nrn2758

Mesulam, M.M., 1999. Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. Philos. Trans. R. Soc. Lond., B, Biol. Sci. 354, 1325–1346. https://doi.org/10.1098/rstb.1999.0482

Middlebrooks, J.C., 1992. Narrow-band sound localization related to external ear acoustics. The Journal of the Acoustical Society of America 92, 2607–2624. https://doi.org/10.1121/1.404400

Molenberghs, P., Gillebert, C.R., Peeters, R., Vandenberghe, R., 2008. Convergence between Lesion-Symptom Mapping and Functional Magnetic Resonance Imaging of Spatially Selective Attention in the Intact Brain. Journal of Neuroscience 28, 3359–3373. https://doi.org/10.1523/JNEUROSCI.5247-07.2008

Molenberghs, P., Gillebert, C.R., Schoofs, H., Dupont, P., Peeters, R., Vandenberghe, R., 2009. Lesion neuroanatomy of the Sustained Attention to Response task. Neuropsychologia 47, 2866–2875. https://doi.org/10.1016/j.neuropsychologia.2009.06.012

Mort, D.J., Malhotra, P., Mannan, S.K., Rorden, C., Pambakian, A., Kennard, C., Husain, M., 2003. The anatomy of visual neglect. Brain 126, 1986–1997. https://doi.org/10.1093/brain/awg200

Muchnik, C., Efrati, M., Nemeth, E., Malin, M., Hildesheimer, M., 1991. Central auditory skills in blind and sighted subjects. Scand Audiol 20, 19–23.

Muir, K.W., Buchan, A., von Kummer, R., Rother, J., Baron, J.-C., 2006. Imaging of acute stroke. The Lancet Neurology 5, 755–768. https://doi.org/10.1016/S1474-4422(06)70545-2

Murray, M.M., Camen, C., Andino, S.L.G., Bovet, P., Clarke, S., 2006. Rapid Brain Discrimination of Sounds of Objects. J. Neurosci. 26, 1293–1302. https://doi.org/10.1523/JNEUROSCI.4511-05.2006

Niemeyer, W., Starlinger, I., 1981. Do the blind hear better? Investigations on auditory processing in congenital or early acquired blindness. II. Central functions. Audiology 20, 510–515.

Ogawa, S., Tank, D.W., Menon, R., Ellermann, J.M., Kim, S.G., Merkle, H., Ugurbil, K., 1992. Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. Proc. Natl. Acad. Sci. U.S.A. 89, 5951–5955.

Panico, F., Sagliano, L., Nozzolillo, C., Trojano, L., Rossetti, Y., 2018. Cerebellar contribution to spatial realignment: A tDCS study during multiple-step prism adaptation. Neuropsychologia 112, 58–65. https://doi.org/10.1016/j.neuropsychologia.2018.03.008

Parton, A., Malhotra, P., Husain, M., 2004. Hemispatial neglect. J. Neurol. Neurosurg. Psychiatry 75, 13–21.

Petitet, P., O'Reilly, J.X., O'Shea, J., 2017. Towards a neuro-computational account of prism adaptation. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2017.12.021

Phan, T.G., Donnan, G.A., Wright, P.M., Reutens, D.C., 2005. A Digital Map of Middle Cerebral Artery Infarcts Associated With Middle Cerebral Artery Trunk and Branch Occlusion. Stroke 36, 986–991. https://doi.org/10.1161/01.STR.0000163087.66828.e9

Pinek, B., Brouchon, M., 1992. Head turning versus manual pointing to auditory targets in normal subjects and in subjects with right parietal damage. Brain Cogn 18, 1–11.

Pinek, B., Duhamel, J.R., Cavé, C., Brouchon, M., 1989. Audio-spatial deficits in humans: differential effects associated with left versus right hemisphere parietal damage. Cortex 25, 175–186.

Poirier, C., Collignon, O., Scheiber, C., Renier, L., Vanlierde, A., Tranduy, D., Veraart, C., De Volder, A.G., 2006. Auditory motion perception activates visual motion areas in early blind subjects. NeuroImage 31, 279–285. https://doi.org/10.1016/j.neuroimage.2005.11.036

Poldrack, R.A., Mumford, J.A., Nichols, T.E., 2011. Handbook of Functional MRI Data Analysis. Cambridge University Press.

Rauschecker, J.P., Tian, B., 2000. Mechanisms and streams for processing of "what" and "where" in auditory cortex. PNAS 97, 11800–11806. https://doi.org/10.1073/pnas.97.22.11800

Recanzone, G.H., 1998. Rapidly induced auditory plasticity: The ventriloquism aftereffect. PNAS 95, 869–875.

Recanzone, G.H., Cohen, Y.E., 2010. Serial and parallel processing in the primate auditory cortex revisited. Behavioural Brain Research 206, 1–7. https://doi.org/10.1016/j.bbr.2009.08.015

Redding, G.M., Wallace, B., 2006. Prism adaptation and unilateral neglect: Review and analysis. Neuropsychologia 44, 1–20. https://doi.org/10.1016/j.neuropsychologia.2005.04.009

Retsa, C., Matusz, P.J., Schnupp, J.W.H., Murray, M.M., n.d. What's what in auditory cortices? NeuroImage. https://doi.org/10.1016/j.neuroimage.2018.04.028

Rey, B., Frischknecht, R., Maeder, P., Clarke, S., 2007. Patterns of recovery following focal hemispheric lesions: relationship between lasting deficit and damage to specialized networks. Restor. Neurol. Neurosci. 25, 285–294.

Rivier, F., Clarke, S., 1997. Cytochrome Oxidase, Acetylcholinesterase, and NADPH-Diaphorase Staining in Human Supratemporal and Insular Cortex: Evidence for Multiple Auditory Areas. NeuroImage 6, 288–304. https://doi.org/10.1006/nimg.1997.0304

Rode, G., Pisella, L., Marsal, L., Mercier, S., Rossetti, Y., Boisson, D., 2006. Prism adaptation improves spatial dysgraphia following right brain damage. Neuropsychologia 44, 2487–2493. https://doi.org/10.1016/j.neuropsychologia.2006.04.002

Rode, G., Rossetti, Y., Li, L., Boisson, D., 1998. Improvement of mental imagery after prism exposure in neglect: a case study. Behavioural Neurology 11, 251–258.

Röder, B., Teder-Sälejärvi, W., Sterr, A., Rösler, F., Hillyard, S.A., Neville, H.J., 1999. Improved auditory spatial tuning in blind humans. Nature 400, 162–166. https://doi.org/10.1038/22106

Roman, N., Wang, D., Brown, G.J., 2002. Location-based sound segregation, in: Proceedings of the 2002 International Joint Conference on Neural Networks, 2002. IJCNN '02. Presented at the Proceedings of the 2002 International Joint Conference on Neural Networks, 2002. IJCNN '02, pp. 2299–2303. https://doi.org/10.1109/IJCNN.2002.1007500

Romanski, L. m., Bates, J. f., Goldman-Rakic, P. s., 1999. Auditory belt and parabelt projections to the prefrontal cortex in the Rhesus monkey. J. Comp. Neurol. 403, 141–157. https://doi.org/10.1002/(SICI)1096-9861(19990111)403:2<141::AID-CNE1>3.0.CO;2-V

Romanski, L.M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P.S., Rauschecker, J.P., 1999. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. Nat Neurosci 2, 1131–1136. https://doi.org/10.1038/16056

Rorden, C., Karnath, H.-O., Bonilha, L., 2007. Improving Lesion-Symptom Mapping. Journal of Cognitive Neuroscience 19, 1081–1088. https://doi.org/10.1162/jocn.2007.19.7.1081

Rorden, C., Mattingley, J.B., Karnath, H.O., Driver, J., 1997. Visual extinction and prior entry: impaired perception of temporal order with intact motion perception after unilateral parietal damage. Neuropsychologia 35, 421–433.

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., Perenin, M.-T., 1998. Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 395, 166–169. https://doi.org/10.1038/25988

Ruff, R.M., Hersh, N.A., Pribram, K.H., 1981. Auditory spatial deficits in the personal and extrapersonal frames of reference due to cortical lesions. Neuropsychologia 19, 435–443.

Salminen, N.H., Tiitinen, H., Miettinen, I., Alku, P., May, P.J.C., 2010. Asymmetrical representation of auditory space in human cortex. Brain Res. 1306, 93–99. https://doi.org/10.1016/j.brainres.2009.09.095

Sanchez-Longo, L.P., Forster, F.M., 1958. Clinical Significance of Impairment of Sound Localization. Neurology 8, 119–119. https://doi.org/10.1212/WNL.8.2.119

Saupe, K., Koelsch, S., Rübsamen, R., 2010. Spatial selective attention in a complex auditory environment such as polyphonic music. J. Acoust. Soc. Am. 127, 472–480. https://doi.org/10.1121/1.3271422

Saygin, A.P., 2007. Superior temporal and premotor brain areas necessary for biological motion perception. Brain 130, 2452–2461. https://doi.org/10.1093/brain/awm162

Saygın, A.P., Wilson, S.M., Dronkers, N.F., Bates, E., 2004. Action comprehension in aphasia: linguistic and non-linguistic deficits and their lesion correlates. Neuropsychologia 42, 1788–1804. https://doi.org/10.1016/j.neuropsychologia.2004.04.016

Schönwiesner, M., Krumbholz, K., Rübsamen, R., Fink, G.R., von Cramon, D.Y., 2007. Hemispheric asymmetry for auditory processing in the human auditory brain stem, thalamus, and cortex. Cereb. Cortex 17, 492–499. https://doi.org/10.1093/cercor/bhj165

Schotten, M.T. de, Tomaiuolo, F., Aiello, M., Merola, S., Silvetti, M., Lecce, F., Bartolomeo, P., Doricchi, F., 2014. Damage to White Matter Pathways in Subacute and Chronic Spatial Neglect: A Group Study and 2 Single-Case Studies with Complete Virtual "In Vivo"

Tractography Dissection. Cereb. Cortex 24, 691–706. https://doi.org/10.1093/cercor/bhs351

Shulman, G.L., McAvoy, M.P., Cowan, M.C., Astafiev, S.V., Tansy, A.P., d'Avossa, G., Corbetta, M., 2003. Quantitative Analysis of Attention and Detection Signals During Visual Search. Journal of Neurophysiology 90, 3384–3397. https://doi.org/10.1152/jn.00343.2003

Shulman, G.L., Pope, D.L.W., Astafiev, S.V., McAvoy, M.P., Snyder, A.Z., Corbetta, M., 2010. Right Hemisphere Dominance during Spatial Selective Attention and Target Detection Occurs Outside the Dorsal Frontoparietal Network. J. Neurosci. 30, 3640–3651. https://doi.org/10.1523/JNEUROSCI.4085-09.2010

Sonoda, S., Mori, M., Goishi, A., 2001. Pattern of localisation error in patients with stroke to sound processed by a binaural sound space processor. J Neurol Neurosurg Psychiatry 70, 43–49. https://doi.org/10.1136/jnnp.70.1.43

Soroker, N., Calamaro, N., Glicksohn, J., Myslobodsky, M.S., 1997. Auditory inattention in right-hemisphere-damaged patients with and without visual neglect. Neuropsychologia 35, 249–256. https://doi.org/10.1016/S0028-3932(96)00038-3

Sperber, C., Karnath, H.-O., 2017. On the validity of lesion-behaviour mapping methods. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2017.07.035

Spierer, L., Bellmann-Thiran, A., Maeder, P., Murray, M.M., Clarke, S., 2009. Hemispheric competence for auditory spatial representation. Brain 132, 1953–1966. https://doi.org/10.1093/brain/awp127

Spierer, L., Meuli, R., Clarke, S., 2007. Extinction of auditory stimuli in hemineglect: Space versus ear. Neuropsychologia, Advances in Multisensory Processes 45, 540–551. https://doi.org/10.1016/j.neuropsychologia.2006.04.012

Stecker, G.C., Harrington, I.A., Middlebrooks, J.C., 2005. Location Coding by Opponent Neural Populations in the Auditory Cortex. PLOS Biology 3, e78. https://doi.org/10.1371/journal.pbio.0030078

Stevens, A.A., Weaver, K.E., 2009. Functional characteristics of auditory cortex in the blind. Behavioural Brain Research 196, 134–138. https://doi.org/10.1016/j.bbr.2008.07.041

Striemer, C.L., Danckert, J.A., 2010. Through a prism darkly: re-evaluating prisms and neglect. Trends in Cognitive Sciences 14, 308–316. https://doi.org/10.1016/j.tics.2010.04.001

Tanaka, H., Hachisuka, K., Ogata, H., 1999. Sound lateralisation in patients with left or right cerebral hemispheric lesions: relation with unilateral visuospatial neglect. J Neurol Neurosurg Psychiatry 67, 481–486.

Thiran, A.B., Clarke, S., 2003. Preserved use of spatial cues for sound segregation in a case of spatial deafness. Neuropsychologia 41, 1254–1261. https://doi.org/10.1016/S0028-3932(03)00014-9

Tissieres, I., Elamly, M., Clarke, S., Crottaz-Herbette, S., 2017a. For Better or Worse: The Effect of Prismatic Adaptation on Auditory Neglect. Neural Plasticity. https://doi.org/10.1155/2017/8721240

Tissieres, I., Fornari, E., Clarke, S., Crottaz-Herbette, S., 2017b. Supramodal effect of rightward prismatic adaptation on spatial representations within the ventral attentional system. Brain Struct Funct 1–13. https://doi.org/10.1007/s00429-017-1572-2

Todd, J.J., Fougnie, D., Marois, R., 2005. Visual Short-Term Memory Load Suppresses Temporo-Parietal Junction Activity and Induces Inattentional Blindness. Psychological Science 16, 965–972. https://doi.org/10.1111/j.1467-9280.2005.01645.x

Ungerleider, L.G., Haxby, J.V., 1994. "What" and "where" in the human brain. Current Opinion in Neurobiology 4, 157–165. https://doi.org/10.1016/0959-4388(94)90066-3

Ungerleider, Mishkin, M, 1982. Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys - ScienceDirect. URL https://www.sciencedirect.com/science/article/pii/016643288290081X

Vallar, G., Perani, D., 1986. The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. Neuropsychologia 24, 609–622.

van der Zwaag, W., Gentile, G., Gruetter, R., Spierer, L., Clarke, S., 2011. Where sound position influences sound object representations: A 7-T fMRI study. NeuroImage 54, 1803–1811. https://doi.org/10.1016/j.neuroimage.2010.10.032

Vazquez, A.L., Noll, D.C., 1998. Nonlinear aspects of the BOLD response in functional MRI. Neuroimage 7, 108–118. https://doi.org/10.1006/nimg.1997.0316

Verdon, V., Schwartz, S., Lovblad, K.-O., Hauert, C.-A., Vuilleumier, P., 2010. Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. Brain 133, 880–894. https://doi.org/10.1093/brain/awp305

Viceic, D., Fornari, E., Thiran, J.-P., Maeder, P.P., Meuli, R., Adriani, M., Clarke, S., 2006. Human auditory belt areas specialized in sound recognition: a functional magnetic resonance imaging study. NeuroReport 17, 1659. https://doi.org/10.1097/01.wnr.0000239962.75943.dd

Voss, P., Gougoux, F., Zatorre, R.J., Lassonde, M., Lepore, F., 2008. Differential occipital responses in early- and late-blind individuals during a sound-source discrimination task. NeuroImage 40, 746–758. https://doi.org/10.1016/j.neuroimage.2007.12.020

Walker, G.M., Schwartz, M.F., Kimberg, D.Y., Faseyitan, O., Brecher, A., Dell, G.S., Coslett, H.B., 2011. Support for anterior temporal involvement in semantic error production in aphasia: New evidence from VLSM. Brain and Language, First Neurobiology of Language Conference: NLC 2009 117, 110–122. https://doi.org/10.1016/j.bandl.2010.09.008

Wallace, M., Stein, B., 2007. Early Experience Determines How the Senses Will Interact | Journal of Neurophysiology. URL https://www.physiology.org/doi/abs/10.1152/jn.00497.2006.

Wallace, M.N., Johnston, P.W., Palmer, A.R., 2002. Histochemical identification of cortical areas in the auditory region of the human brain. Exp Brain Res 143, 499–508. https://doi.org/10.1007/s00221-002-1014-z

Wortis, S.B., Pfeffer, A.Z., 1948. Unilateral auditory-spatial agnosia. J. Nerv. Ment. Dis. 108, 181–186.

Wozny, D.R., Shams, L., 2011. Recalibration of Auditory Space following Milliseconds of Cross-Modal Discrepancy. J. Neurosci. 31, 4607–4612. https://doi.org/10.1523/JNEUROSCI.6079-10.2011

Yang, N.Y.H., Zhou, D., Chung, R.C.K., Li, C.W.P., Fong, K.N.K., 2013. Rehabilitation Interventions for Unilateral Neglect after Stroke: A Systematic Review from 1997 through 2012. Front. Hum. Neurosci. 7. https://doi.org/10.3389/fnhum.2013.00187

Zatorre, R.J., Penhune, V.B., 2001. Spatial Localization after Excision of Human Auditory Cortex. J. Neurosci. 21, 6321–6328.

Zatorre, R.J., Ptito, A., Villemure, J.G., 1995. Preserved auditory spatial localization following cerebral hemispherectomy. Brain 118 (Pt 4), 879–889.

Zwiers, M.P., Van Opstal, A.J., Cruysberg, J.R., 2001. A spatial hearing deficit in early-blind humans. J. Neurosci. 21, RC142: 1-5.

CHAPTER 6 RESEARCH PAPERS

Tissieres et al., 2018

Tissieres et al., In preparation (final stage)

Tissieres et al., 2017a

Tissieres et al., 2017b

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Original article

Exploring auditory neglect: Anatomo-clinical correlations of auditory extinction

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ABSTRACT

Background: The key symptoms of auditory neglect include left extinction on tasks of dichotic and/or diotic listening and rightward shift in locating sounds. The anatomical correlates of the latter are relatively well understood, but no systematic studies have examined auditory extinction. Here, we performed a systematic study of anatomo-clinical correlates of extinction by using dichotic and/or diotic listening tasks.

Methods: In total, 20 patients with right hemispheric damage (RHD) and 19 with left hemispheric damage (LHD) performed dichotic and diotic listening tasks. Either task consists of the simultaneous presentation of word pairs; in the dichotic task, 1 word is presented to each ear, and in the diotic task, each word is lateralized by means of interaural time differences and presented to one side.

Results and conclusion: RHD was associated with exclusively contralesional extinction in dichotic or diotic listening, whereas in selected cases, LHD led to contra- or ipsilesional extinction. Bilateral symmetrical extinction occurred in RHD or LHD, with dichotic or diotic listening. The anatomical correlates of these extinction profiles offer an insight into the organisation of the auditory and attentional systems. First, left extinction in dichotic versus diotic listening involves different parts of the right hemisphere, which explains the double dissociation between these 2 neglect symptoms. Second, contralesional extinction in the dichotic task relies on homologous regions in either hemisphere. Third, ipsilesional extinction in dichotic listening after LHD was associated with lesions of the intrahemispheric white matter, interrupting callosal fibres outside their midsagittal or periventricular trajectory. Fourth, bilateral symmetrical extinction was associated with large parieto-fronto-temporal LHD or smaller parieto-temporal RHD, which suggests that divided attention, supported by the right hemisphere, and auditory streaming, supported by the left, likely play a critical role.

1. Introduction

Although the auditory manifestations of neglect are often not explored in clinical settings, they offer highly interesting insights into the organisation of the auditory and attentional systems and eventually into the mechanisms of therapeutic interventions [1,2]. Auditory neglect is characterized by inattention to sounds emanating from the left part of space after a right hemispheric lesion [3]. The failure to report stimuli on the left side was initially documented in tasks of dichotic listening, with simultaneous auditory stimuli presented to either ear [4–6]. However, the extinction of left-sided stimuli can also be related to space and not ear, as demonstrated by tests of diotic listening [7–9]. In this latter test, sounds are lateralized by means of interaural time differences and 2 stimuli are presented simultaneously on the right and left side. Another manifestation of auditory neglect is sound mislocalization, in particular alloacusis (i.e., the misplacement of sounds presented on the left to the right), the shift of the central position to the right, and an overall tendency to misplace stimuli, with a tendency toward the right side [10,11].

The 3 key features of auditory neglect can occur in a given patient together or separately. A double dissociation between extinction on diotic listening and rightward shift in sound localization was documented in 4 neglect patients, 2 with extinction on diotic listening and normal performance in sound

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localization, and the other 2 with rightward shift on sound localization and normal performance in diotic listening [7]. The site of lesion differed between the 2 groups: the former had lesions centred on basal ganglia and the latter had lesions on parieto-fronto-temporal cortices. A later study reported a double dissociation between extinction in dichotic versus diotic tasks in 15 consecutive patients with neglect: 5 presented significant asymmetry on diotic but not dichotic tasks, and 6 presented significant asymmetry in dichotic but not diotic tasks [8]. All but 1 of these patients also presented deficits in sound localization. This latter study did not address the issue of anatomical correlates.

The occurrence of double dissociations among the key symptoms of auditory neglect suggests that the 3 aptitudes depend at least in part on distinct neural substrates. Sound localization depends critically on the right parietal cortex, as established in a series of studies using Voxel-Lesion Symptom-Mapping (VLSM) [12,13]. However, no systematic study has investigated the anatomo-clinical correlates of extinction.

Understanding the anatomical substrate of extinction in auditory neglect may help to disentangle the puzzling effect of prismatic adaptation, which has been repeatedly shown to alleviate visuo-spatial neglect symptoms [14]. Prismatic adaptation was shown to alleviate left extinction on dichotic listening [15,16], but it did not restore the imbalance in diotic listening or localization; in some instances it even worsened left-sided extinction in diotic listening [16]. Here we used dichotic and/or diotic listening in a systematic study of anatomo-clinical correlates of extinction.

2. Methods

2.1. Patient population

We recruited 97 brain-damaged patients in the Neuropsychology and Neurorehabilitation Service, Centre Hospitalier Universitaire Vaudois, in Lausanne, between 2014 and 2017 as part of an ongoing study. A total of 39 patients fulfilled the inclusion criteria of the current study:

- first unilateral focal stroke;
- brain imaging available;
- absence of hearing deficits;
- absence of major comprehension deficit at moment of testing;
- absence of psychiatric or other neurological comorbidities.

All but 2 patients were right handed. Twenty patients sustained right hemispheric damage (RHD, 12 males) and 19 left hemispheric damage (LHD, 11 males). The study was approved by the ethics committee of the Canton de Vaud, Switzerland, and all patients gave informed consent.

2.2. Dichotic and diotic listening tasks, neuropsychological evaluation

The dichotic and diotic tasks consist of 30 simultaneously presented word pairs; in the dichotic task, 1 word is presented to each ear, and in the diotic task, each word is lateralized by means of interaural time differences and presented to each side [7]. Auditory extinction is defined as a decrease in reporting simultaneously presented words and is characterized by the lateralization index ([right–left side]/[right + left side] × 100). Normative data were published previously: for the dichotic task, the mean (SD) right-ear report is 29 [1.7] and the left-ear report is 28.9 [2.7], with no significant difference between ears; the mean lateralization index is 0.99 [4.5]. For the diotic task, the mean (SD) right-side report is 26.2 [4.6] and the left-side report is 24.9 [5], with no significant difference between sides; the mean lateralization index is 3.52 [6.0] [7]. Detailed neuropsychological evaluation, including localization of sounds lateralized by means of interaural time difference, was performed as previously described (Bellmann et al., 2001; Duffour-Nikolov et al., 2012).

2.3. Statistical analyses of behavioural data

Behavioural scores were analyzed by mixed-design ANOVA with the within-subject factors Stimulus Side (left, right) and Task (dichotic, diotic) and the between-subjects factor Lesion Side (LHD, RHD). Analyses involved using R (R Development Core Team, 2008, Vienna, Austria).

2.4. Voxel-Lesion Symptom-Mapping (VLSM)

Lesions from MRI or CT scans were drawn on axial slices by using MITK 3M3 software and normalized on the Montreal Neurological Institute's (MNI) brain template by using the SPM12 software (Wellcome Department of Cognitive Neurology, London, UK). VLSM involved use of the Non-Parametric Mapping toolbox (NPM) from the MRICroN software package [17]. The minimal group size for statistical analyses was defined at 15% (i.e., tests were restricted to voxels with at least 3 patients in each group). The test used in these analyses was the Brunner-Munzel test, FDR-corrected, tBM-map intensity [0,2.4]. A first set of analyses was conducted on the total number of correctly reported words (total left + right ears/sides). A second set was conducted on the number of correctly reported words separately for the right and left ears/sides. Finally, a last set was performed on a modified lateralization index. VLSM analyses as implemented in the NPM software package require that higher values of behavioral data correspond to better performances. Therefore, to fit these requirements, the lateralization index was separated into 2 measures (i.e., left and right ears/sides) and multiplied by −1 (higher values correspond to fewer deficits). Furthermore, in each VLSM analysis, patients included presented the respective extinction plus the patients within the normative range.

3. Results

Independent samples t-test confirmed that patient groups did not differ significantly in lesion size (Table 1, Supplementary Fig. 1; $t(38) = 27.85$, $P = 0.82$, LHD: mean [SD] 89456 [66954] mm3; RHD: mean 84266 [73797] mm3) or age ($t(38) = 35.61$, $P = 0.35$, LHD: mean [SD] 52.9 [12.8] years old; RHD: mean = 55.35 [11.4] years old).

3.1. Behavioural results

Performance profiles were analyzed by number of items reported for each ear/side, total number of items, and the lateralization index (Fig. 1). We observed contralesional extinction after RHD and LHD but ipsilesional extinction only after LHD (Fig. 1C). Furthermore, in some cases, RHD or LHD led to a bilateral decrease in reporting, without significant asymmetry; we refer to this situation as bilateral extinction.

Performance in dichotic versus diotic tasks was compared by 2 × 2 × 2 ANOVA for the number of correctly reported words (Fig. 1; Table 2) with the within-subject factors Stimulus Side (left, right) and Task (dichotic, diotic) and between-subjects factor Lesion Side (LHD, RHD). We found a significant main effect of Task [$F(1,36) = 8.598$, $P = 0.006$] but not Stimulus Side [$F(1,36) = 1.155$, $P = 0.29$] or Lesion Side [$F(1,36) = 2.754$, $P = 0.106$]. Interactions were significant between Stimulus Side and Task [$F(1,36) = 4.147$,

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Table 1
Clinical and demographical characteristics of patients included in the study ($n = 39$).

Patient	Sex	Age (year)	Delay (day)	Regions involved in the lesion	Volume (mm3)
R1	M	46.8	33	Right IFG, STG, MFG, Insula, Precentral, Postcentral, SMG, IPL, Putamen	216742
R2	F	53.0	136	Right Insula, IFG, Precentral, STG, Putamen	56934
R3	F	63.4	37	Right IFG, Precentral, Postcentral, Insula, SMG, IPL, Putamen, STG, Temporal pole, Caudate, MFG	187341
R4	M	64.4	11	Right Putamen, Caudate, GP	4146
R5	M	56.9	22	Right Fusiform, Hippocampus, Parahippocampus, Precuneus, Posterior Cingulate, Calcarine, Cuneus, Thalamus	108636
R6	M	58.0	42	Right Lingual, Cuneus, Calcarine, Inf. Occipital, Fusiform	52896
R7	M	51.0	15	Right IFG, Insula, STG, Precentral, Putamen	44647
R8	M	54.5	105	Right IPL, SMG, Middle Occipital, STG, MTG, Superior Occipital, Precuneus	68839
R9	F	42.3	16	Right Thalamus, GP, Putamen	4899
R10	F	41.8	16	Right IFG, MFG, Insula, STG, SMG, IPL, Precentral, Putamen, Caudate, Postcentral	128796
R11	F	50.4	40	Right Precentral, IFG, Postcentral, Insula, STG, MFG	69679
R12	M	61.7	27	Right STG, Thalamus, IPL, Putamen, Precentral	34849
R13	M	69.0	29	Right MFG, STG, IFG, Insula, Precentral, Postcentral, IPL, SMG, SFG, Putamen	258635
R14	F	66.1	44	Right Insula, Putamen, Caudate, STG, SMG, IPL, Precentral, IFG	63508
R15	F	52.1	24	Right STG, IFG, MTG, Insula, Precentral, Postcentral, MFG, IPL, SMG	143126
R16	F	69.4	16	Right Inferior Occipital, Fusiform, Lingual, ITG, Middle Occipital	29452
R17	M	74.5	45	Right Precentral, MFG, IFG, Postcentral	4395
R18	M	58.2	1593	Right Putamen, Insula, Caudate	24713
R19	M	49.1	214	Right IFG, STG, Insula, MFG, Putamen, Temporal Pole, Precentral, ITG, Caudate	148454
R20	M	26.1	17	Right Putamen, Caudate, GP, Thalamus	34641
L1	F	54.8	116	Left Postcentral, Precentral, IFG, MFG, Insula, IPL, SMG, Putamen	11491
L2	F	63.9	1066	Left Postcentral, Precentral, IPL, STG, IPL, Middle Occipital, Insula, MTG, SMG, Precuneus, SPL, Cuneus	212322
L3	M	59.0	173	Left IFG, MFG, Insula, STG, Precentral, Postcentral, SMG, Temporal Pole, IPL	120586
L4	F	43.6	77	Left Hippocampus, ParaHippocampus, Amygdala	5768
L5	F	57.0	455	Left IFG, Insula, STG, Precentral, Putamen, MFG, Temporal pole, Caudate	110585
L6	M	46.7	275	Left STG, MTG, Insula, SMG, IPL, IFG, Precentral, Postcentral	90908
L7	M	67.4	96	Left STG, MTG, IPL, Insula, Middle Occipital, SMG, Precuneus Middle Occipital	116536
L8	M	57.0	59	Left MTG, STG, ITG, Insula, Temporal Pole, Fusiform	59600
L9	F	39.4	34	Left IFG, Putamen, Caudate, Insula, MFG	39308
L10	M	72.2	67	Left GP, Putamen, Thalamus	2049
L11	F	35.2	58	Left IPL, Postcentral, Insula, IFG, STG, Precentral, MFG, Putamen	175608
L12	M	70.9	25	Left Putamen, Claustrum	3667
L13	M	53.0	46	Left Caudate, Insula	1622
L14	F	48.0	199	Left STG, MTG, IFG, Insula, IPL, SMG, Postcentral, Precentral, MFG, Putamen	185755
L15	M	65.8	137	Left STG, IFG, Insula, MTG, Precentral, Putamen, Postcentral, caudate, MFG	146120
L16	M	21.3	173	Left IPL, STG, Postcentral, SMG, Insula	60113
L17	M	49.6	96	Left STG, IFG, Insula, MTG, MFG, Temporal Pole, Putamen, Caudate	120671
L18	F	47.9	46	Left MFG, IFG, Precentral, Insula, Postcentral, STG	98284
L19	M	52.7	177	Left Postcentral, IPL, Precentral, Insula, SMA, STG, SFG, SMG, MFG, Temporal pole, Cingulate, IFG	138679

Patient number (L for LHD, R for RHD). GP, globus pallidus; IFG, inferior frontal gyrus; Inf. Occipital, inferior occipital; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; SFG, superior frontal gyrus; SMA, supplementary motor area; SMG, supramarginal gyrus; SPL, superior parietal lobule; STG, superior temporal gyrus.

$P = 0.049$], between Lesion Side and Stimulus Side [$F(1,36) = 20.163$, $P < 0.001$] and between Stimulus Side, Lesion Side and Task [$F(1,36) = 18.504$, $P < 0.001$] but not between Lesion Side and Task [$F(1,36) = 0.029$; $P = 0.865$].

Asymmetry in reporting, assessed with the lateralization index, was compared by 2 × 2 ANOVA with the within-subject factor Task (dichotic, diotic) and between-subjects factor Lesion Side (LHD, RHD). We found significant main effects of Task [$F(1,36) = 5.407$, $P = 0.026$] and Lesion Side [$F(1,36) = 13.732$, $P < 0.001$] and a significant interaction [$F(1,36) = 10.656$, $P = 0.002$].

Performance in the dichotic task was analyzed with 2 × 2 ANOVA (Fig. 1A; Table 2) with the within-subject factor Ear (left, right) and between–subjects factor Lesion Side (LHD, RHD). The main effects of Ear [$F(1,37) = 0.228$, $P = 0.636$] and Lesion Side [$F(1,37) = 2.48$, $P = 0.124$] were not significant. Their interaction was significant [$F(1,37) = 22.057$, $P < 0.001$], driven by significantly fewer items reported for the right ear by LHD patients (left ear, 24.2 ± 7.4; right ear: 15.1 ± 12.6; $t(18) = 2.653$, $P = 0.016$) and the left ear by RHD patients (left ear: 17.4 ± 10.6; right ear: 28.3 ± 2.7; $t(19) = -4.292$; $P < 0.001$). The lateralization index (Fig. 1B; Table 2) differed significantly between patient groups ($t(37) = -4.350$, $P < 0.001$), LHD patients presenting right ear loss (mean [SD] –31.7 [51.9]) and RHD patients left ear loss (31.1 [8.35]).

Performance in the diotic task was analyzed by 2 × 2 ANOVA (Fig. 1A; Table 2) with the within-subject factor Stimulus Side (left, right) and between-subjects factor Lesion Side (LHD, RHD). The main effects of Stimulus Side [$F(1,36) = 4.871$, $P = 0.034$] and Lesion Side [$F(1,36) = 2.321$, $P = 0.136$] were not significant. Their interaction was significant [$F(1,36 = 7.427$, $P = 0.009$], driven by fewer items reported on the left side by RHD patients (left side, mean [SD] 18.5 [7.2]; right side: 22.9 [4.5]; $t(19) = -4.478$, $P < 0.001$) and equal number of items on either side by LHD patients (left side: 17.8 [6.8]; right side: 17.2 [8.7]; $t(17) = 0.381$, $P = 0.708$). The lateralization index differed significantly (Fig. 1B; Table 2; $t(35) = -2.667$, $P = 0.012$), LHD patients presenting right extinction (mean [SD] –6.2 [28.23]) and RHD patients left extinction (19.3 [14.80]).

3.2. Anatomo-clinical correlations

The anatomical correlates of contralesional extinction were analyzed by using VLSM with a patient subgroup that included

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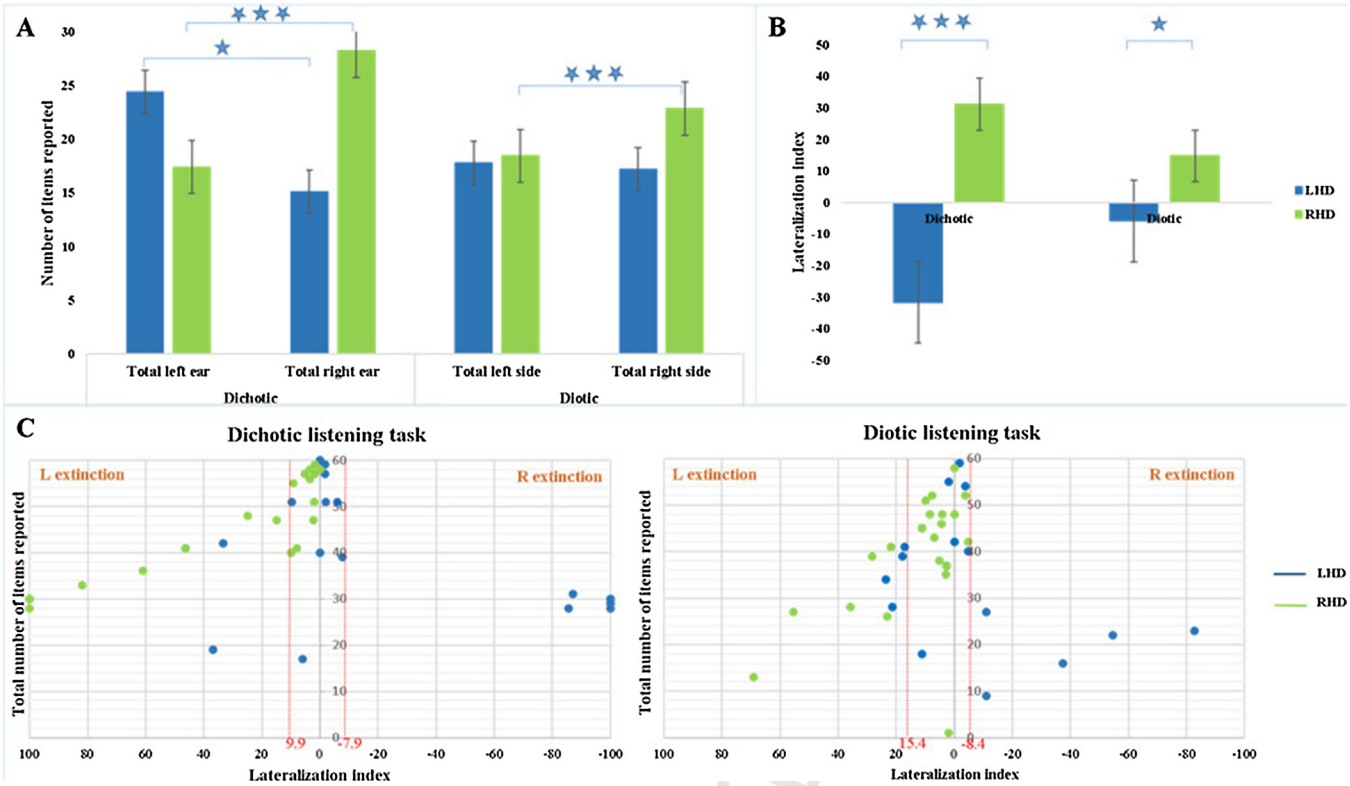

Fig. 1. Performance in dichotic and diotic tasks. A. Total number of items reported for each ear/side by patients with left hemisphere damage (LHD) and right hemisphere damage (RHD). B. Lateralization index for each group. C. Scatterplots illustrating the lateralization index by the total number of items reported for each patient group and both tasks. Negative values for the lateralization index represent right ear/side extinction and positive values left ear/side extinction. Red line delimits normal performance [7]. Error bars represent the standard error of the mean. $^{*}P < 0.05$, $^{***}P < 0.001$.

those with significant deviation of the lateralization index toward the side under consideration and those with normal lateralization index (Fig. 2). In the dichotic task, contralesional extinction was associated with damage to the superior temporal, precentral and inferior frontal gyri in the left hemisphere and the superior temporal, postcentral and inferior frontal gyri as well as the inferior parietal lobule in the right hemisphere. In the diotic task, contralesional extinction was associated with damage to the superior temporal, precentral and postcentral gyri in the left hemisphere and the superior and middle temporal gyri as well as the inferior parietal lobule in the right hemisphere.

The correlates of the number of correctly reported words for either ear/side were analyzed by dichotic and diotic tasks and are reported in Supplementary Fig. 2.

Ipsilesional extinction was observed during the dichotic task in 2 LHD patients (L3, L12) and in the diotic task in 4 LHD patients (L1, L10, L11, L12) but not in RHD patients. Analysis of 5 LHD individual cases highlighted the critical role of deep interhemispheric white matter (Fig. 3). Ipsilesional extinction in the dichotic task was associated with a large fronto-temporo-parietal (L3) or a small basal ganglia lesion (L12). Ipsilesional extinction in the diotic task was associated with a large fronto-temporo-parietal lesion including basal ganglia (L1, L11) or a small basal ganglia lesion (L10, L12).

Bilateral symmetrical extinction was assessed in a subpopulation of patients who did not present significant asymmetry in reporting (Fig. 4). For dichotic listening, this was the case for 10 patients with LHD and 10 with RHD. In each group, 3/10 patients had deficient scores in reporting items presented to both the right and left ear. For diotic listening, this was the case for 11 patients with LHD and 13 with RHD. Four LHD and 3 RHD patients had deficient scores in reporting items presented on both the right and left side. The anatomical correlate of decreased total number reported without a significant asymmetry showed clear hemispheric differences; a large region was highlighted in the left hemisphere and a much smaller one in the right hemisphere. For dichotic listening, these regions included the inferior parietal lobule, posterior parts of the middle and inferior frontal gyri, the insula, and the internal capsula on the left side and the planum temporale on the right side. For diotic listening, critical regions included the inferior parietal lobule, posterior parts of the middle and inferior frontal gyri, supratemporal plane, superior temporal gyrus, insula, basal ganglia, internal capsula, and paraventricular white matter on the left side and the inferior parietal lobule and posterior part of the planum temporale on the right side.

4. Discussion

We found RHD associated with exclusively contralesional extinction both in dichotic and diotic tasks and LHD with contra- or ipsilesional extinction. In addition, we observed bilateral symmetrical extinction after RHD or LHD, in dichotic or diotic listening. These different types of extinctions offer an interesting insight into the organisation of the auditory and attentional systems.

4.1. Left extinction after RHD

The anatomical correlates of left extinction differed in part between ear- versus space-related tasks. Left ear extinction in RHD was associated with lesions of the inferior parietal lobule, superior and middle temporal gyri, planum temporale, insula, posterior

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Table 2
Behavioural performance of patients with right hemispheric damage (R1 to R20) and left hemispheric damage (L1 to L19) on the dichotic listening, diotic listening and localization tasks ($n = 39$).

Patient	Dichotic listening				Diotic listening				Localization			
	Lateralization index	Total left ear	Total right ear	Total	Lateralization index	Total left side	Total right side	Total	Global score	Alloacusis	Center	Index of response asymmetry
R1	**46.3**	11	30	41	2.7	18	19	37	**34**	**14**	0.83	**6**
R2	**100**	0	28	28	7.6	24	28	52	57	0	2.5	0
R3	**14.9**	20	27	47	0	24	24	48	56	0	−2.5	0
R4	**10**	18	22	40	**69.2**	2	11	13	56	**1**	8.33	1
R5	2.1	23	24	47	8.3	22	26	48	55	0	**12.08**	0
R6	**25**	18	30	48	**22**	16	25	41	56	0	**15.3**	0
R7	9.1	25	30	55	9.8	23	28	51	57	0	0	0
R8	**61.1**	7	29	36	**23.1**	10	16	26	**51**	**1**	**29.17**	0
R9	0	29	29	58	4.2	23	25	48	55	0	4.17	0
R10	1.7	29	30	59	0	29	29	58	**50**	0	**27.92**	−1
R11	3.6	27	29	56	2.9	17	18	35	59	**1**	2.92	1
R12	**100**	0	30	30	**55.6**	6	21	27	58	0	**18.33**	0
R13	**81.8**	3	30	33	**28.2**	14	25	39	56	0	**42.08**	0
R14	1.8	28	29	57	2	25	26	51	**53**	**11**	**52.5**	**11**
R15	**100**	0	30	30	**35.7**	9	19	28	**52**	0	**22.5**	0
R16	**46.3**	11	30	41	**11.1**	20	25	45	55	0	5.42	0
R17	2	25	26	51	5.3	18	20	38	**50**	0	−2.92	0
R18	5.3	27	30	57	4.4	22	24	46	54	0	5.83	0
R19	3.5	28	30	58	−3.9	27	25	52	57	0	**−14.17**	0
R20	7.9	19	22	41	7	20	23	43	58	0	2.08	0
L1	5.9	8	9	17	**21.4**	11	17	28	**52**	0	4.17	0
L2	−7.7	21	18	39	−4.8	22	20	42	**49**	0	−0.83	1
L3	**36.8**	6	13	19	11.1	8	10	18	58	**4**	1.25	1
L4	−1.7	30	29	59	−1.7	30	29	59	58	0	4.58	0
L5	**−87.1**	29	2	31	−5	21	19	40	59	0	2.08	0
L6	**−85.7**	26	2	28	**−54.6**	17	5	22	59	0	0	0
L7	**−100**	30	0	30	**−37.5**	11	5	16	56	0	6.67	0
L8	−5.9	27	24	51	0	21	21	42	59	0	2.92	0
L9	0	30	30	60	1.8	27	28	55	57	0	0	0
L10	3.5	28	30	58	**18**	16	23	39	58	0	1.67	0
L11	−1.8	29	28	57	**17.1**	17	24	41	58	0	**25.42**	0
L12	**33.3**	14	28	42	**23.5**	13	21	34	57	0	**44.17**	0
L13	0	20	20	40	2.7	18	19	37	57	0	0	0
L14	**−100**	30	0	30					**54**	0	2.08	0
L15	**−100**	29	0	29	−11.1	5	4	9	58	0	0	0
L16	**−100**	28	0	28	−11.1	15	12	27	**54**	0	**23**	0
L17	**−100**	29	0	29	**−82.6**	21	2	23	57	**1**	1.17	1
L18	9.8	23	28	51	−3.7	28	26	54	57	0	−5	0
L19	−2	26	25	51	11.1	20	25	45	58	0	0.42	0

For the dichotic and diotic listening tasks, the lateralization index, number of items reported for each ear/side and total number of items reported for both ears/sides are reported. For the localization task, the global score corresponding to the total number of correct responses, the number of alloacusis, the mean angle reported for stimuli presented on the center and the index of response bias (for more details on these measures see Bellmann et al. (2001)) are reported. Values outside the limits of normal performance are in bold.

parts of the inferior and middle frontal gyri, and, partially, paraventricular white matter. This large region corresponds to that described in previous studies of auditory neglect [4–8]. Furthermore, the involvement of the supramarginal and superior temporal gyri was expected from a previous study of repetitive transcranial magnetic stimulation used in normal subjects for either region and yielding (transient) left ear extinction [18].

Left extinction in the diotic task was correlated with lesions of a much smaller region, limited to the posterior part of the superior temporal gyrus, the planum temporale and parts of the middle temporal gyrus. Together with previously published data, this finding clearly indicates that left ear and left side extinction depends on partially different neural substrates. Damage to the parietal and frontal cortex is not essential for left side extinction in diotic listening, as it is for left ear extinction in dichotic listening. As reported previously, left extinction in diotic listening can be associated with lesions centred on basal ganglia [7]. Basal ganglia was not critical in our study, most likely because the neglect profiles in the 2 studies differed. Here we included 20 patients with right hemispheric damage, 7 with left extinction in diotic and dichotic tasks, associated in all but 1 with significant rightward shift in sound localization. Thus, we analysed the anatomical correlates of the association between left extinction and rightward shift in sound localization. This was not addressed in the first study, which reported 2 cases of left extinction on diotic plus dichotic listening without auditory spatial deficits, thereby highlighting regions outside the parieto-temporal cortex. Taken together, these studies indicate that both the inferior parietal lobule and basal ganglia contribute to diotic listening performance, possibly to different aspects of this task.

The difference in the neural substrate of left extinction in dichotic versus diotic tasks offers an explanation for the previously described double dissociation between these 2 key symptoms of auditory neglect [8] and the differential effect of prismatic adaptation [16]. The latter study [16] confirmed the previously reported alleviation of left ear extinction by rightward prismatic adaptation [15] but found no or even detrimental effect on extinction in diotic tasks [16]. The differential role of the parietal cortex versus basal ganglia in auditory spatial attention may contribute to this difference but needs further investigation.

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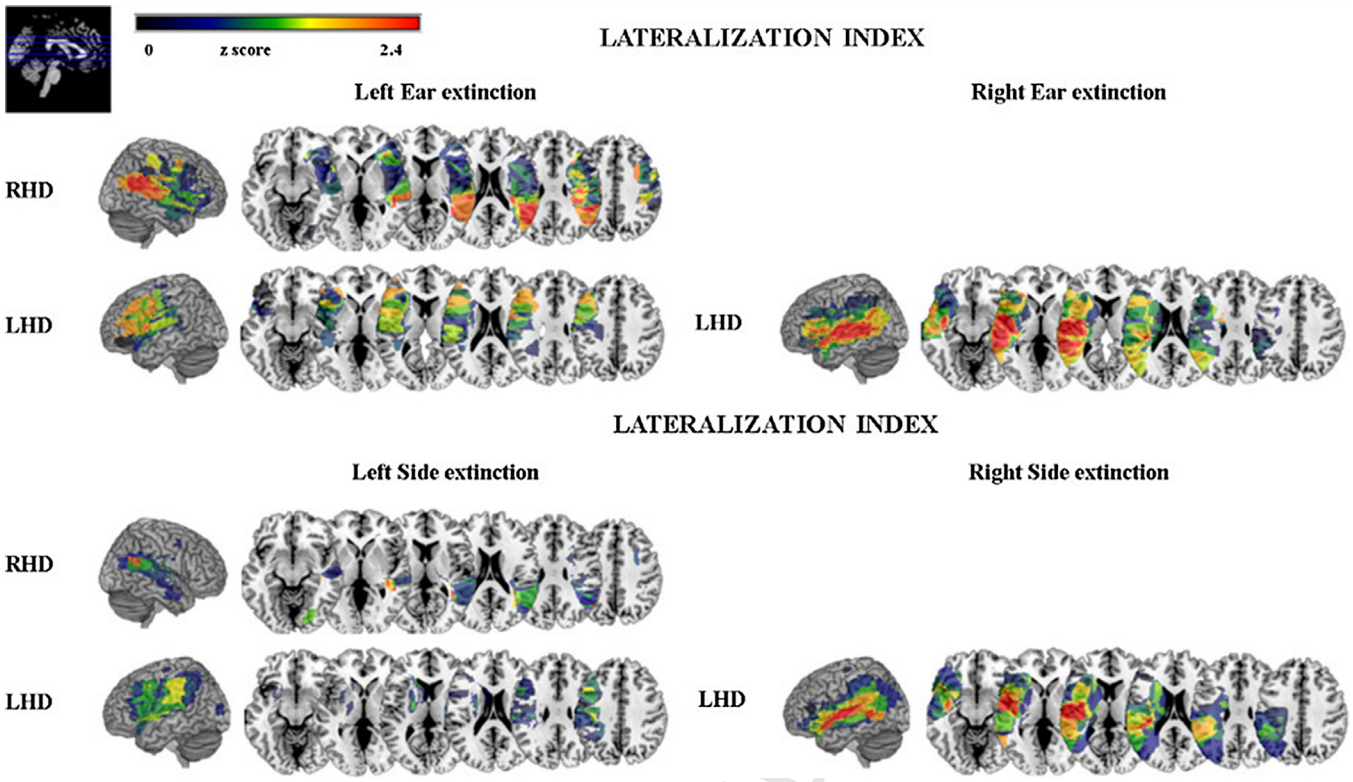

Fig. 2. Voxel-Lesion Symptom-Mapping (VLSM) analysis of unilateral extinction in dichotic (top part) and diotic tasks (bottom part) after RHD and LHD.

Additionally, the reported double dissociation also confirms that distinct mechanisms were tested with each task and that differences in performance could not be attributed to differences in task difficulty.

4.2. Contralesional extinction after LHD

Right extinction on dichotic or diotic tasks was associated with LHD, involving the inferior parietal lobule, superior and middle temporal gyri, supratemporal plane, insula, lenticular nucleus, posterior parts of inferior and middle frontal gyri, and paraventricular white matter. Furthermore, the contralesional ear extinction in LHD involved an approximately similar set of regions as in RHD, in agreement with previous lesion and activation studies. The extinction of contralesional stimuli during dichotic listening in RHD or LHD was already reported in the early, seminal study by De Renzi et al. [19]. Subsequent activation studies highlighted the involvement of the superior temporal gyrus bilaterally as well as the left middle temporal gyrus and right inferior temporal gyrus [20,21] and by increasing the attentional load, inferior frontal gyrus, anterior cingulate regions, and intraparietal sulcus bilaterally [22].

4.3. Ipsilesional extinction after LDH

Ipsilesional extinction was present in 5 patients with LHD. Because this is a relatively low number for a group analysis, we analysed each case individually (Fig. 3). The observation that LHD but not RHD can lead to ipsilesional extinction is congruent with previous reports. Left ear extinction has been reported outside the neglect syndrome, with damage to the callosal pathway, particularly the splenium and/or isthmus [23–26]. In the present study we found a significant decrease in left ear reporting after LHD. None of these cases sustained damage to the corpus callosum per se (i.e., at midsagittal plane) or to periventricular white matter, but callosal fibres were most likely damaged further down in their intrahemispheric trajectory, in the white matter of the inferior parietal lobule, insula and inferior and middle frontal gyri.

Ipsilesional, left side extinction on diotic listening, was reported in a case of left parieto-fronto-occipital lesion [8]. Our study confirms this finding with 4 new cases and highlights the critical role of fronto-parietal convexity and underlying white matter.

4.4. Bilateral extinction

The bilateral decrease in reporting items without a significant asymmetry constitutes a very special case of extinction. Hypothetically, 2 different mechanisms are likely involved. First, the ability to segregate sound objects on the basis of spatial cues may be critical [9,27,28]. Speech intelligibility was repeatedly shown to benefit from spatial separation of sound streams [29,30], and activation studies highlighted the role of the supratemporal plane in streaming [31,32]. More specifically, the combined encoding of the meaning of sound objects and their position was shown to depend on a predominantly left-hemispheric network, involving the posterior temporal and prefrontal cortices [33]. This critical role of a left hemispheric network is supported by our findings, showing that LHD was indeed associated with bilateral, symmetrical decrease of reporting. For dichotic listening, the critical regions included the inferior parietal lobule, posterior parts of middle and inferior frontal gyri, insula, and internal capsula. For diotic listening, the supratemporal plane, basal ganglia and paraventricular white matter were involved, in addition to the same set of regions. Second, the right hemispheric attentional system may play a role in following two streams of stimuli at the same time. Divided attention tasks engage a widespread, predominantly right hemispheric network involving the prefrontal cortex, inferior parietal lobule and claustrum [34]. The VLSM

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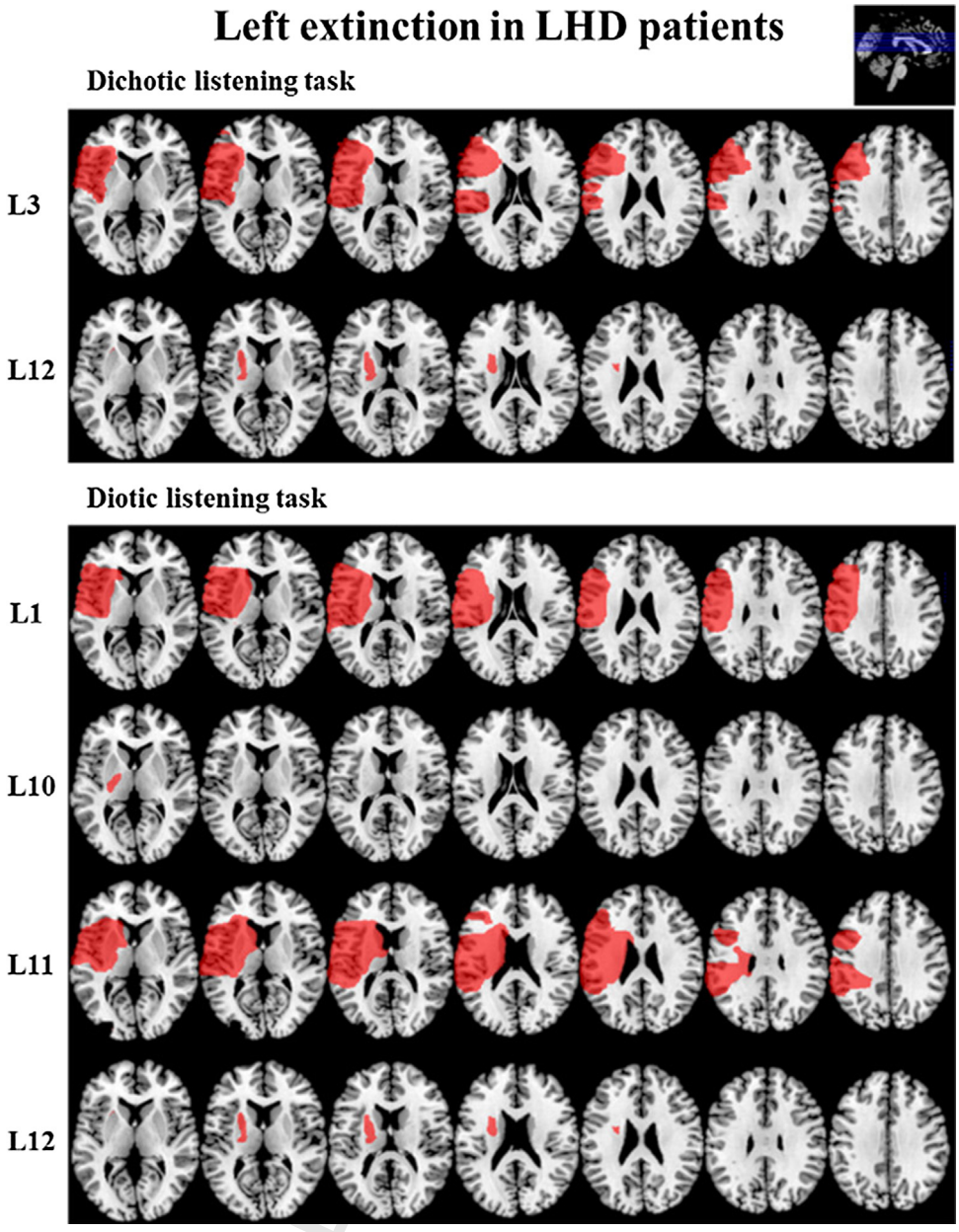

Fig. 3. Brain lesions of 5 LHD patients presenting ipsilesional extinction in dichotic (L3, L12) and diotic tasks (L1, L10, L11, L12).

analysis of bilateral extinction within the right hemisphere highlighted only very small clusters in the dichotic task and only marginally larger regions within the inferior parietal lobule and the posterior part of the planum temporale for the diotic task.

5. Conclusions

The anatomo-clinical correlates of different types of auditory extinction offer interesting insights into the organisation of the auditory and attentional systems. First, they unravel a difference in the neural substrate of left extinction in dichotic versus diotic tasks and hence offer an explanation for a previously described double dissociation between the 2 key symptoms of auditory neglect. Second, contralesional extinction in dichotic listening appears to rely on a very similar neural substrate in either hemisphere; thus, both right and left auditory cortex are involved, each critical for information provided by the contralesional ear. Third, ipsilesional extinction in dichotic listening after LHD was associated with lesions involving intrahemispheric white matter; thus, the callosal disconnection, which is believed to cause this deficit, can also occur in cases of intrahemispheric and not just midsagittal or periventricular interruptions of the callosal pathway. Fourth, bilateral symmetrical extinction was associated with LHD in a large parieto-fronto-temporal region and with RHD in a smaller parieto-temporal region, which indicates that divided attention, supported by the right hemisphere, and auditory streaming, supported by the left, likely play a critical role.

These findings are of direct clinical relevance for the neurorehabilitation of auditory spatial deficits. First, they underline once more the heterogeneity of the neglect syndrome and its anatomical substrate. This heterogeneity is most likely one of the reasons why meta-analyses of randomized control trials tend to reveal a relative lack of efficiency (for a review see [35]). Identifying responders and non-responders to a specific therapeu-

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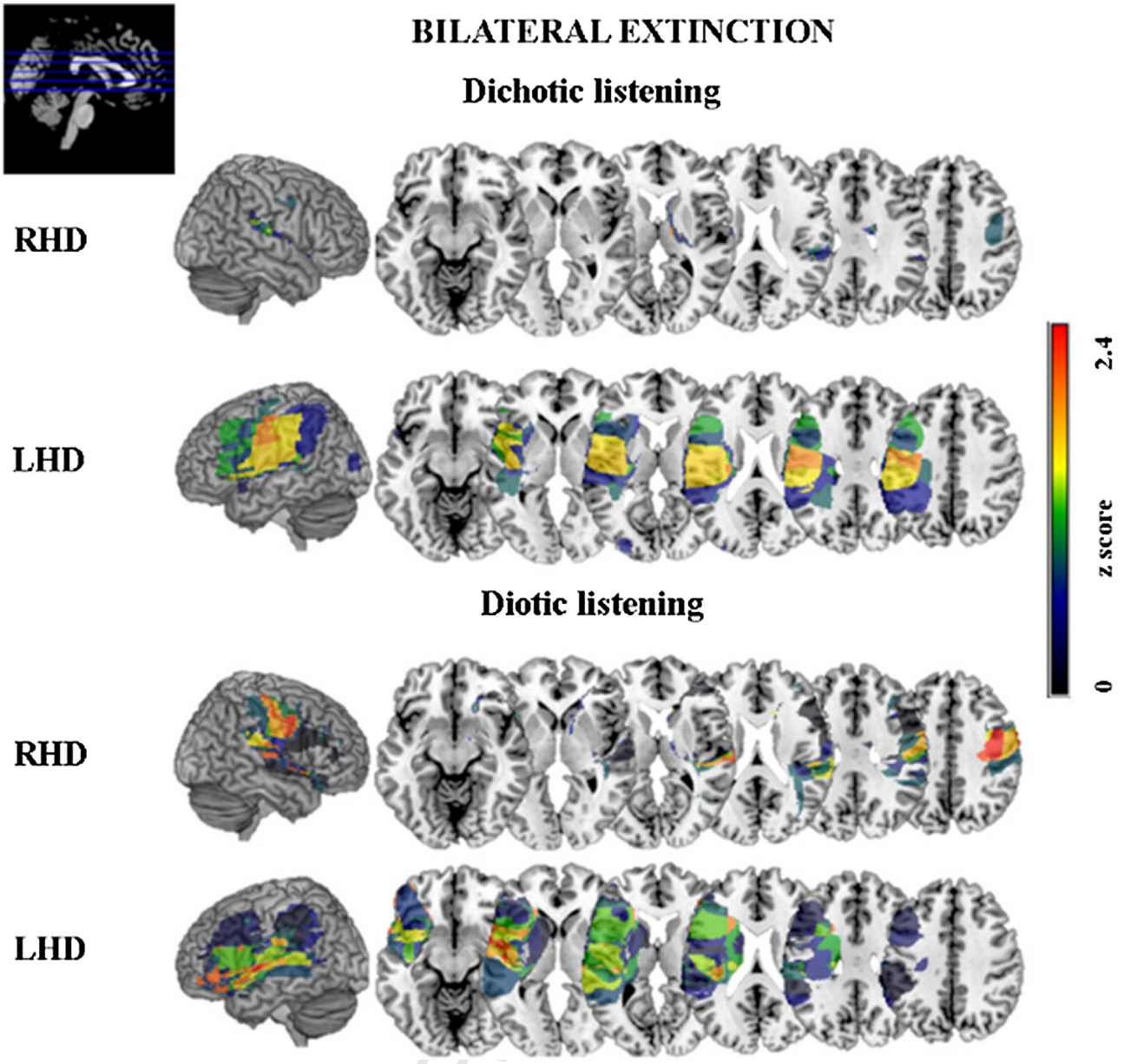

Fig. 4. VLSM analysis of bilateral extinction without significant asymmetry in dichotic (top part; 10 RHD, 10 LHD) and diotic tasks (bottom part; 13 RHD, 11 LHD).

tic intervention should improve the impact of treatments; a first study identified the lesion profile of patients with auditory neglect who responded to prismatic adaptation [16].

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Authors contributions

Conception and design of the study: SC, SCH, IT.
Drafting of the original protocol and acquisition of data: SC, SCH.
Design of the statistical analysis plan: SCH, IT.
Drafting of the present manuscript and final approval: IT, SCH, SC.

Disclosure of interest

The authors have not supplied their declaration of competing interest. Q2

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2018.05.001.

References

[1] Clarke S, Thiran AB. Auditory neglect: what and where in auditory space. Cortex 2004;40:291–300.
[2] Gokhale S, Lahoti S, Caplan LR. The neglected neglect: auditory neglect. JAMA Neurol 2013;70:1065–9.
[3] Renzi ED, Gentilini M, Barbieri C. Auditory neglect. J Neurol Neurosurg Psychiatr 1989;52:613–7.
Q3 [4] Deouell LY, Soroker N. What is extinguished in auditory extinction?
[5] Heilman KM, Valenstein E. Auditory Neglect in Man. Arch Neurol 1972;26:32–5.
[6] Hugdahl K, Wester K, Asbjørnsen A. Auditory neglect after right frontal lobe and right pulvinar thalamic lesions. Brain Lang 1991;41:465–73.
[7] Bellmann A, Meuli R, Clarke S. Two types of auditory neglect. Brain: J Neurol 2001;124:676–87.
[8] Spierer L, Meuli R, Clarke S. Extinction of auditory stimuli in hemineglect: Space versus ear. Neuropsychologia 2007;45:540–51.
[9] Thiran AB, Clarke S. Preserved use of spatial cues for sound segregation in a case of spatial deafness. Neuropsychologia 2003;41:1254–61.
[10] Bisiach E, Cornacchia L, Sterzi R, Vallar G. Disorders of perceived auditory lateralization after lesions of the right hemisphere. Brain J Neurol 1984;107:37–52.
[11] Soroker N, Calamaro N, Glicksohn J, Myslobodsky MS. Auditory inattention in right-hemisphere-damaged patients with and without visual neglect. Neuropsychologia 1997;35:249–56.
[12] Spierer L, Bellmann-Thiran A, Maeder P, Murray MM, Clarke S. Hemispheric competence for auditory spatial representation. Brain 2009;132:1953–66.
[13] Tanaka H, Hachisuka K, Ogata H. Sound lateralisation in patients with left or right cerebral hemispheric lesions: relation with unilateral visuospatial neglect. J Neurol Neurosurg Psychiatr 1999;67:481–6.
[14] Farnè A, Rossetti Y, Toniolo S, Làdavas E. Ameliorating neglect with prism adaptation: visuo-manual and visuo-verbal measures. Neuropsychologia 2002;40:718–29.
[15] Jacquin-Courtois S, O'Shea J, Luauté J, et al. Rehabilitation of spatial neglect by prism adaptation: A peculiar expansion of sensorimotor after-effects to spatial cognition. Neurosci Biobehav Rev 2013;37:594–609.
Q4 [16] Tissieres I, Elamly M, Clarke S, Crottaz-Herbette S. For better or worse: the effect of prismatic adaptation on auditory neglect. https://www.hindawi.com/journals/np/2017/8721240/abs/.
[17] Rorden CH, Karnath -O, Bonilha L. Improving Lesion-Symptom Mapping. J Cogn Neurosci 2007;19:1081–8.
[18] Bareham CA, Georgieva SD, Kamke MR, Lloyd D, Bekinschtein TA, Mattingley JB. Role of the right inferior parietal cortex in auditory selective attention: an rTMS study. Cortex 2018;99:30–8.
[19] Renzi ED, Gentilini M, Pattacini F. Auditory extinction following hemisphere damage. Neuropsychologia 1984;22:733–44.
[20] Hugdahl K, Brønnick K, Kyllingsbrk S, Law I, Gade A, Paulson OB. Brain activation during dichotic presentations of consonant-vowel and musical instrument stimuli: a 15O-PET studyfn2fn2. The present study was financially supported by a grant to Olaf B. Paulson (coordinator) from the Danish Research Councils interdisciplinary research program, and by a grant to Kenneth Hugdahl from the Norwegian Medical Research Council (NFR), and from the MacArthur Foundation/Mind-Body Network, Chicago, il, USA. The John and Birthe Meyer Foundation is gratefully acknowledged for the donation of the Cyclotron and PET-scanner. Neuropsychologia 1999;37:431–40.
[21] van den Noort M, Specht K, Rimol LM, Ersland L, Hugdahl K. A new verbal reports fMRI dichotic listening paradigm for studies of hemispheric asymmetry. NeuroImage 2008;40:902–11.
[22] Pugh KR, offywitz BA, Shaywitz SE, et al. Auditory selective attention: an fMRI investigation. NeuroImage 1996;4:159–73.
[23] Kimura D. Functional Asymmetry of the Brain in Dichotic Listening; Q5 1967;3:163–78.
[24] Pollmann S, Maertens M, Yves D, Lepsien J, Hugdahl K. Dichotic listening in patients with splenial and nonsplenial callosal lesions. Neuropsychology 2002;16:56–64.
[25] Sparks R, Geschwind N. Dichotic Listening in Man After Section of Neocortical Commissures. Cortex 1968;4:3–16.
[26] Sugishita M, Otomo K, Yamazaki K, Shimizu H, Yoshioka M, Shinohara A. Dichotic listening in patients with partial section of the corpus callosum. Brain 1995;118:417–27.
[27] Clarke S, Geiser E. Roaring lions and chirruping lemurs: How the brain encodes sound objects in space. Neuropsychologia 2015;75:304–13.
[28] Duffour-Nikolov C, Tardif E, Maeder P, et al. Auditory spatial deficits following hemispheric lesions: Dissociation of explicit and implicit processing. Neuropsychol Rehabil 2012;22:674–96.
[29] Carhart R, Tillman TW, Johnson KR. Effects of interaural time delays on masking by two competing signals. J Acoust Soc Am 1968;43:1223–30.
[30] Schubert ED, Schultz MC. Some aspects of binaural signal selection. J Acoust Soc Am 1962;34:844–9.
[31] Krumbholz K. Representation of Interaural Temporal Information from Left Q6 and Right Auditory Space in the Human Planum Temporale and Inferior Parietal Lobe. Cerebral Cortex Oxford Academic. https://academic.oup.com/cercor/article/15/3/317/375182.
[32] Schadwinkel S, Gutschalk A. Activity associated with stream segregation in human auditory cortex is similar for spatial and pitch cues. Cereb Cortex 2010;20:2863–73.
[33] Bourquin NM-P, Murray MM, Clarke S. Location-independent and location-linked representations of sound objects. NeuroImage 2013;73:40–9.
[34] Vohn R. Management of attentional resources in within-modal and cross-modal divided attention tasks: An fMRI study - Vohn. Human Brain Mapping – Wiley Online Library; 2007, http://onlinelibrary.wiley.com/doi/10.1002/hbm.20350/full.
[35] Clarke S, Bindschaedler C, Crottaz-Herbette S. Impact of cognitive neuroscience on stroke rehabilitation. Stroke 2015;46:1408–13.

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Left and right hemispheric lesions impair implicit use of spatial cues in auditory streaming

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ABSTRACT

Previous studies reported a double dissociation between deficits in explicit sound localization and in sound object segregation on the basis of implicit use of spatial cues, suggesting the existence of a position-linked representation of sound objects that is distinct from the position-independent representation within the ventral auditory stream and from the explicit sound localization processing within the dorsal stream. Here we provide evidence for the anatomical substrate of spatial-cue based sound object segregation.

Fifty-seven participants (17 controls; 20 patients with left and 20 with right hemispheric damage) were assessed for explicit sound localization and for the effect of spatial release from masking (SRM). The latter used two simultaneous environmental sounds; the position of the masker varied (a central and 2 positions within each hemispace, simulated with interaural time differences) whereas the target remained central. Voxel-based Lesion-Symptom Mapping (VLSM) was applied to either task.

Performance in the explicit localization task depended critically on the right parietal cortex, confirming the role of the right dorsal auditory pathway in explicit localization.

For the SRM task, separate VLSM analysis was performed for each of the 5 masker positions. It highlighted the critical role of a large temporo-parieto-frontal region within the left hemisphere, independently of the position of the masker. In addition, a smaller parieto-temporal region was highlighted, more specifically when the masker was central or to the right.

Thus, explicit and implicit use of spatial cues depend on at least partially distinct neural networks. The involvement of a left temporo-parieto-frontal network in the SRM effect is in agreement with the role of a left temporo-frontal network in position-linked representation of sound objects, which was reported in a previous EEG study.

Abbreviations

SRM: Spatial Release from Masking task

LHD: left hemispheric damaged

RHD: right hemispheric damaged

CTRL: control group

IID: interaural intensity differences

ITD: interaural time differences

VLSM: Voxel-Lesion Symptom-Mapping

Key-words

Lesion studies, auditory spatial processing, attention, sound object segregation, unilateral neglect

Introduction

Patients who sustained left or right hemispheric lesions often complain of major difficulties when they are confronted with noisy surroundings. These complaints can occur without history of classical neuropsychological syndromes, such as speech and language deficits, attentional deficits or auditory agnosia, as well as without peripheral auditory loss or damage to brainstem auditory structures. The key features of these complaints, being unable to focus on specific speakers and extreme tiredness after even short periods of exposure to noisy surroundings are reminiscent of faulty auditory streaming, i. e. the segregation of different sound objects, which constitute an auditory scene.

Sound object segregation is the ability to separate competing oncoming sounds into distinct sound objects. This important component of the auditory scene analysis involves the processing of implicit spatial cues in order to correctly separate the competing sounds (Bregman, 1994; Roman et al., 2002). Deficits following brain lesions were shown in numerous studies (Carlyon et al., 2001; Carlyon, 2004; Darwin, 1997; Litovsky et al., 2002; Thiran and Clarke, 2003). Neural correlates of sound object segregation were investigated in distinct neuroimaging studies and results showed a bilateral involvement of the primary and associative auditory cortex as well as a contribution of subcortical structures (Arnott et al., 2011; Dyson and Alain, 2003; Litovsky et al., 2002; Pressnitzer et al., 2008).

'Auditory Scene Analysis' (Bregman, 1994; Carlyon, 2004) refers to the ability to correctly listen to one sound when it is surrounded by noise. Two sounds starting and stopping synchronously and with a same pitch will be perceived as coming from a unique source (Assmann and Summerfield, 1990). For the listener to segregate both sounds and be able to

recognize the sound object of interest several binaural cues are needed. An important cue is interaural intensity differences (IIDs). Studies have shown that if two people are simultaneously talking to a listener, his ability to understand one speech is increased if he attends to the hear that is closer from him (Bronkhorst and Plomp, 1988; Culling and Summerfield, 1995). Lots of studies have investigated the role of interaural time differences (ITDs) and did not found any implication of this cue in this mechanism (Culling and Summerfield, 1995; Darwin, 1997; Gockel and Carlyon, 1998; Licklider, 1948). However, one study investigated the role of spatial location in sound segregation in a free-field set-up and found that some participants could use ITDs to perform the task following training (Drennan et al., 2003). Studies investigating Binaural Masking Level Difference (BMLD) have highlighted another cue used to segregate sounds, it is the decorrelation induced by the second sound on the two ears (Grantham, D.W, 1995; Jeffress, L.A. et al., 1952). Indeed, it has been demonstrated that the waveforms from one sound stream are correlated when arriving at both ears (Akeroyd and Summerfield, 2000; Culling and Colburn, 2000; Culling and Summerfield, 1995). When there is a second sound stream, it will have energies in several identical frequency regions meaning that for several auditory nerve fibers it will be a mixture of both sound streams. The listener will use the second sound stream to decorrelate the information arriving in both ears, first based on the fact that the second sound stream does not arrive from the same position and by this reason has not the same IIDs or ITDs and second based on the frequency regions where this second stream has the most energy. Decorrelation actually enhances signal detection and has been shown to be related to the inferior colliculus (Palmer & Shackleton, 2002). Another study shown the involvement of the intraparietal sulcus in the auditory streaming, suggesting that at a later stage there are supra-modal regions that treat the output of the perceptual organization (Cusack, 2005).

Spatial release from masking (SRM) is a paradigm used to investigate the role of implicit spatial cues in sound object detection (Carhart et al., 1967; Culling et al., 2004; Hawley et al., 1999, 2004; Saupe et al., 2010; Thiran and Clarke, 2003). During auditory scene analysis, the listener has to identify sounds that can overlap temporally, spectrally or spatially. Informational masking refers to the difficulty to identify sounds when they are highly similar (Kidd et al., 2002; Neff, 1995). It has been demonstrated that when informational masking is large, spatial cues become more important (Arbogast et al., 2002; Kidd et al., 1998). The SRM paradigm investigates the increased performance in target detection when the target and the masker sound are spatially separated. Indeed, spatially separating both sounds elicits a certain amount of release from masking.

Right-hemispheric dominance for sound localization was demonstrated by several studies including healthy controls or patients following unilateral brain lesions (Brunetti et al., 2005; Duhamel et al., 1986; Haeske-Dewick et al., 1996; Kaiser et al., 2000; Maeder et al., 2001; Spierer et al., 2009; Tanaka et al., 1999).

Double dissociations between deficits in sound localization and sound object segregation observed in stroke patients (Duffour-Nikolov et al., 2012) suggest that the implicit and explicit use of spatial cues might rely on distinct, or at least partially distinct, neural correlates.

The two objectives of the present study were to investigate the neural substrates of the implicit use of spatial cues and to understand the impact of unilateral neglect. Two different tasks targeting separately the implicit (SRM) and explicit (auditory lateralization paradigm) use of spatial cues abilities were used as well as anatomo-clinical correlations with the Voxel-Lesion Symptom-Mapping (VLSM) method. This mass-univariate statistical method was chosen to

test the impact of each voxel of the brain lesions of the patients on their performances at the auditory spatial tasks. By testing independently each voxel it allows determining its specific importance for these cognitive functions. In comparison to other neuroimaging methods in lesion studies, VLSM is essential because it says that if a stroke causes a behavioural deficit then the territory affected is essential for the normal functioning of this behaviour (Sperber and Karnath, 2017).

The above quoted evidence suggests that the implicit use of spatial cues is at least partially independent of the explicit use of spatial cues in sound localization. Understanding the nature of deficits of auditory streaming may help to define therapeutic approaches.

Materials and Methods

Sample

Fifty-seven subjects were included in this study: i) 17 healthy young right-handed subjects (8 males; mean age = 26.47y, SD = 3.64) with no history of neurological or psychiatric disorders; ii) 20 patients following a first left-sided unilateral stroke (12 males; mean age = 51.3y, SD = 14.8); iii) 20 patients following a first right-sided unilateral stroke (12 males; mean age = 55.4y, SD = 11.4). All patients but two were right-handed. An independent samples t-test confirmed that both patient groups did not differ in lesion size (Figure 1.A): ($t(38) = 27.85$, $p = .351$, LBD: M=119285 ml; RBD: M= 84266 ml), nor in age ($t(38) = 35.61$, $p = .35$, LBD: M=51.35 years old; RBD: M= 55.35 years old). Clinical and demographical data are provided in the Supplementary Table 1. All participants provided an informed consent form according to the procedures approved by the Ethic Committee of the Canton de Vaud, Switzerland.

Patients were tested on the subacute phase of the stroke (on average 126.5 days after the brain lesion (SD = 253.7, range [11, 1593]). On the delay post-stroke, an independent sample t-test was performed and showed that RBD patients were tested significantly sooner than LBD patients (t (38) = 27.88, p= .03, LBD: M= 128.95 days; RBD: M= 47.1 days). The range in delay post-stroke is however equivalent for both groups, LBD [25; 1066] and RBD [11; 1593]. LBD patients were tested significantly later than RBD patients. This is related to the inclusion criteria. Indeed, to be able to complete the tasks, participants needed to fully understand what was expected from the task and to be able to express their understanding. With Voxel-lesion Symptom-mapping it is very important to equally sample all groups' lesions (to have small and large lesions in each group). In order to have right and left hemispheric lesions as comparable as possible in order to get powerful statistical results, the patients with large lesions to the left hemisphere were included too. This implies aphasic patients with comprehension and expression deficits. So, to do not exclude these patients, an additional delay was added for them to recover enough. However, an impact of the delay post-stroke was excluded by investigating its effect on the behavioural measures of interest (see Results section).

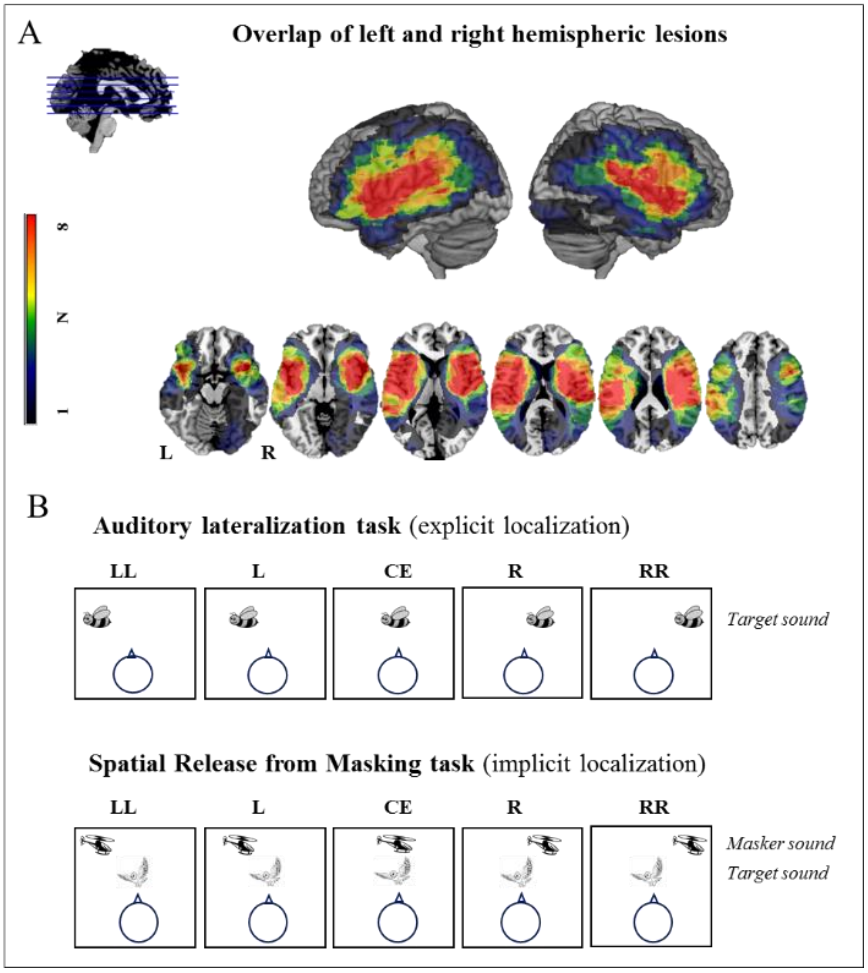

Figure 1. A. Group lesions overlap for LHD (n = 20) and RHD (n = 20) patients. B. Illustration of the two paradigms used in the present study.

Spatial Release from Masking task (implicit use of spatial cues)

This test is a detection task that consists of two sound objects presented concurrently, one being masked by the second (Figure 1.B). The target, which is an 800 ms cry of a tawny owl (20-5000 Hz, centered between 350 and 900 Hz; "All Birds of Europe", Delachaux & Niestlé) was always presented at the same spatial position, simulated to be at the center of the head (0° ITD). The masker consisted of a 2.5 seconds helicopter sound (20-5500 Hz, the frequency region containing the dominant sound energy around 700 Hz; Nathan Sound Loto) and was presented at 5 different spatial location simulated by ITD, one being identical to the cue and four lateral positions. The task's requirement was to detect the target hidden by the masking sound. 86

items were presented to the subjects, of whom 43 were the masker alone and 35 the masker with the target. In order to avoid expectation of the target, 8 trials (distractors) were added to the test but not included in the result analysis. In half of them target began 500 ms after the masking sound and in the other half 1500 ms after. Subjects were instructed to respond by answering "yes" when they detected the target. Performance was measured by calculating a d prime. The current task is close to the task validated on a control population of 60 subjects (mean age: 41.8y, SD 15.9y; Bellmann-Thiran & Clarke, 2003) and on stroke patients (Duffour-Nikolov et al., 2012). The differences between our task and the previous ones is the number of masker sound positions, in the current study we kept only five positions (i.e. far left, left, center, right, far right). In the control population mentioned above, when the masker is presented centrally, individual performance are heterogenous: over 60% of the subjects fail completely to detect the target, others detect it less often and a small number of subjects detects it as often as when the masker is in the periphery. On average, normal subjects detect the target less often when the masker is in central than in peripheral positions creating a U-shaped curve of performance (see Figure 3 in Thiran & Clarke, 2003). To extract from the behavioural performances the ability to use spatial cues, an index was calculated. This index corresponds to the distance between the performance for a lateral position and the performance for the central position. If a patient cannot use the spatial cues to improve target detection, then the performances for the lateral positions will be similar to the performance for the central position. If the patient can use the spatial cues, then the performances for the lateral positions will be higher. This measure was used for VLSM analyses.

Auditory lateralization task (explicit use of spatial cues)

This test has been described in previous studies (Clarke et al., 2000; Bellman et al., 2001) (Figure 1.B). It consists of 60 sounds of a bumblebee, ranging from 20 to 10000 Hz presented

during 2 seconds including 100 ms rising and falling times. Five different azimuthal positions (12 sounds at each position) were simulated by varying the ITD creating one central (no ITD) and four lateral intra-cranial positions, two in each hemispace. For lateral positions, the ITD was 0.3 ms (intermediate lateralization) or 1 ms (extreme lateralization). The task consisted to indicate precisely the perceived position of the blumblebee on a graduated semi-circle affixed on the headphone (from 0° at the vertex to 90° at each ear) with the index finger of the ipsilesional hand and of the right hand for the control group. Performance at this task was measured by calculating a relative score, i.e. the Global score, based on the comparison of the relative positions attributed to two consecutive stimuli (Spierer et al., 2009). When a stimulus was correctly placed to the left or to the right of the previous stimulus in correspondence with the difference in ITD or within ±10° of the previous location for identical stimuli, the response was counted as correct (maximal score 59).

Statistical analyses of behavioural data

For each task, mixed-design ANOVA's were performed using a specific hierarchy. The first ANOVA meant to assess the difference between patients and control subjects on behavioural performances. The second ANOVA meant to assess differences between groups (LHD, RHD, CTRL) on behavioural performances. Finally, a Post-Hoc ANOVA selecting only the two groups of patients meant to assess the impact of the lesion side on behavioural performances.

Delay post-stroke was investigated using a mixed-design ANOVA for SRM behavioural measures and a one-way ANOVA for the auditory lateralization task measure.

Analyses were processed using R (R Development Core Team, 2008, Vienna, Austria).

Voxel-Lesion Symptom-Mapping

Voxel-lesion symptom-mapping (VLSM) was used to investigate the relationship between the anatomy of the brain lesions and the behavioural deficits observed following a first unilateral stroke. VLSM is a mass-univariate analysis method allowing testing each voxel separately and determining its impact on a particular behaviour of interest when this voxel is damaged.

Lesions were drawn on MRI or CT scans of the 40 patients on axial slices using the MITK 3M3 software and then normalized on the standard Montreal Neurological Institute's (MNI) brain template (Rorden and Brett, 2000; Brett et al., 2001). Then, VLSM statistical analyses were performed on the normalized lesions with the Non-Parametric Mapping toolbox (NPM) from MRICroN software package (Rorden et al., 2007). Minimal group-size for analysis was set to 15% of patients, i.e. t-tests were restricted to voxels where there were at least three patients in each group (with or without lesion). The statistical test used was the Brunner-Munzel test, FDR-corrected, tBM-map intensity [0, 4].

In order to extract the brain regions only important for the implicit use of spatial cues we used the following normalized behavioural measure (Supplementary Table 2): we calculated the distance between the accuracy for the central position and each of the four lateral positions (LL-CE, L-CE, RR-CE, R-CE). If a patient presents a small distance it will mean that he cannot benefit from the implicit spatial cues to improve his accuracy for the lateral position. VLSM analyses were performed on these normalized behavioural data.

Behavioural results

Spatial Release from Masking Task (implicit use of spatial cues)

ANOVA 1 – Group (patients, CTRL) vs Mask position (far left, left, center, right, far right)

A mixed-design ANOVA with the Greenhouse-Geisser correction was conducted with the factor Group (patients, CTRL) as a between-subjects factor and the factor Mask position (far left, left, center, right, far right) as a within-subject factor (Supplementary Table 2). Results showed a main effect of Group [F (1, 55) = 33.694, $p < .001$], a main effect of Mask position [F (4, 55) = 44.319, $p < .001$] and an interaction between Group and Mask position [F (4, 55) = 6.543, $p < .001$]. These results mean that patients performed significantly worse than controls and that performance for the central position of the masker sound was significantly worse than for the other positions, showing the spatial release from masking effect. Interaction between Group and Mask position is related to the fact that controls only show a decreased performance for central masker sound positions, whereas patients show a gradient of decrease in performance between positions. Post-hoc independent samples t-tests, Bonferroni-corrected, were conducted to understand these significant results. Results show that both groups (patients and CTRL) have statistically different performances for each mask position: far left-controls (M=4.3, SD=0.27), far left-patients (M=3.3, SD=1.35); t (46) = 4.73, $p < .005$. Left-controls (M=4.3, SD=0.37), left-patients (M=2.1, SD=1.57); t (48) = 8.15, $p < .005$. Center-controls (M=2.92, SD=1.18), center-patients (M=0.67, SD=1.3); t (55) = 6.15, $p < .005$. Right-controls (M=4.1, SD=0.55), right-patients (M=1.97, SD=1.34); t (55) = 8.41, $p < .005$. Far right-controls (M=4.1, SD=0.59), far right-patients (M=2.98, SD=1.58); t (54) = 3.98, $p < .005$.

ANOVA 2 – Group (LHD, RHD, CTRL) vs Mask position (far left, left, center, right, far right)

A mixed-design ANOVA with the Greenhouse-Geisser correction was conducted with the factor Group (LHD, RHD, CTRL) as a between-subjects factor and the factor Mask position (far left, left, center, right, far right) as a within-subject factor. Results showed a main effect of Group [F (2, 54) = 21.85, p < .001], a main effect of Mask position [F (4, 54) = 64.02, p < .001] and an interaction between Group and Mask position [F (8, 54) = 3.83, p = .003]. The main effect of Group is related to the fact that both groups of patients' performance was significantly lower than the control group's performance. Main effect of Mask Position is related to the fact that each group showed the spatial release from masking effect, meaning a lower performance when the masker sound was at the central position. The interaction between Group and Mask position is related to the fact that controls only show a significant decrease of performance for the central position, whereas both groups of patients shows significant decreases, gradually from central to lateral positions.

ANOVA 3 – Group (LHD, HBD) vs Mask position (far left, left, center, right, far right)

A mixed-design ANOVA with the Greenhouse-Geisser correction was conducted with the Mask position at the SRM task (far left, left, center, right, far right) as a within-subject factor and Group (LHD, RHD) as a between-subjects factor. Results showed a significant main effect of Group [F (1, 38) = 4.86, p = .03] and a main effect of Mask position [F (4, 38) = 55.16, p <.001], but no interaction between these two factors. Post-hoc independent-samples t-tests showed that both groups have significantly different results at two mask positions: right, LHD (M=2.48, SD=1.32), RHD (M=1.47, SD=1.2); t (38) = 2.53, p = .016; and far right, LHD (M=3.55, SD=1.33), RHD (M=2.42, SD=1.64); t (38) = 2.41, p = .02.

Auditory lateralization task (explicit use of spatial cues)

ANOVA 1 – Group (Patients, CTRL)

A one-way ANOVA was conducted on the Global score (Supplementary Table 2) with the factors Group (patients, controls) and did not show any significant result [F (1, 56) = 0.17, p = .681].

ANOVA 2 – Group (LHD, RHD, CTRL)

A one-way ANOVA was conducted on the Global score with the factors Group (LHD, RHD, CTRL) and did not show any significant result [F (2, 56) = 2.747, p = .073].

ANOVA 3 – Group (LHD, RHD)

A one-way ANOVA on the Global score at the explicit localization task with the factors Group (LHD, RHD) showed a tendency, but no significant result [F (1, 40) = 3.97, p = .053].

Delay Post-Stroke

The effect of the delay post-stroke was investigated using a mixed-design ANOVA on the SRM behavioural measures and a one-way ANOVA on the auditory lateralization measure in order to ensure that delay would not affect the performances at either task. On the SRM task, an ANOVA was performed to assess the effect of the fixed variable Delay on the factor Mask position (far left, left, center, right, far right). Results showed no statistical significant effect for the interaction of Delay and Mask Position [F (4, 35) = .493, p = .991], indicating that the delay post-stroke does not modulate the accuracy for any masker position. On the auditory lateralization task, results showed no statistical significant effect for the Delay on the relative

score [F (1, 39) = 4.189, p = .057], indicating that the delay post-stroke has no effect on auditory localization.

Imaging results

Voxel-Lesion Symptom-Mapping

VLSM results show the regions in both hemispheres important for the correct use of implicit spatial cues for auditory streaming (Figure 2).

In the left hemisphere, the regions important for sound object segregation in the left auditory space are located on the precentral and postcentral gyri and on the inferior frontal cortex. For sound object segregation in the right auditory space, the regions important are located on the precentral, middle temporal and angular gyri.

In the right hemisphere, the regions important for sound object segregation in the left auditory space are located on the supramarginal and inferior frontal gyri. For sound object segregation in the right auditory space, the regions important are located on the supramarginal, angular, inferior frontal and superior temporal gyri.

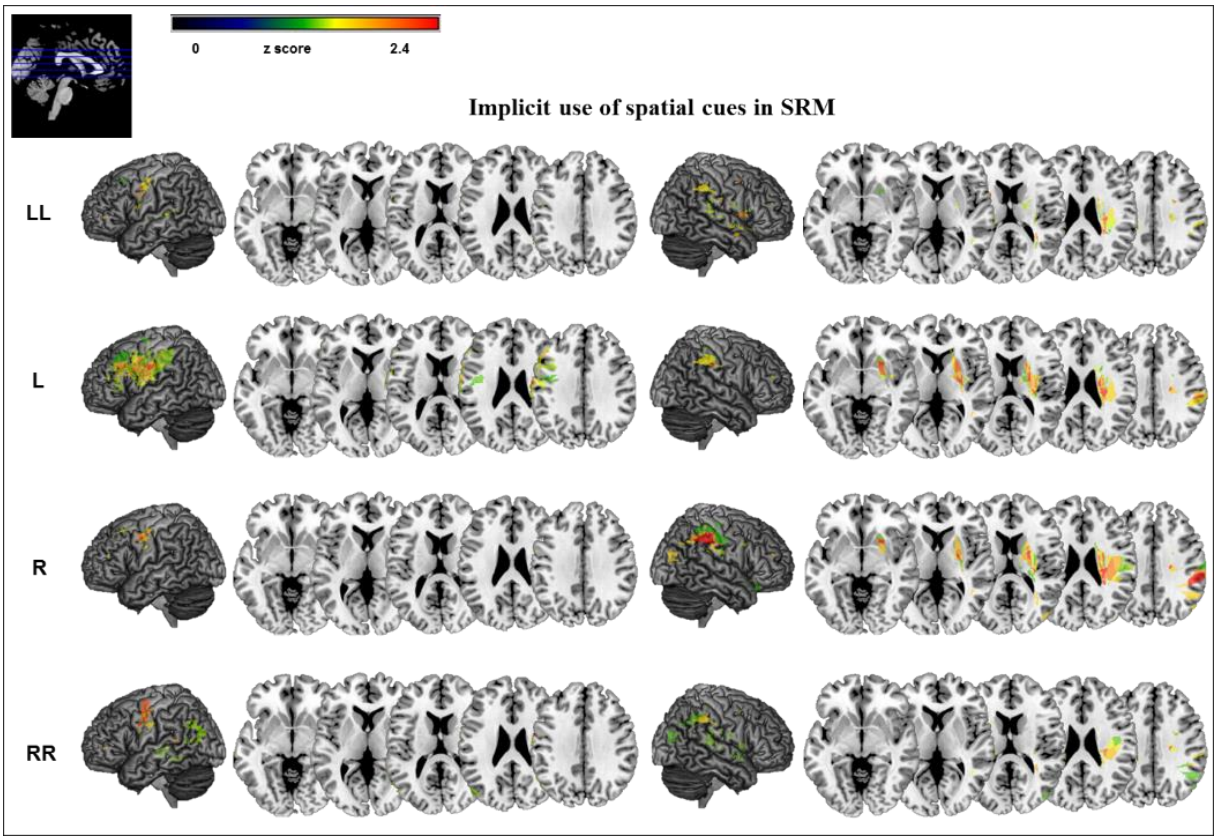

Figure 2. VLSM results showing the relationship between the performances at the SRM task, as calculated with the normalized behavioural index and brain lesions, for both patient groups (n = 40). The tBM-maps only show the voxels significantly important for the performance at the task, first for the left hemisphere, then for the right hemisphere. Brunner-Munzel test, FDR-corrected, tBM-map intensity [0, 2.4].

Discussion

Aim of the present study was to compare two mechanisms involving different spatial mechanisms in large group of patients with similar brain lesions. This was with the specific objective to determine if both mechanisms rely on the same neural structures or not. Results clearly demonstrated that sound object segregation involves bilateral regions but relies predominantly in left fronto-temporo-parietal areas, while the explicit use of spatial cues involved in sound object localization relies on the right dorsal attentional pathway (Supplementary Figure).

Our findings demonstrate that the cortical regions shown to be involved more specifically in sound object segregation on the basis of the implicit spatial cues, meaning not on the basis of the other features of sounds like fundamental frequency, spectral or temporal envelope, are linked to the precentral, middle temporal and angular gyri on the left and to the supramarginal, angular, inferior frontal and superior temporal gyri on the right.

Vision and audition differ in their processing of spatial information. In vision, research on selective attention demonstrated over the years how it can be explicitly directed in space or implicitly guided with exogenous cues (Posner et al., 1980). In vision, encoding of object's location requires fewer demands than their timing's encoding. Auditory spatial information is processed more indirectly than in the visual modality (Middlebrooks and Green, 1991). Indeed, given the anatomy and function of the auditory system, its highly precise mechanism is temporal processing while spatial processing actually requires more than just the encoding of time. The importance of explicit spatial cues in the visual domain biased studies on auditory space processing towards explicit sound localization. Both mechanisms, processing of explicit (i.e. exogenous) and implicit (i.e. endogenous) spatial cues, co-exist in each modality but due to the fact that research was biased towards vision's studies, less is known about the use of implicit spatial cues than about the explicit use of spatial cues.

Moreover, our results also permitted to see the impact of left unilateral neglect on the implicit use of spatial cues. Indeed, RHD patients showed an asymmetry of performance. Their performance was globally lower than the one of the LHD group for all positions, but more so for positions on the right hemispace. This result was driven by the masker sound, when presented on the left hemispace and therefore neglected by the patient, having less impact on the detection of the central target.

Strong evidences arising from our results are supporting previous findings on the impact of the implicit use of spatial cues in sound object segregation. The behavioural results indicate that the performance for each group was different for neighbouring positions, with a masking effect decreasing when the distance between competing sounds increases. This result demonstrates that the spatial separation of the competing sounds has an effect on the signal detection. Overall, at a group level, all three groups have a preserved spatial release from masking effect. However, it is well-known that selecting one sound over a mixture of sounds is a process that involves exogenous stimulus-driven mechanisms, as well as endogenous attentional mechanisms (see Sussman, 2017 for a review). In fact, distinction between both patient groups in the right hemifield is telling us that for RHD patients when the masker sound is at a position on the right hemifield it has more impact than when it is on the left hemifield, because when the masker sound is on the left hemifield, the RHD patients are neglecting it. Again, these behavioural results suggest that the neural networks involved in unilateral spatial neglect need to be preserved for the correct execution of this task.

Third auditory pathway

The processing of sounds in the human auditory cortex is divided around two main streams. Sound object recognition is known to rely on superior and middle temporal regions as well as the inferior frontal cortex, whereas sound location processing relies on parietal and superior frontal regions (Ahveninen et al., 2006; Alain et al., 2001; Arnott et al., 2004; Clarke et al., 2002, 2000; De Santis et al., 2007; Engelien et al., 1995; Romanski et al., 1999; Tian et al., 2001). These two distinct main streams are known as the ventral and the dorsal auditory streams and together form the dual pathway theory. However, the dorsal stream has been shown to be also involved in sound object recognition when the semantic category of these sound objects involves motor action (De Lucia et al., 2010; Gazzola et al., 2006; Hauk et al., 2006; Lahav et

al., 2007; Lewis et al., 2005; Pizzamiglio et al., 2005; Doehrmann et al., 2008). There is also evidence that both mechanisms, sound object recognition and sound location processing, are interacting at different levels during auditory processing from the auditory caudal belt areas, the supratemporal plane (Da Costa et al., 2011, 2013; Tian et al., 2001), the anterior lateral area (Wallace et al., 2002), the planum temporale (Da Costa et al., 2015; Shrem and Deouell, 2014). Belt areas are been shown to be the location where both auditory streams separate and where there is a combination of them (Clarke, S. and Morosan, P., 2012). EEG results (Bourquin et al., 2013) demonstrated that these two mechanisms could also be found latter in the inferior frontal cortex (see (Clarke and Geiser, 2015) for a review).

Our study supports previous results (Bourquin et al., 2013; Da Costa et al., 2015) suggesting the existence of a third pathway underlying position-linked representations of sound objects that would predominantly involve the left hemisphere.

Improving the implicit use of auditory spatial cues after hemispheric damage

Patients who sustained right hemispheric damage and who present deficits in auditory streaming on the basis of spatial cues may benefit from therapeutic approaches that either strengthen the attentional system or enhance the contribution of the left-dominant implicit representation of the auditory space.

Patients who sustained left hemispheric damage and who present deficits in auditory streaming on the basis of spatial cues may benefit from therapeutic approaches that rely on the right-dominant attentional system or the right-dominant explicit representation of the auditory space.

Conclusion

Using a lesion-behaviour mapping method and a large number of patients, we were able to distinguish the different neural correlates underlying the implicit and explicit use of spatial cues. Regions necessary for sound object segregation are bilateral, but predominantly located in the left hemisphere and involve fronto-temporo-parietal areas. Moreover, we showed the impact of neglect on the implicit use of spatial cues confirming the relation between spatial attention and sound object segregation. Deficits in implicit spatial processing can impact patient's everyday life activities, such as going to shopping, working, going to the restaurant or understanding someone's speech in a noisy environment. Today, recommendation is to keep patients away from noisy environments and from acoustically overwhelming situations. A better understanding of the mechanisms involved in this deficit is therefore highly relevant to help develop new therapies and neurorehabilitation protocols.

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References

Ahveninen, J., Jääskeläinen, I.P., Raij, T., Bonmassar, G., Devore, S., Hämäläinen, M., Levänen, S., Lin, F.-H., Sams, M., Shinn-Cunningham, B.G., Witzel, T., Belliveau, J.W., 2006. Task-modulated "what" and "where" pathways in human auditory cortex. Proc. Natl. Acad. Sci. 103, 14608–14613. https://doi.org/10.1073/pnas.0510480103

Akeroyd, M.A., Summerfield, A.Q., 2000. Integration of monaural and binaural evidence of vowel formants. J. Acoust. Soc. Am. 107, 3394–3406. https://doi.org/10.1121/1.429410

Alain, C., Arnott, S.R., Hevenor, S., Graham, S., Grady, C.L., 2001. "What" and "where" in the human auditory system. Proc. Natl. Acad. Sci. 98, 12301–12306.

Arbogast, T.L., Mason, C.R., Kidd, G., 2002. The effect of spatial separation on informational and energetic masking of speech. J. Acoust. Soc. Am. 112, 2086–2098. https://doi.org/10.1121/1.1510141

Arnott, S.R., Bardouille, T., Ross, B., Alain, C., 2011. Neural generators underlying concurrent sound segregation. Brain Res. 1387, 116–124. https://doi.org/10.1016/j.brainres.2011.02.062

Arnott, S.R., Binns, M.A., Grady, C.L., Alain, C., 2004. Assessing the auditory dual-pathway model in humans. NeuroImage 22, 401–408. https://doi.org/10.1016/j.neuroimage.2004.01.014

Assmann, P.F., Summerfield, Q., 1990. Modeling the perception of concurrent vowels: vowels with different fundamental frequencies. J. Acoust. Soc. Am. 88, 680–697.

Bourquin, N.M.-P., Murray, M.M., Clarke, S., 2013. Location-independent and location-linked representations of sound objects. NeuroImage 73, 40–49. https://doi.org/10.1016/j.neuroimage.2013.01.026

Bregman, A.S., 1994. Auditory Scene Analysis: The Perceptual Organization of Sound. MIT Press.

Bronkhorst, A.W., Plomp, R., 1988. The effect of head-induced interaural time and level differences on speech intelligibility in noise. J. Acoust. Soc. Am. 83, 1508–1516.

Brunetti, M., Belardinelli, P., Caulo, M., Del Gratta, C., Della Penna, S., Ferretti, A., Lucci, G., Moretti, A., Pizzella, V., Tartaro, A., Torquati, K., Olivetti Belardinelli, M., Romani, G. l., 2005. Human brain activation during passive listening to sounds from different locations: An fMRI and MEG study. Hum. Brain Mapp. 26, 251–261. https://doi.org/10.1002/hbm.20164

Carhart, R., Tillman, T.W., Johnson, K.R., 1967. Release of masking for speech through interaural time delay. J. Acoust. Soc. Am. 42, 124–138.

Carlyon, R.P., 2004. How the brain separates sounds. Trends Cogn. Sci. 8, 465–471. https://doi.org/10.1016/j.tics.2004.08.008

Carlyon, R.P., Cusack, R., Foxton, J.M., Robertson, I.H., 2001. Effects of attention and unilateral neglect on auditory stream segregation. J. Exp. Psychol. Hum. Percept. Perform. 27, 115–127.

Clarke, S., Bellmann, A., Meuli, R.A., Assal, G., Steck, A.J., 2000. Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. Neuropsychologia 38, 797–807. https://doi.org/10.1016/S0028-3932(99)00141-4

Clarke, S., Geiser, E., 2015. Roaring lions and chirruping lemurs: How the brain encodes sound objects in space. Neuropsychologia 75, 304–313. https://doi.org/10.1016/j.neuropsychologia.2015.06.012

Clarke, S., Morosan, P., 2012. Architecture, Connectivity, and Transmitter Receptors of Human Auditory Cortex. https://doi.org/http://dx.doi.org/10.1007/978-1-4614-2314-0_2
Clarke, S., Thiran, A.B., Maeder, P., Adriani, M., Vernet, O., Regli, L., Cuisenaire, O., Thiran, J.-P., 2002. What and Where in human audition: selective deficits following focal hemispheric lesions. Exp. Brain Res. 147, 8–15. https://doi.org/10.1007/s00221-002-1203-9
Culling, J.F., Colburn, H.S., 2000. Binaural sluggishness in the perception of tone sequences and speech in noise. J. Acoust. Soc. Am. 107, 517–527.
Culling, J.F., Hawley, M.L., Litovsky, R.Y., 2004. The role of head-induced interaural time and level differences in the speech reception threshold for multiple interfering sound sources. J. Acoust. Soc. Am. 116, 1057–1065.
Culling, J.F., Summerfield, Q., 1995. The role of frequency modulation in the perceptual segregation of concurrent vowels. J. Acoust. Soc. Am. 98, 837–846.
Cusack, R., 2005. The intraparietal sulcus and perceptual organization. J. Cogn. Neurosci. 17, 641–651. https://doi.org/10.1162/0898929053467541
Da Costa, S., van der Zwaag, W., Marques, J.P., Frackowiak, R.S.J., Clarke, S., Saenz, M., 2011. Human primary auditory cortex follows the shape of Heschl's gyrus. J. Neurosci. Off. J. Soc. Neurosci. 31, 14067–14075. https://doi.org/10.1523/JNEUROSCI.2000-11.2011
Da Costa, Bourquin, N.M.-P., Knebel, J.-F., Saenz, M., Zwaag, W. van der, Clarke, S., 2015. Representation of Sound Objects within Early-Stage Auditory Areas: A Repetition Effect Study Using 7T fMRI. PLOS ONE 10, e0124072. https://doi.org/10.1371/journal.pone.0124072
Da Costa, S., van der Zwaag, W., Miller, L.M., Clarke, S., Saenz, M., 2013. Tuning in to sound: frequency-selective attentional filter in human primary auditory cortex. J. Neurosci. Off. J. Soc. Neurosci. 33, 1858–1863. https://doi.org/10.1523/JNEUROSCI.4405-12.2013
Darwin, C.J., 1997. Auditory grouping. Trends Cogn. Sci. 1, 327–333. https://doi.org/10.1016/S1364-6613(97)01097-8
De Lucia, M., Cocchi, L., Martuzzi, R., Meuli, R.A., Clarke, S., Murray, M.M., 2010. Perceptual and Semantic Contributions to Repetition Priming of Environmental Sounds. Cereb. Cortex 20, 1676–1684. https://doi.org/10.1093/cercor/bhp230
De Santis, L., Clarke, S., Murray, M.M., 2007. Automatic and Intrinsic Auditory "What" and "Where" Processing in Humans Revealed by Electrical Neuroimaging. Cereb. Cortex 17, 9–17. https://doi.org/10.1093/cercor/bhj119
Doehrmann, O., Naumer, M., Volz, S., Kaiser, J. and Altmann, C. 2008. Probing category selectivity for environmental sounds in the human auditory system. Neuropsychologia, 46(11): 2776-2786.
Drennan, W.R., Gatehouse, S., Lever, C., 2003. Perceptual segregation of competing speech sounds: the role of spatial location. J. Acoust. Soc. Am. 114, 2178–2189.
Duffour-Nikolov, C., Tardif, E., Maeder, P., Thiran, A.B., Bloch, J., Frischknecht, R., Clarke, S., 2012. Auditory spatial deficits following hemispheric lesions: Dissociation of explicit and implicit processing. Neuropsychol. Rehabil. 22, 674–696. https://doi.org/10.1080/09602011.2012.686818
Duhamel, J.R., Pinek, B., Brouchon, M., 1986. Manual pointing to auditory targets: performances of right versus left handed subjects. Cortex J. Devoted Study Nerv. Syst. Behav. 22, 633–638.
Dyson, B.J., Alain, C., 2003. Representation of concurrent acoustic objects in primary auditory cortex. J. Acoust. Soc. Am. 115, 280–288. https://doi.org/10.1121/1.1631945

Engelien, A., Silbersweig, D., Stern, E., Huber, W., Döring, W., Frith, C., Frackowiak, R.S.J., 1995. The functional anatomy of recovery from auditory agnosiaA PET study of sound categorization in a neurological patient and normal controls. Brain 118, 1395–1409. https://doi.org/10.1093/brain/118.6.1395

Gazzola, V., Aziz-Zadeh, L., Keysers, C., 2006. Empathy and the somatotopic auditory mirror system in humans. Curr. Biol. CB 16, 1824–1829. https://doi.org/10.1016/j.cub.2006.07.072

Gockel, H., Carlyon, R.P., 1998. Effects of ear of entry and perceived location of synchronous and asynchronous components on mistuning detection. J. Acoust. Soc. Am. 104, 3534–3545.

Haeske-Dewick, H., Canavan, A.G.M., Hömberg, V., 1996. Sound localization in egocentric space following hemispheric lesions. Neuropsychologia 34, 937–942. https://doi.org/10.1016/0028-3932(95)00167-0

Hauk, O., Shtyrov, Y., Pulvermüller, F., 2006. The sound of actions as reflected by mismatch negativity: rapid activation of cortical sensory–motor networks by sounds associated with finger and tongue movements. Eur. J. Neurosci. 23, 811–821. https://doi.org/10.1111/j.1460-9568.2006.04586.x

Hawley, M.L., Litovsky, R.Y., Colburn, H.S., 1999. Speech intelligibility and localization in a multi-source environment. J. Acoust. Soc. Am. 105, 3436–3448.

Hawley, M.L., Litovsky, R.Y., Culling, J.F., 2004. The benefit of binaural hearing in a cocktail party: effect of location and type of interferer. J. Acoust. Soc. Am. 115, 833–843.

Kaiser, J., Lutzenberger, W., Preissl, H., Ackermann, H., Birbaumer, N., 2000. Right-Hemisphere Dominance for the Processing of Sound-Source Lateralization. J. Neurosci. 20, 6631–6639.

Jeffress, L., Blodgett, H. and Deatherage, B. 1952. The Masking of Tones by White Noise as a Function of the Interaural Phases of Both Components. I. 500 Cycles: The Journal of the Acoustical Society of America: Vol 24, No 5, 1952. URL http://asa.scitation.org/doi/abs/10.1121/1.1906930.

Kidd, G., Mason, C.R., Arbogast, T.L., 2002. Similarity, uncertainty, and masking in the identification of nonspeech auditory patterns. J. Acoust. Soc. Am. 111, 1367–1376. https://doi.org/10.1121/1.1448342

Kidd, G., Mason, C.R., Rohtla, T.L., Deliwala, P.S., 1998. Release from masking due to spatial separation of sources in the identification of nonspeech auditory patterns. J. Acoust. Soc. Am. 104, 422–431. https://doi.org/10.1121/1.423246

Lahav, A., Saltzman, E., Schlaug, G., 2007. Action representation of sound: audiomotor recognition network while listening to newly acquired actions. J. Neurosci. Off. J. Soc. Neurosci. 27, 308–314. https://doi.org/10.1523/JNEUROSCI.4822-06.2007

Lewis, J.W., Brefczynski, J.A., Phinney, R.E., Janik, J.J., DeYoe, E.A., 2005. Distinct cortical pathways for processing tool versus animal sounds. J. Neurosci. Off. J. Soc. Neurosci. 25, 5148–5158. https://doi.org/10.1523/JNEUROSCI.0419-05.2005

Licklider, J.C.R., 1948. The Influence of Interaural Phase Relations upon the Masking of Speech by White Noise. J. Acoust. Soc. Am. 20, 150–159. https://doi.org/10.1121/1.1906358

Litovsky, R.Y., Fligor, B.J., Tramo, M.J., 2002. Functional role of the human inferior colliculus in binaural hearing. Hear. Res. 165, 177–188.

Maeder, P.P., Meuli, R.A., Adriani, M., Bellmann, A., Fornari, E., Thiran, J.-P., Pittet, A., Clarke, S., 2001. Distinct Pathways Involved in Sound Recognition and Localization: A Human fMRI Study. NeuroImage 14, 802–816. https://doi.org/10.1006/nimg.2001.0888

Middlebrooks, J.C., Green, D.M., 1991. Sound localization by human listeners. Annu. Rev. Psychol. 42, 135–159. https://doi.org/10.1146/annurev.ps.42.020191.001031
Moore, B.C.J., 1995. Hearing. Academic Press.
Neff, D.L., 1995. Signal properties that reduce masking by simultaneous, random-frequency maskers. J. Acoust. Soc. Am. 98, 1909–1920. https://doi.org/10.1121/1.414458
Palmer, A., Shackleton, T., 2002. The Physiological Basis of the Binaural Masking Level Difference ttps://www.researchgate.net/publication/279704944_The_Physiological_Basis_of_the_Binaural_Masking_Level_Difference (accessed 8.15.17).
Pizzamiglio, L., Aprile, T., Spitoni, G., Pitzalis, S., Bates, E., D'Amico, S., Di Russo, F., 2005. Separate neural systems for processing action- or non-action-related sounds. NeuroImage 24, 852–861. https://doi.org/10.1016/j.neuroimage.2004.09.025
Posner, M.I., Snyder, C.R., Davidson, B.J., 1980. Attention and the detection of signals. J. Exp. Psychol. 109, 160–174.
Pressnitzer, D., Sayles, M., Micheyl, C., Winter, I.M., 2008. Perceptual Organization of Sound Begins in the Auditory Periphery. Curr. Biol. 18, 1124–1128. https://doi.org/10.1016/j.cub.2008.06.053
Roman, N., Wang, D., Brown, G.J., 2002. Location-based sound segregation, in: Proceedings of the 2002 International Joint Conference on Neural Networks, 2002. IJCNN '02. Presented at the Proceedings of the 2002 International Joint Conference on Neural Networks, 2002. IJCNN '02, pp. 2299–2303. https://doi.org/10.1109/IJCNN.2002.1007500
Romanski, L.M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P.S., Rauschecker, J.P., 1999. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. Nat. Neurosci. 2, 1131–1136. https://doi.org/10.1038/16056
Rorden, C., Karnath, H.-O., Bonilha, L., 2007. Improving Lesion-Symptom Mapping. J. Cogn. Neurosci. 19, 1081–1088. https://doi.org/10.1162/jocn.2007.19.7.1081
Saupe, K., Koelsch, S., Rübsamen, R., 2010. Spatial selective attention in a complex auditory environment such as polyphonic music. J. Acoust. Soc. Am. 127, 472–480. https://doi.org/10.1121/1.3271422
Shrem, T., Deouell, L.Y., 2014. Frequency-dependent auditory space representation in the human planum temporale. Front. Hum. Neurosci. 8, 524. https://doi.org/10.3389/fnhum.2014.00524
Sperber, C., Karnath, H.-O., 2017. On the validity of lesion-behaviour mapping methods. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2017.07.035
Spierer, L., Bellmann-Thiran, A., Maeder, P., Murray, M.M., Clarke, S., 2009. Hemispheric competence for auditory spatial representation. Brain 132, 1953–1966. https://doi.org/10.1093/brain/awp127
Sussman, E.S., 2017. Auditory Scene Analysis: An Attention Perspective. J. Speech Lang. Hear. Res. JSLHR 60, 2989–3000. https://doi.org/10.1044/2017_JSLHR-H-17-0041
Tanaka, H., Hachisuka, K., Ogata, H., 1999. Sound lateralisation in patients with left or right cerebral hemispheric lesions: relation with unilateral visuospatial neglect. J. Neurol. Neurosurg. Psychiatry 67, 481–486.
Thiran, A.B., Clarke, S., 2003. Preserved use of spatial cues for sound segregation in a case of spatial deafness. Neuropsychologia 41, 1254–1261. https://doi.org/10.1016/S0028-3932(03)00014-9
Tian, B., Reser, D., Durham, A., Kustov, A., Rauschecker, J.P., 2001. Functional specialization in rhesus monkey auditory cortex. Science 292, 290–293. https://doi.org/10.1126/science.1058911

Wallace, M.N., Johnston, P.W., Palmer, A.R., 2002. Histochemical identification of cortical areas in the auditory region of the human brain. Exp. Brain Res. 143, 499–508. https://doi.org/10.1007/s00221-002-1014-z

Supplementary Table 1

Patient's demographical and clinical data: sex, age at time of auditory testing, delay between stroke and auditory testing in days, lesion site and etiology, brain regions involved in the lesion, lesion volume (mm3), comorbidities. GP (global pallidus), IFG (inferior frontal gyrus), Inf. Occipital (inferior occipital), IPL (inferior parietal lobule), ITG (inferior temporal area), MFG (middle frontal gyrus), MTG (middle temporal gyrus), SFG (superior frontal gyrus), SMA (supplementary motor area), SMG (supramarginal gyrus), SPL (superior parietal lobule), STG (superior temporal gyrus).

Patient	Sex	Age (years)	Delay (days)	Regions involved in the lesion	Volume (mm3)
L1	F	54.8	116	Left Postcentral, Precentral, IFG, MFG, Insula, IPL, SMG, Putamen	11491
L2	F	63.9	1066	Left Postcentral, Precentral, IPL, STG, IPL, Middle Occipital, Insula, MTG, SMG, Precuneus, SPL, Cuneus	212322
L3	M	59.0	173	Left IFG, MFG, Insula, STG, Precentral, Postcentral, SMG, Temporal Pole, IPL	120586
L4	F	43.6	77	Left Hippocampus, ParaHippocampus, Amygdala	5768
L5	F	57.0	455	Left IFG, Insula, STG, Precentral, Putamen, MFG, Temporal pole, Caudate	110585
L6	M	46.7	275	Left STG, MTG, Insula, SMG, IPL, IFG, Precentral, Postcentral	90908
L7	M	67.4	96	Left STG, MTG, IPL, Insula, Middle Occipital, SMG, Precuneus	116536
L8	M	18.1	150	Left MFG, SFG, STG, MTG, Precuneus, IFG, Cingulate, Calcarine, ParaHippocampus, Precentral, Postcentral, Cuneus, IPL, SMA, Insula, Middle Occipital	686030
L9	M	57.0	59	Left MTG, STG, ITG, Insula, Temporal Pole, Fusiform	59600
L10	F	39.4	34	Left IFG, Putamen, Caudate, Insula, MFG	39308
L11	M	72.2	67	Left GP, Putamen, Thalamus	2049
L12	F	35.2	58	Left IPL, Postcentral, Insula, IFG, STG, Precentral, MFG, Putamen	175608
L13	M	70.9	25	Left Putamen, Claustrum	3667
L14	M	53.0	46	Left Caudate, Insula	1622
L15	F	48.0	199	Left STG, MTG, IFG, Insula, IPL, SMG, Postcentral, Precentral, MFG, Putamen	185755
L16	M	65.8	137	Left STG, IFG, Insula, MTG, Precentral, Putamen, Postcentral, caudate, MFG	146120
L17	M	21.3	173	Left IPL, STG, Postcentral, SMG, Insula	60113
L18	M	49.6	96	Left STG, IFG, Insula, MTG, MFG, Temporal Pole, Putamen, Caudate	120671
L19	F	47.9	46	Left MFG, IFG, Precentral, Insula, Postcentral, STG	98284
L20	M	52.7	177	Left Postcentral, IPL, Precentral, Insula, SMA, STG, SFG, SMG, MFG, Temporal pole, Cingulate, IFG	138679
R1	M	46.8	33	Right IFG, STG, MFG, Insula, Precentral, Postcentral, SMG, IPL, Putamen	216742
R2	F	53.0	136	Right Insula, IFG, Precentral, STG, Putamen	56934
R3	F	63.4	37	Right IFG, Precentral, Postcentral, Insula, SMG, IPL, Putamen, STG, Temporal pole, Caudate, MFG	187341
R4	M	64.4	11	Right Putamen, Caudate, GP	4146
R5	M	56.9	22	Right Fusiform, Hippocampus, Parahippocampus, Precuneus, Posterior Cingulate, Calcarine, Cuneus, Thalamus	108636
R6	M	58.0	42	Right Lingual, Cuneus, Calcarine, Inf. Occipital, Fusiform	52896
R7	M	51.0	15	Right IFG, Insula, STG, Precentral, Putamen	44647
R8	M	54.5	105	Right IPL, SMG, Middle Occipital, STG, MTG, Superior Occipital, Precuneus	68839
R9	F	42.3	16	Right Thalamus, GP, Putamen	4899
R10	F	41.8	16	Right IFG, MFG, Insula, STG, SMG, IPL, Precentral, Putamen, Caudate, Postcentral	128796
R11	F	50.4	40	Right Precentral, IFG, Postcentral, Insula, STG, MFG	69679
R12	M	61.7	27	Right STG, Thalamus, IPL, Putamen, Precentral	34849
R13	M	69.0	29	Right MFG, STG, IFG, Insula, Precentral, Postcentral, IPL, SMG, SFG, Putamen	258635
R14	F	66.1	44	Right Insula, Putamen, Caudate, STG, SMG, IPL, Precentral, IFG	63508
R15	F	52.1	24	Right STG, IFG, MTG, Insula, Precentral, Postcentral, MFG, IPL, SMG	143126
R16	F	69.4	16	Right Inferior Occipital, Fusiform, Lingual, ITG, Middle Occipital	29452
R17	M	74.5	45	Right Precentral, MFG, IFG, Postcentral	4395
R18	M	58.2	1593	Right Putamen, Insula, Caudate	24713
R19	M	49.1	214	Right IFG, STG, Insula, MFG, Putamen, Temporal Pole, Precentral, ITG, Caudate	148454
R20	M	26.1	17	Right Putamen, Caudate, GP, Thalamus	34641

Supplementary Table 2

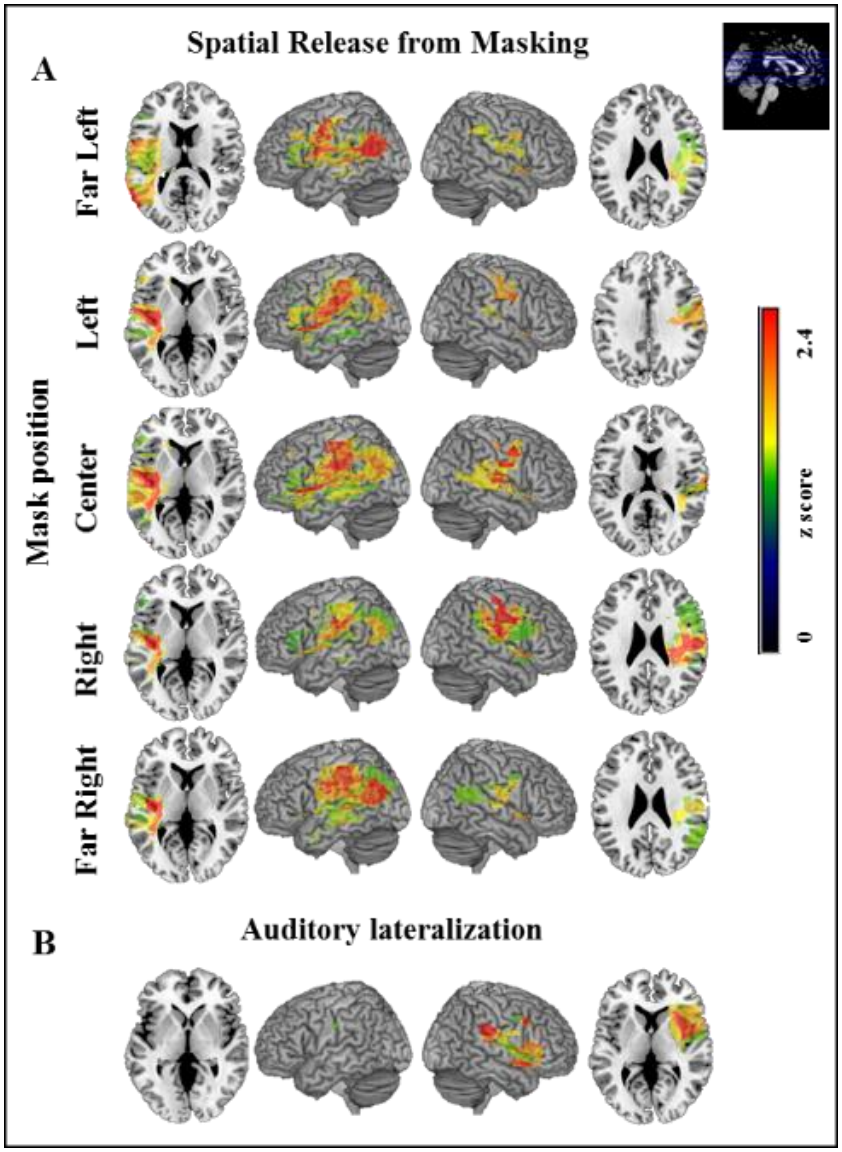
Behavioral performances at the SRM and auditory lateralization tasks. In bold are highlighted participants' scores outside the normative ranges driven by a deficit. In bold and italic are highlighted the scores outside the normative ranges driven by an excessively correct performance. Normative data for the SRM are (mean ± SD): LL 3.99 ± 1.29, L 3.32 ± 1.02, R 3.26 ± 1.05, RR 4 ± 1.39, LL/RR 1.12 ± 0.44, L/R 1.04 ± 0.47; and for the global score at the sound lateralization task: 54.59 ± 1.73.

Control group												
	SRM: d'					**SRM: Normalized d'**						**Auditory lateralization**
Subject	**LL**	**L**	**CE**	**R**	**RR**	**LL**	**L**	**R**	**RR**	**LL/RR**	**L/R**	**Global score**
C1	4.379	4.379	4.379	4.379	4.379	0.00	0.00	0.00	0.00	1.00	1.00	57
C2	4.379	4.379	2.755	4.379	4.379	1.62	1.62	1.62	1.62	1.00	1.00	54
C3	4.379	4.379	3.257	4.379	4.379	1.12	1.12	1.12	1.12	1.00	1.00	54
C4	4.379	4.379	4.379	4.379	4.379	0.00	0.00	0.00	0.00	1.00	1.00	54
C5	3.257	4.379	4.379	3.257	2.369	-1.12	0.00	***-1.12***	***-2.01***	0.56	**0.00**	53
C6	4.379	4.379	2.369	4.379	4.379	2.01	2.01	2.01	2.01	1.00	1.00	56
C7	4.379	4.379	2.755	4.379	4.379	1.62	1.62	1.62	1.62	1.00	1.00	56
C8	4.379	3.257	2.369	4.379	3.257	2.01	0.89	2.01	0.89	**2.26**	0.44	54
C9	4.379	3.257	0.000	2.755	4.379	**4.38**	3.26	2.76	**4.38**	1.00	1.18	54
C10	4.379	4.379	2.369	4.379	4.379	2.01	2.01	2.01	2.01	1.00	1.00	57
C11	4.379	4.379	2.369	3.257	3.257	2.01	2.01	0.89	0.89	**2.26**	**2.26**	55
C12	4.379	4.379	4.379	4.379	4.379	0.00	0.00	0.00	0.00	1.00	1.00	54
C13	4.379	4.379	2.009	4.379	4.379	2.37	2.37	2.37	2.37	1.00	1.00	52
C14	4.379	4.379	2.800	4.379	4.379	1.58	1.58	1.58	1.58	1.00	1.00	52
C15	4.379	4.379	2.800	4.379	4.379	1.58	1.58	1.58	1.58	1.00	1.00	58
C16	4.379	4.379	2.000	3.300	4.379	2.38	2.38	1.30	2.38	1.00	1.83	53
C17	4.379	4.379	4.379	4.379	4.379	0.00	0.00	0.00	0.00	1.00	1.00	55

LHD group												
	SRM: d'					**SRM: Normalized d'**						**Auditory lateralization**
Subject	**LL**	**L**	**CE**	**R**	**RR**	**LL**	**L**	**R**	**RR**	**LL/RR**	**L/R**	**Global score**
L1	0.888	0	-1.122	0	1.623	2.01	1.12	1.12	2.75	0.73	1.00	52
L2	2.009	0.746	-0.386	1.132	0.000	2.40	1.13	1.52	0.39	**6.21**	0.75	**49**
L3	4.379	1.62	0	1.62	4.379	**4.38**	1.62	1.62	**4.38**	1.00	1.00	58
L4	4.379	4.379	4.379	4.379	4.379	0.00	0.00	0.00	0.00	1.00	1.00	58
L5	1.25	-1.62	1.12	0.5	3.26	0.13	***-2.74***	-0.62	2.14	***0.06***	**4.42**	***59***
L6	3.26	3.26	1.25	3.26	4.379	2.01	2.01	2.01	3.13	0.64	1.00	***59***
L7	3.257	2.755	0	1.122	2.755	3.26	2.76	1.12	2.76	1.18	**2.46**	56
L8	4.379	2.756	0	2.755	4.379	**4.38**	2.76	2.76	**4.38**	1.00	1.00	57
L9	2.755	1.62	0	1.62	2.01	2.76	1.62	1.62	2.01	1.37	1.00	***59***
L10	4.379	4.379	2.755	4.379	4.379	1.62	1.62	1.62	1.62	1.00	1.00	57
L11	4.379	4.379	1.634	3.257	4.379	2.75	2.75	1.62	2.75	1.00	1.69	58
L12	4.379	3.257	1.122	3.257	4.379	3.26	2.14	2.14	3.26	1.00	1.00	58
L13	4.379	2.755	2.369	2.755	4.379	2.01	0.39	0.39	2.01	1.00	1.00	57
L14	4.379	3.257	0	2.009	4.379	**4.38**	3.26	2.01	**4.38**	1.00	1.62	57
L15	1.248	0	0	2.009	1.248	1.25	0.00	2.01	1.25	1.00	***0.00***	54
L16	4.379	2.755	0	2.369	4.379	**4.38**	2.76	2.37	**4.38**	1.00	1.16	58
L17	4.379	3.257	1.623	2.755	4.379	2.76	1.63	1.13	2.76	1.00	1.44	54
L18	4.379	4.379	1.122	4.379	4.379	3.26	3.26	3.26	3.26	1.00	1.00	57
L19	3.257	4.379	3.257	4.379	4.379	0.00	1.12	1.12	1.12	***0.00***	1.00	57
L20	4.379	1.122	0.000	1.623	3.257	**4.38**	1.12	1.62	3.26	1.34	0.69	58

RHD group												
	SRM: d'					SRM: Normalized d'						Auditory lateralization
Subject	LL	L	CE	R	RR	LL	L	R	RR	LL/RR	L/R	Global score
R1	1.623	0	0	0	1.122	1.62	0.00	0.00	1.12	1.45	***0.00***	**34**
R2	4.379	1.623	1.122	2.369	3.257	3.26	0.50	1.25	2.14	1.53	0.40	57
R3	3.257	1.122	0	0.502	3.257	3.26	1.12	0.50	3.26	1.00	**2.24**	56
R4	4.379	4.379	2.755	3.257	4.379	1.62	1.62	0.50	1.62	1.00	**3.24**	56
R5	2.369	2.369	0	0.888	3.257	2.37	2.37	0.89	3.26	0.73	**2.67**	55
R6	3.257	1.634	-1.122	1.623	2.755	**4.38**	2.76	2.75	3.88	1.13	1.00	56
R7	4.379	3.257	0	2.369	4.379	**4.38**	3.26	2.37	**4.38**	1.00	1.37	57
R8	2.755	2.009	1.122	1.122	1.634	1.63	0.89	0.00	0.51	**3.19**	***0.00***	51
R9	4.379	2.009	-0.89	1.25	1.13	**5.27**	2.90	2.14	2.02	**2.61**	1.35	55
R10	2.755	2.369	1.634	0.888	2.755	1.12	0.74	-0.75	1.12	1.00	***-0.99***	**50**
R11	2.755	1.248	-1.623	0	1.122	**4.38**	2.87	1.62	2.75	1.59	1.77	***59***
R12	1.122	0	0	0	0	1.12	0.00	0.00	0.00	0.00	1.00	58
R13	4.379	3.257	-1.122	2.369	3.257	**5.50**	**4.38**	**3.49**	**4.38**	1.26	1.25	56
R14	2.755	1.248	1.623	0	1.248	1.13	-0.38	***-1.62***	-0.38	***-3.02***	0.23	53
R15	0.746	1.132	-0.36	0.888	0	1.11	1.49	1.25	0.36	**3.07**	1.20	52
R16	-0.746	-1.132	0.888	1.248	-0.746	***-1.63***	***-2.02***	0.36	***-1.63***	1.00	***-5.61***	55
R17	4.379	3.256	2.009	4.379	4.379	2.37	1.25	2.37	2.37	1.00	0.53	**50**
R18	3.257	0	0	1.122	2.369	3.26	0.00	1.12	2.37	1.37	***0.00***	54
R19	3.257	2.755	1.623	2.755	4.379	1.63	1.13	1.13	2.76	0.59	1.00	57
R20	4.379	1.62	0	2.37	4.379	**4.38**	1.62	2.37	**4.38**	1.00	0.68	58

Supplementary Figure



VLSM results showing the relationship between the performances at the SRM and auditory lateralization tasks and brain lesions, for both patient groups (n = 40). In A. are reported the results for the SRM task, when the mask is at positions far left, left, center (target and mask are at the same position), right and far right. In B. are reported the results of the VLSM for the auditory lateralization task. The tBM-maps only show the voxels significantly important for the performance at the tasks, first for the left hemisphere, then for the right hemisphere. Brunner-Munzel test, FDR-corrected, tBM-map intensity [0, 4].

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Research Article

For Better or Worse: The Effect of Prismatic Adaptation on Auditory Neglect

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Patients with auditory neglect attend less to auditory stimuli on their left and/or make systematic directional errors when indicating sound positions. Rightward prismatic adaptation (R-PA) was repeatedly shown to alleviate symptoms of visuospatial neglect and once to restore partially spatial bias in dichotic listening. It is currently unknown whether R-PA affects only this ear-related symptom or also other aspects of auditory neglect. We have investigated the effect of R-PA on left ear extinction in dichotic listening, space-related inattention assessed by diotic listening, and directional errors in auditory localization in patients with auditory neglect. The most striking effect of R-PA was the alleviation of left ear extinction in dichotic listening, which occurred in half of the patients with initial deficit. In contrast to nonresponders, their lesions spared the right dorsal attentional system and posterior temporal cortex. The beneficial effect of R-PA on an ear-related performance contrasted with detrimental effects on diotic listening and auditory localization. The former can be parsimoniously explained by the SHD-VAS model (shift in hemispheric dominance within the ventral attentional system; Clarke and Crottaz-Herbette 2016), which is based on the R-PA-induced shift of the right-dominant ventral attentional system to the left hemisphere. The negative effects in space-related tasks may be due to the complex nature of auditory space encoding at a cortical level.

1. Introduction

Unilateral spatial neglect tends to include distinct auditory deficits, which are often referred to as auditory neglect and are investigated with a variety of experimental paradigms [1]. The key feature of auditory neglect, impaired attention to left-sided stimuli, has been initially revealed in tasks of *dichotic listening*. In this paradigm, simultaneous auditory stimuli are presented to either ear; extinction or significant decrease in reporting stimuli presented to the left ear has been considered as a manifestation of auditory neglect [2, 3]. Although often present in auditory neglect, left ear extinction on dichotic listening has been also reported in two conditions which are unrelated to neglect. Left ear extinction is a key feature of the callosal disconnection syndrome [4, 5] and is associated with lesions of the splenium and isthmus of the corpus callosum [6, 7]. Furthermore, contralateral ear extinction has been reported to occur as often after left as right hemispheric lesions, when the damage extended to auditory-related structures [8]. The ambiguity in the interpretation of left ear extinction as a sign of auditory neglect has led to the introduction of the *diotic listening paradigm*, which consists of two simultaneous stimuli presented to the right or left by means of interaural time differences. Extinction or significant decrease in reporting stimuli lateralized to the left and/or bilateral decrease in reported stimuli is a characteristic of the right hemispheric lesions and depends critically on the integrity of basal ganglia [9–11]. *Auditory mislocalization* and in particular systematic directional errors to the ipsilesional side are believed to be another manifestation of auditory neglect [12–14]. Particularly striking symptom is *alloacusis*, that is, the misplacement of auditory stimuli across the midline. The three key features of auditory neglect, left-sided extinction on dichotic or diotic listening, and the distortion of auditory space perception can occur independently of each other and involve distinct neural networks; very likely, they correspond to different types of auditory neglect [9–11]. The three key features of auditory neglect

are often associated with visuospatial neglect symptoms [1, 10, 11, 14], which are treated with different approaches, including prismatic adaptation [15–22].

Prismatic adaptation has gained much interest, partly because of its well-documented effect on visuospatial neglect [15–22]. It consists of a visuomotor task during which the subject points to visual targets while wearing glasses mounted with right-deviating prisms. After an initial phase, when the subject overshoots the targets to the right, the pointing becomes correct. After the removal of the prisms, the first trials show pointing errors to the left, referred to as the aftereffect [20]. A series of neuroimaging studies was carried out in normal subjects to investigate neural mechanisms underlying the effect of R-PA on visual attention. The stages of visuomotor adaptation were shown to involve the posterior parietal cortex and the cerebellum on the right side [23–27]. An overall effect of a brief exposure to R-PA is the change of visuospatial representations in the inferior parietal lobule (IPL) in both hemispheres. As demonstrated in a recent study, the representation of the left, center, and right visual fields is enhanced in the left IPL and the representation of the right visual field decreased in the right IPL [28]. Thus, R-PA appears to shift the right-dominant ventral attentional system to the left hemisphere; in neglect, this shift is likely to restore the alerting input to the dorsal attentional system on either side and contribute thus to the alleviation of attentional deficits in visuospatial neglect [29].

Several lines of evidence suggest that visual and auditory attention relies on a supramodal attentional network. Activation studies have shown that in the context of spatial and nonspatial attentional tasks visual and auditory stimuli involve the same cortical regions and hence most likely a shared attentional network [30–33]. Similarly, the frequent cooccurrence of visual and auditory attentional deficits in unilateral neglect was proposed to reflect the supramodal nature of the syndrome [1, 34]. Further support comes from two studies which reported that R-PA alleviates specific symptoms of auditory neglect. A first study focused on the effect of R-PA on dichotic listening and reported in a group of 6 patients an alleviation of left ear extinction on dichotic listening, without affecting general arousal [35]. A second study investigated the effect of R-PA on spatial gradients in visual and auditory target detection and described in a group of 12 patients an overall improvement of auditory target detection, without restoring the spatial gradient of attention [36]. It is currently unknown whether R-PA affects other symptoms of auditory neglect.

The effect of R-PA on specific symptoms of auditory neglect may rely on the shift of the right-dominant ventral attentional system to the left IPL, as postulated in the SHD-VAS model for visuospatial attention [37]. If so, the alleviation of auditory neglect symptoms would depend on the integrity of the right dorsal attentional system and its access to the left IPL. We have investigated how R-PA affects key features of auditory neglect, namely performance on dichotic and diotic listening and auditory localization, and what the underlying anatomical constraints are. We hypothetized that the restoration of the alerting input from ventral attentional system via the left IPL may alleviate auditory neglect symptoms if the remaining parts of the involved network are intact. Thus, we postulated that for the effect of R-PA to occur, the dorsal attentional system (within the right hemisphere) and the afferent interhemispheric pathway from the left IPL need to be intact. We have expected that these mechanisms are likely to play a role in dichotic and diotic listening tasks. We did not expect a systematic improvement of sound localization performance, because of the great complexity in auditory space encoding (for detailed description see discussion [38–40]).

2. Methods

2.1. Participants. Ten consecutive stroke patients with unilateral spatial neglect and without history of psychiatric or previous neurological affections participated in this study (6 men, mean age 59.6 years ± 7.1; Table 1). The inclusion criteria were (i) a first unilateral right hemispheric ischemic stroke; (ii) normal or corrected to normal visual acuity, compatible with performing visual tasks without prescription glasses (so that prisms can be worn); and (iii) normal hearing thresholds at a tonal audiometry and less than 12 dB difference between the ears (average across all frequencies). All patients sustained an ischemic infarction in the territory of the right middle cerebral artery (Figure 1) and presented at the time of testing visuospatial and auditory neglect. The mean delay between the R-PA and the stroke was 95 days ± 34. The patients were recruited among the patients of the Neuropsychology and Neurorehabilitation clinic of the Lausanne University Hospital (CHUV), and all provided an informed consent. Seventeen normal subjects served as control population for comparing the aftereffect in the ecological R-PA paradigm used here with the aftereffect observed in a shorter version R-PA used in a previous study (8 men, mean age 26.5 years ± 3.6; [28]). The study was conducted in accordance with the Declaration of Helsinki (1964) and was approved by the Ethic Committee of the Canton de Vaud, Switzerland.

2.2. Prismatic Adaptation. The ecological R-PA paradigm involved an adaptation phase during which the subject wore prisms which deviated the entire visual field 10° to the right (as in previous studies [17, 18, 20, 29, 41, 42]). The adaptation phase lasted 30 minutes during which the subject carried out a sequence of six different visuomotor activities, three of which resulted in sound production: (i) playing a sequence of 3 tones on a colour-coded xylophone according to the colours on a card shown by the experimenter; (ii) ringing 3 coloured bells in a sequence chosen from a group of 7 according to the colours on a card shown by the experimenter; (iii) placing five cups according to the pattern shown by the experimenter; (iv) picking up one bell identified by its colour among seven bells and ringing it; (v) placing a token in a column (among five) which the experimenter designated by its number (Puissance4® game); and (vi) placing Scrabble® tokens in the correct order to form three-letter words presented visually by the experimenter. Each activity lasted 5 minutes. The movements during these activities are slower than simple pointing movements in the classical adaptation;

Table 1: Patients' characteristics including the delay between the stroke and the testing session. STG: superior temporal gyrus; MTG: middle temporal gyrus; IFG: inferior frontal gyrus; IPL: inferior parietal lobule; SMG: supramarginal gyrus; AG: angular gyrus; SPL: superior parietal lobule; ITG: inferior temporal gyrus; HG: Heschl gyrus; TTG: transverse temporal gyrus; GP: globus pallidus; SFG: superior frontal gyrus.

Patient	Sex	Age	Handedness	Neurological and neuropsychological deficits	Regions involved in lesion	Delay (days)	Lesion vol (cm^3)
P1	M	53	Right	Left hemisyndrome (upper and lower limbs), multimodal neglect, nonspatial attentional deficits, executive dysfunction	STG, MTG, insula, IFG, temporal pole, putamen, caudate, precentral	54	135.4
P2	M	59	Right	Left unilateral homonymous hemianopia, severe multimodal neglect, executive dysfunction	STG, MTG, precentral, postcentral, IPL, IFG, insula, SMG, temporal pole, putamen, MFG, AG	80	182.6
P3	F	64	Right	Mild multimodal neglect and nonspatial attentional deficits	Insula, STG, temporal pole, MTG, putamen, IFG, caudate	59	93.1
P4	M	51	Left	Left hemisyndrome (upper and lower limbs), multimodal neglect, visuospatial apraxia, deficits in working memory and calculation, executive dysfunction	MFG, IFG, MTG, STG, precentral, postcentral, insula, SMG, temporal pole, occipital, putamen, precuneus, AG, SPL, ITG, HG, TTG, caudate	154	202.6
P5	M	57	Right	Horner syndrome on the right side, left unilateral homonymous hemianopia, severe multimodal neglect, nonspatial attentional deficits, deficit in anterograde episodic memory, executive dysfunction	Middle occipital, cuneus, superior occipital, MTG, cuneus, precuneus, AG, calarine	121	19.7
P6	M	59	Right	Left hemisyndrome (predominantly upper limb), left unilateral homonymous hemianopia, multimodal neglect, nonspatial attentional deficits, visuospatial apraxia, deficit in anterograde episodic memory, executive dysfunction	IFG, MFG, STG, precentral, insula, putamen, postcentral, temporal pole, precentral, MTG	89	118.7
P7	F	69	Right	Severe visuospatial neglect, nonspatial attentional deficits, mild executive dysfunction	IFG, MFG, STG, insula, putamen, temporal pole, MTG	122	70.6
P8	F	73	Right	Multimodal neglect, visuospatial apraxia, deficit in anterograde episodic memory, executive dysfunction	Insula, STG, IFG, putamen, MTG, HG, TTG	60	44.1
P9	M	58	Right	Left hemisyndrome (upper and lower limbs), severe multimodal neglect, deficit in anterograde episodic memory, executive dysfunction	Insula, putamen, caudate, GP, thalamus	127	382.0
P10	F	53	Right	Visuospatial neglect, nonspatial attentional deficits	MFG, STG, IFG, MTG, IPL, insula, postcentral, precentral, SMG, AG, precuneus, putamen, caudate, temporal pole, thalamus, hippocampus, parahippocampal gyrus, SFG	84	38.1

to reach the total number of movements which was shown to be critical for maximal adaptation to occur [43], we increased the duration of the adaptation phase to 30 minutes.

The aftereffect of R-PA, that is, visuomotor pointing error which occurs during the first pointing after the removal of the prisms, was assessed as in the previous studies [17, 18, 20, 37, 41, 42]. Briefly, the subject's head was positioned on chinrest and two black dots placed at a distance of 57 cm 14° to the left or to the right of his body midline; the proximal two-thirds of the distance between the subject and the dots were hidden. When positioned in the apparatus, the subject was asked to look at one of the dots, close his eyes, and point to the dot; this procedure was repeated twice for each dot. The aftereffect was expressed in degrees, corresponding to the average of the four measures. All patients performed the ecological R-PA paradigm, and all but one (P6) were tested for visuo-pointing errors before and after R-PA. P6 was not able to perform the aftereffect measure because he could not maintain the eyes closed during the pointing.

2.3. Evaluation of Auditory Neglect

2.3.1. Dichotic Listening Task. The dichotic listening task consisted of thirty pairs of disyllabic words presented simultaneously, one word to the left and another to the right ear (same paradigm as in [9, 11, 44]). The subjects were instructed to be attentive to both ears and to report both words. Performance was assessed by the total number of

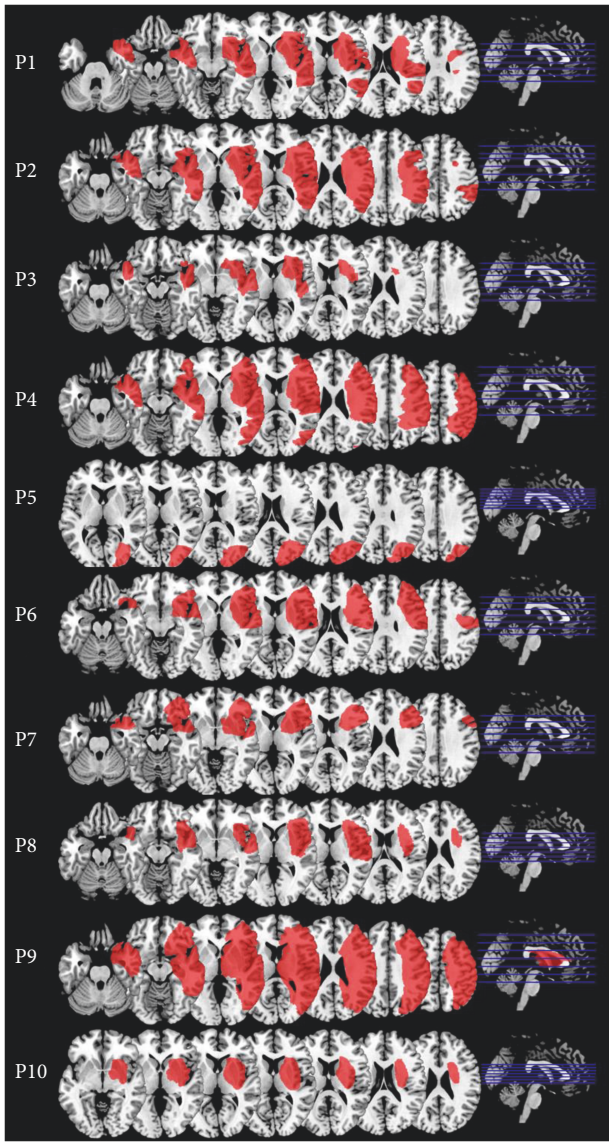

Figure 1: Lesions of individual patients displayed on axial slices of a normalized MRI template (positions of the slices in blue).

correct responses for each ear and by the lateralization index (right minus left ear, divided by right plus left ear, multiplied by 100). The performance of a control population was published previously [9]. The mean number of items reported for the right ear stimuli was 29.2 (SD = 1.685) and for the left ear stimuli 28.85 (SD = 2.74); the number of items reported for the left versus right ears did not differ significantly ($p = 0.1004$). The mean lateralization index was 0.986 (SD = 4.45).

2.3.2. Diotic Listening Task. The diotic listening task consisted of thirty pairs of words presented simultaneously. Both words were presented at the same intensity level to both ears, but one was lateralized to the right hemispace and the other one to the left hemispace, using interaural time difference of 1 ms (same paradigm as in [9, 11, 44]). For both tasks, performance was assessed by the total number of correct responses for each side separately and by the lateralization index (right minus left side, divided by right plus left side, multiplied by 100). The performance of a control population was published previously [9]. The mean number of items reported for the right space was 26.15 (SD = 4.632) and for the left space 24.867 (SD = 5.02). There was a significant advantage for the right space ($p = 0.0001$). The mean lateralization index was 3.521 (SD = 5.96).

2.3.3. Auditory Localization Task. The auditory localization task comprised 60 stimuli which were lateralized with interaural time differences (same paradigm as in [9, 11, 44–51]. The stimuli were bumblebee sounds, ranging from 20 to 10,000 Hz presented during 2 s including 100 ms rising and falling times. Five different azimuthal positions (12 sounds at each position) were simulated by interaural time differences (ITD), creating one central (no ITD) and four lateral positions, two in each hemispace. For the lateral positions, the ITD was 0.3 ms or 1 ms. The task consisted in indicating precisely the perceived position of the blumblebee on a graduated semicircle affixed on the headphone (from 0° at the vertex to 90° at each ear) with the right index finger. The overall performance of auditory localization was assessed by the relative positions attributed to two consecutive stimuli (global score). Responses were counted as correct when the position of the sound was indicated to the left or to the right of the previous stimulus in agreement with the difference in ITD or within ±10° of the previous location for identical stimuli; the maximal number of correct responses was 59. To quantify directional bias, more specific measures were used: (i) the number and the direction of alloacusis and (ii) the discrimination between neighbouring positions, by means of *t*-test between reported positions of nearby lateralizations (LL versus L; R versus RR). The performance of a control population was published previously [9, 44]. The mean global score was 57.15 (SD = 1.79). The mean for the central stimulus was −0.09° (SD = 4.5°). The mean index of response bias was 0.00 (SD = 0.74). Control subjects never exhibited alloacusis. Ten percent of control subjects failed to discriminate the two positions within one hemispace, never within both hemispaces.

2.4. Evaluation of Visuospatial Neglect. All patients were assessed for visuospatial aspects of neglect using the bells test and the line bisection task ("Batterie d'évaluation de la négligence spatiale" (BEN)) [52], as well as the evaluation of unilateral extinction for visual and tactile stimuli, search for neglect symptoms in visual target detection, graphical production, and motor performance (as in [9–11, 44, 50, 51]).

2.5. Statistical Analysis of Behavioural Data. Behavioural data from the dichotic and diotic tasks were tested for normality using the Shapiro-Wilk normality test, and due to the nonnormality of the distribution, the effect of R-PA was evaluated at the group level by a repeated measures nonparametric *F*-test. This method, used in a previous study [53], is a bootstrapping of the subjects (with replacement) and permutation of the within-subject factors. An *F* value is calculated on each cycle, for each randomization.

Table 2: Performance in dichotic and diotic listening tasks before (pre-R-PA) and after (post-R-PA) exposure to R-PA, listing the number of words reported for the left and right ears as well as the lateralization index. Scores outside the normal range are highlighted in bold.

	Dichotic listening task						Diotic listening task					
	Pre-R-PA			Post-R-PA			Pre-R-PA			Post-R-PA		
Patient	Left	Right	Lat. index	Left	Right	Lat. index	Left	Right	Lat. index	Left	Right	Lat. index
P1	**1**	30	**93.6**	**4**	29	**75.8**	**10**	**13**	13.0	15	26	**26.8**
P2	**3**	29	**81.3**	**4**	30	**76.5**	22	21	−2.3	20	22	4.8
P3	**19**	29	**20.8**	29	29	0.0	25	26	2.0	27	28	1.8
P4	**15**	27	**28.6**	**15**	27	**28.6**	18	24	14.3	16	29	**28.9**
P5	**19**	29	**20.8**	25	30	9.1	19	24	11.6	29	28	−1.8
P6	**22**	28	**12.0**	26	29	5.5	23	27	8.0	24	26	4.0
P7	29	30	1.7	30	30	0.0	25	27	3.9	28	30	3.5
P8	**20**	30	**20**	26	30	7.1	20	19	−2.6	24	27	5.9
P9	**7**	30	**62.2**	**2**	30	**87.5**	17	20	5.6	17	19	5.6
P10	29	28	−1.8	30	29	−1.7	26	27	1.9	28	29	1.8

Repeating this for 1000 cycles generates an empirical distribution of F values from which a corresponding p value is obtained. These analyses were processed using Python (Python Software Foundation, https://www.python.org/). For the dichotic listening task factors, ear (left, right) and session (pre- and post-R-PA) were used, for diotic listening side (left, right) and session (pre- and post-R-PA).

2.6. Lesion Analysis. Lesions were outlined on MRI ($n = 4$) or CT scan ($n = 6$) anatomical sequences using the Medical Imaging Interaction Toolkit (MITK) software (http://mitk.org). The superposition of the lesions was calculated using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK).

3. Results

3.1. Rightward Prismatic Adaptation and Its Aftereffects. The visuomotor effect of R-PA was evaluated by the presence of the aftereffect, that is, leftward deviation in pointing immediately after prism removal. Seventeen control subjects performed the ecological R-PA paradigm; their mean aftereffect was −8.55° (SD = 2.61°), which is within the range of aftereffects obtained with a shorter version of the R-PA paradigm in a previous study [28]. All but one patient (P6) were able to perform the pointing measures before and after R-PA, and all presented the expected leftward shift. The mean aftereffect was −5.88° (SD = 3.28°).

3.2. Dichotic Listening. The effect of R-PA was evaluated at a group level by a repeated measures nonparametric F-test [53]. The number of items reported for either ear yielded a significant main effect of ear ($F(1, 9) = 11.12$, $p = 0.002$) and a significant main effect of session ($F(1, 9) = 5.13$, $p = 0.023$), but only a trend for the interaction ($F(1, 9) = 3.36$, $p = 0.056$). The lateralization index did not differ significantly between pre- and post-R-PA (Wilcoxon signed-rank test, $Z = -1.481$, $p = 0.139$).

At an individual level, we have identified 8 patients who had a significant decrease of the left ear reporting and an abnormal lateralization index prior to R-PA (Table 2). After R-PA, 4 patients (P3, P5, P6, and P8) normalized their performance on dichotic listening, both in terms of items reported for the left ear and lateralization index. Four other patients (P1, P2, P4, and P9) did not improve their performance and presented after R-PA a significant decrease of left ear reporting and abnormal lateralization index.

The patients who responded to R-PA versus those who did not differ in terms of the site and extent of their lesion. The nonresponders tended to have larger lesions (range: 135.4–383.0 cm^3; Table 1) than responders (range: 19.7–118.7 cm^3). In nonresponders, but not in responders, the lesions extended over large parts of the temporoparietofrontal cortex and the underlying white matter, including the superior parietal lobule, the intraparietal sulcus, and the posterior part of the temporal lobe. The patients who had normal performance in dichotic listening before R-PA (P7 and P10) had a relatively small lesion (38.1 and 70.6 cm^3), which largely spared the temporoparietal cortex.

In summary, R-PA had a striking effect on left ear extinction in dichotic listening in some but not all patients with initial deficit. In responders, the superior parietal lobule, the intraparietal sulcus, and the posterior part of the temporal lobe tended to be spared, but not in nonresponders.

3.3. Diotic Listening. The effect of R-PA was evaluated at a group level by a repeated measures nonparametric F-test [53]. The number of items reported for either side yielded a significant main effect of side ($F(1, 9) = 9.95$, $p = 0.006$) and a significant main effect of session ($F(1, 9) = 7.93$, $p = 0.014$), but no significant interaction ($F(1, 9) = 0.94$, $p = 0.375$). The lateralization index did not differ significantly between pre- and post-R-PA (Wilcoxon signed-rank test, $Z = -0.652$, $p = 0.515$).

At an individual level, we have identified one patient (P1) who had a significant decrease of reporting for both the right and left spaces prior to R-PA, albeit with a lateralization index within the normal range (Table 2). After R-PA, this patient normalized his reporting for the right space, but remained deficient for the left space; the lateralization index was then outside the normal range, favouring

Table 3: Performance in auditory localization before (pre-R-PA) and after (post-R-PA) exposure to R-PA. Scores outside the normal range are in bold. The global score corresponds to the number of stimuli correctly placed to the left or the right of the previous stimulus. The perceived positions of each of the five stimulus locations are indicated in degrees (positive in the right, negative in the left space). The ability to discriminate between the two positions within either hemispace (LL versus L; R versus RR) was assessed by *t*-tests; positions which failed to be discriminated are highlighted in bold. In the control population, 10% of subjects failed to discriminate the two positions within one hemispace, never within both hemispaces. The number of alloacusis is indicated separately for those where stimuli presented on the left were indicated on the right (L to R) and those where stimuli presented on the right were indicated on the left (R to L). Control subjects never presented alloacusis.

		Pre-R-PA								Post-R-PA						
		Positions (°)					Alloacusis			Positions (°)					Alloacusis	
Patient	Global score	LL	L	CE	R	RR	L to R	R to L	Global score	LL	L	CE	R	RR	L to R	R to L
P1	**51**	**−57.5**	**−53.8**	−2.1	**44.2**	**59.6**	0	0	**47**	**−43.6**	**−35.5**	−3.5	**29.6**	**49.6**	**2**	**2**
P2	55	−82.5	−66.3	**11.9**	55.8	75.0	0	0	57	**−76.3**	**−70.8**	7.5	49.6	70.8	0	0
P3	56	**−30.4**	**−28.3**	**−23.3**	36.7	43.3	0	0	**54**	−32.5	−20.8	**29.6**	**35.0**	**39.6**	0	0
P4	**42**	**−12.1**	**−14.5**	−5.6	**32.2**	**13.0**	**4**	**5**	**42**	**−9.5**	**0.5**	5.0	**28.0**	**27.3**	**7**	**1**
P5	56	**−46.3**	**−41.3**	**−9.2**	**40.0**	**43.8**	0	0	55	−68.3	−52.1	**−26.7**	26.7	47.9	0	0
P6	54	**−40.4**	**−36.7**	**−10.4**	28.3	44.2	0	0	59	**−37.1**	**−36.3**	**−15.4**	22.5	32.9	0	0
P7	54	−59.5	3.5	**41.3**	**58.9**	**68.0**	**4**	0	**46**	**−27.9**	**−28.8**	**17.0**	**29.4**	**60.0**	**3**	0
P8	**52**	−50.8	−37.1	**−24.6**	42.1	57.1	0	0	53	−67.1	−64.2	**−32.1**	**64.2**	**77.9**	0	0
P9	54	**−73.3**	**−68.3**	−0.8	**57.5**	**67.1**	0	0	**44**	**21.7**	**−30.9**	**40.8**	**56.7**	**76.3**	**11**	**1**
P10	**52**	−60.8	−64.2	7.5	**71.3**	**72.3**	0	0	**50**	**−75.0**	**−73.8**	**−48.5**	**82.7**	**80.4**	0	0

the right space. Another patient (P4), who had a normal performance in diotic listening, including a normal lateralization index, prior to R-PA, increased after R-PA reporting for the right but not the left space; his lateralization index was then outside the normal range, favouring the right space. The two patients in whom R-PA induced a rightward spatial bias (P1 and P4) did have rather large lesions (135.4 and 202.6 cm^3; Table 1) which extended over large parts of the temporoparietofrontal cortex and the underlying white matter.

The remaining 8 patients had right and left space reporting as well as lateralization index within the normal range before and after R-PA. Among them, three had pre-R-PA scores for the right and/or left side reporting in the lower range (P5; P8 and P9). After R-PA, two of them (P5 and P8) increased considerably both scores, whereas the third one (P9) did not. The former two (P5 and P8) sustained rather small lesions (19.7 and 44.1 cm^3; Table 1) which spared the superior parietal lobule, the intraparietal sulcus, and basal ganglia. The latter one (P9) sustained a large lesion (382.0 cm^3), which extended over large parts of the hemisphere and included the superior parietal lobule, the intraparietal sulcus, and basal ganglia.

In summary, R-PA induced in specific cases rightward spatial bias in diotic listening by enhancing the reporting within the right but not the left space. This profile was associated with extended lesions which included the superior parietal lobule, the intraparietal sulcus, and basal ganglia. In a few cases, R-PA improved the left side reporting from low to high normal range. The integrity of the superior parietal lobule, the intraparietal sulcus, and basal ganglia appeared to be essential for this to occur.

3.4. Auditory Localization. At a group level, there was no statistically significant difference between pre- and post-R-PA global score measures ($Z = -1.19$, $p = 0.234$) nor for the number of left-to-right ($Z = -1.461$, $p = 0.144$) or right-to-left alloacusis ($Z = 0$, $p = 1$; for all comparisons, Wilcoxon signed-rank test).

Prior to R-PA, all patients were deficient at one or several of the following scores: (i) global score; (ii) the location attributed to the central stimulus; (iii) discriminating L-LL plus R-RR; and (iv) presence of alloacusis (Table 3). After the exposure to R-PA, only one patient (P2) improved his performance and reached normal range. His lesion was rather large (182.5 cm^3; Table 1) and extended over large parts of the temporoparietofrontal cortex and the underlying white matter.

The remaining nine patients worsened their performance. Three (P1, P4, and P9) enhanced their rightward bias by shifting the position attributed to the central stimulus to the right and/or by increasing the number of left-to-right alloacusis, thus aggravating neglect symptoms. Their lesions were rather large (135.4 and 382.0 cm^3) and extended over large parts of the temporoparietofrontal cortex and the underlying white matter. Two patients (P3 and P7) became deficient on their global score, without increasing a rightward bias. Their lesions were relatively small (93.1 and 70.6 cm^3) and extended over the anterior and posterior temporal lobes, frontal convexity, and/or the underlying white matter. One patient (P10) sustained leftward bias by shifting the position attributed to the central stimulus to the left and failed to discriminate the L-LL positions. Her lesion was relatively small (38.1 cm^3) and subcortical.

In summary, the effect of R-PA on auditory localization was varied and in nine of ten cases detrimental. In specific cases, R-PA induced rightward spatial bias in auditory localization. There did not seem to be clear relationship between the site of lesion and the effect of R-PA on auditory localization.

4. Discussion

4.1. Alleviation of Auditory Neglect by Prismatic Adaptation: Ear versus Space. The most striking effect of R-PA which we have observed was the alleviation of left ear extinction on dichotic listening, present in half of the patients. This beneficial effect on ear-related performance contrasted with the modest or even detrimental effects on space-related measures. In diotic listening, we observed an improvement which was limited to reporting the right-space stimuli and created thus rightward spatial bias. In a few cases, R-PA had mostly negative effect on auditory localization, leading to a rightward spatial bias.

The diverging effects of R-PA on different aspects of auditory neglect may be partially explained by the underlying mechanisms. Whereas, the effect on dichotic listening is likely to depend on the same neural mechanisms as the effect on visuospatial attention, the complexity of the encoding of the auditory space at a cortical level may interfere with the effect on auditory localization and possibly on diotic listening.

4.2. Neural Mechanisms Underlying the Effect of Prismatic Adaptation in Auditory Neglect. Visual attention and orienting have been shown to depend on the dorsal and ventral attentional systems. As demonstrated in a series of seminal studies, the dorsal attentional network, which comprises the superior parietal lobule, the intraparietal sulcus, and the superior frontal cortex of both hemispheres, mediates endogenous allocation of visuospatial attention [54]. Its key region, the intraparietal sulcus, encodes predominantly the contralateral visual space [55]. Exogenous attention, that is, the alerting targets that appear at unattended locations, is mediated by the ventral attentional network, which is lateralized to the right hemisphere and includes the temporoparietal junction, IPL, and posterior part of the superior temporal gyrus; this region receives visual information from the whole visual space [54]. The right-dominant ventral and the bilateral dorsal attentional systems are interconnected, so that the alerting input from the ventral system can activate the dorsal system [56]. There is a reciprocal interconnection between the right and left parts of the dorsal attention system [56–58], characterized by an asymmetrical inhibitory effect by which the right posterior parietal cortex inhibits the left homologous region [57, 58].

A brief exposure to R-PA was shown to shift the right-dominant ventral attentional system to the left IPL. The task used in this study was the detection of visual target presented in the left, central, and right spaces, known to activate the ventral attentional system. R-PA leads to a significant increase of the ipsilateral visual field representation in the left IPL and a significant decrease in the right IPL [28]. This same study demonstrated that R-PA did not have the same effect on other types of visuospatial processing, such as visuospatial working memory. In a later study, the shift of the ventral attentional system from the right to the left hemisphere was demonstrated with the same visual detection task in neglect patients [29]. The model derived from these studies, referred to as SHD-VAS (shift in hemispheric dominance within the ventral attentional system), offers a parsimonious explanation for the effects of R-PA on visuospatial attention in normal subjects and neglect patients (for discussion see [37]). This model may be also relevant for auditoryspatial attention, since the dorsal and the ventral attentional systems are involved in auditory attention. Early activation studies reported that auditory alertness involved an extended right hemispheric network, including frontal, cingular, inferior parietal, temporal, and thalamic regions [32] and shared with visual alertness a common region within the ventral attentional system [33].

In view of the above quoted evidence, it is reasonable to assume that the effect of R-PA on auditory neglect relies on the shift of the right-dominant ventral attentional system to the left hemisphere. For the beneficial effect on attentional orienting to the left, the ventral attentional system within the left hemisphere needs to access the dorsal attentional system within the right hemisphere. Thus, a spared dorsal attentional system and intact inputs from the left IPL are necessary for such beneficial effects.

4.3. Effect of Prismatic Adaptation on Dichotic Listening: What Matters? In our population, R-PA alleviated left ear extinction in dichotic listening in four patients, while it failed to do so in four others. The prerequisite for the beneficial effect of R-PA appeared to be intact with the superior parietal lobule, posterior part of the temporal lobe, as well as the periventricular white matter, which convey fibers joining the middle and posterior parts of the corpus callosum (Figure 2). The key role of the superior parietal lobule and of the callosal connections is in agreement with the SHD-VAS model.

Left ear extinction on dichotic listening has been also reported independently of the neglect syndrome, in cases of callosal disconnection and in particular when the splenium and the isthmus of the corpus callosum were damaged [6, 7]. These posterior parts of the corpus callosum are known to convey fibers from the temporal lobe, whereas the parietal callosal pathway tends to involve more anterior parts [59]. In our patient population, we did not have lesions which damaged specifically either the auditory or the parietal callosal pathway. Thus, it remains unclear whether R-PA would alleviate left ear extinction in cases with focal lesions of the splenium and the isthmus, that is, without damage to the dorsal attentional system and the more anterior callosal pathway.

4.4. Worsening Rightward Bias on Diotic Listening. Our results suggest that in specific conditions, R-PA can enhance rightward spatial bias and thus amplify neglect symptoms. When it happened in diotic listening, the initial condition involved scores that were pathologically low or within lower normal range on both sides. R-PA increased the reporting on the right but not on the left side. The beneficial effect on the right side reporting can be explained by the SHD-VAS model and the ensuing activation of the left dorsal attentional system. Both patients who presented this effect (P1 and P4) sustained damage to the right dorsal attentional system, which precluded reorienting attention to the left.

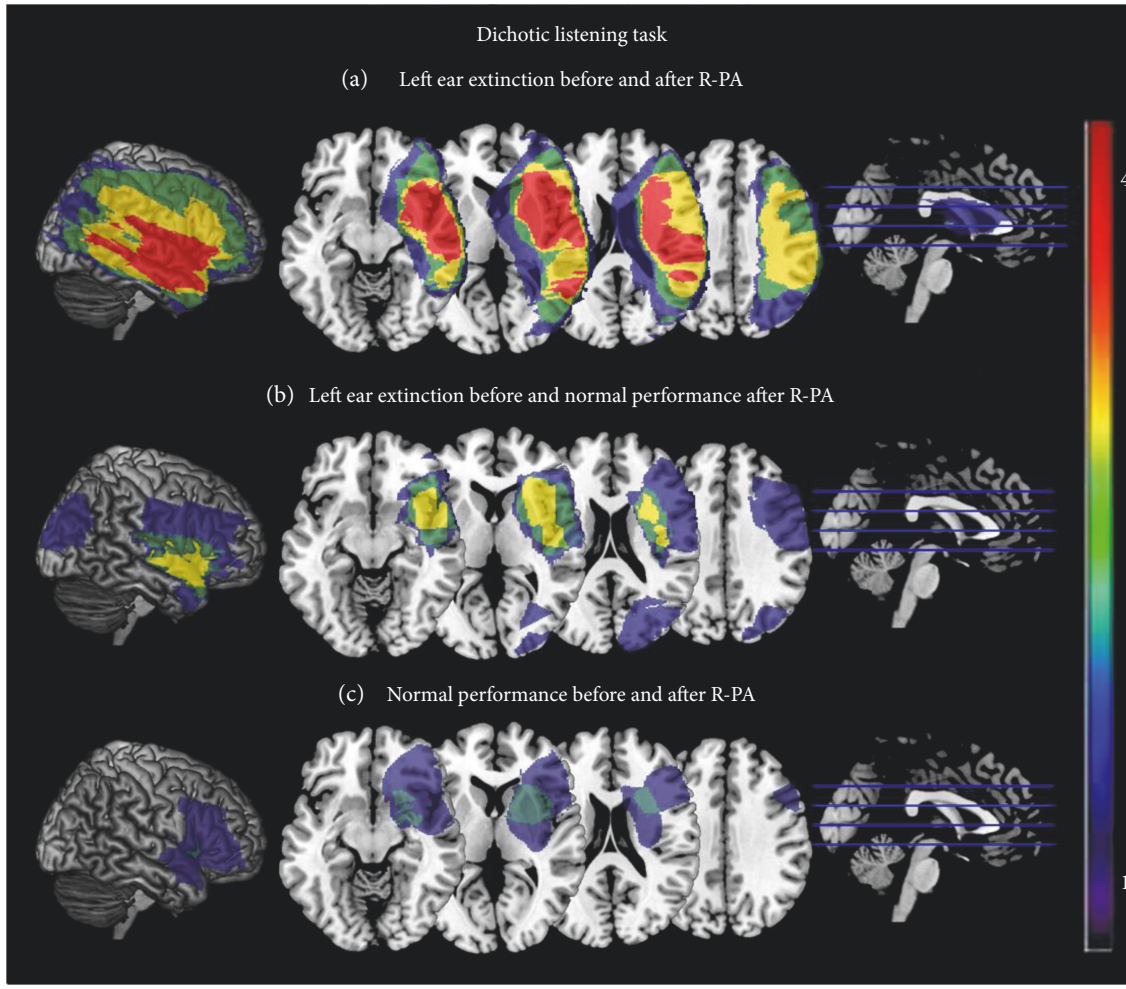

Figure 2: Anatomical correlates of performance in dichotic listening task. Superposition of lesions associated with 3 profiles: (a) Patients with left ear extinction who did not respond to R-PA (P1, P2, P4, and P9). (b) Patients with left ear extinction who responded to R-PA (P3, P5, P6, and P8). (c) Patients without deficits at the dichotic listening task (P7 and P10).

R-PA can enhance the left side reporting in diotic listening, as observed in two patients whose scores were in the lower normal range prior to R-PA and in the upper normal range after it (P5 and P8). Both patients had intact dorsal attentional system on the right side.

4.5. Disturbing Auditory Localization. Our results on auditory localization demonstrate that R-PA can enhance rightward spatial bias and thus aggravate neglect symptoms. Three patients presented this profile (P1, P4, and P9); after prismatic adaptation, they shifted the central position to the right and/or presented more right-to-left alloacusis. All three sustained damage to the right dorsal attentional system, which may explain the paradoxical rightward bias.

Apart from the enhancement of rightward spatial bias, R-PA tended to deteriorate more generally performance in auditory localization and even introduced a pathological leftward spatial bias. The former was observed in two patients whose global score became deficient after R-PA (P3 and P7), the latter in two other patients with a leftward spatial bias for the central position after R-PA (P5 and P10). These varied and rather unfavourable effects of R-PA on auditory localization may be related to the way auditory space is represented at a cortical level. Several lines of evidence indicate that auditory space is not represented in a topographical fashion, but encoded within specific neuronal populations [60–62]. Single neurons in nonhuman primates were reported to have large receptive fields, centered on the contralateral space [62–64]. Human fMRI studies reported a similar organization with preferential responses to contralateral locations and broad spatial tuning [38, 39]. The representation of the auditory space in humans appears to be lateralized, with greater bilaterality in the right and stricter contralaterality in the left hemisphere [40]. This asymmetry is particularly striking within the parietofrontal cortex, as demonstrated in activation [65–68], magnetoencephalography [69], transcranial magnetic stimulation [70, 71], and lesion studies [44]. This frontoparietal asymmetry is further supported by the patterns of structural and functional connectivities [72, 73].

The above quoted evidence suggests that the region invested by the ventral attentional system, and in particular

the IPL, not only supports auditory alertness and attention, but also the representation of auditory space. When shifted to the left hemisphere after R-PA, the ventral attentional system most likely upkeeps its alerting function, and hence the positive effect on dichotic listening, as reported previously [35] and here. The representation of the auditory space, which depends on fine-tuned interactions within neuronal populations, is very likely disturbed by the exposure to R-PA. This may account for the detrimental effect of R-PA on sound localization.

5. Conclusions

The beneficial effect of R-PA on auditory neglect appears to be limited to the alleviation of left ear extinction in dichotic listening. This particular effect can be parsimoniously explained by the SHD-VAS model, that is, shift in hemispheric dominance within the ventral attentional system, induced by R-PA. This model has been initially formulated on the basis of visual activation studies [28, 29], but its predictions appear to be valid for the effect of R-PA on left ear extinction in dichotic listening. In particular, the observation that the right dorsal attentional system needs to be intact to obtain an alleviation of left extinction after R-PA is entirely in adequation with this model. This observation is clinically relevant, since it identifies anatomical profiles of patients for whom R-PA is likely to alleviate ear-related symptoms of auditory neglect.

The effect of R-PA on space-related measures of auditory neglect is varied and mostly detrimental. This is particularly apparent in auditory localization and may be accounted for by the complex way auditory space is represented at a cortical level. Whether the exacerbation of auditory localization deficits after exposure to R-PA has an impact on activities of daily living is currently not known. The effect may be short lived and possibly rapidly corrected as previously described for the realignment of visuo- and auditoryspatial representations in the ventriloquism effect [74–76].

Abbreviations

IPL: Inferior parietal lobule
R-PA: Rightward prismatic adaptation
SHD-VAS: Shift in hemispheric dominance within the ventral attentional system.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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References

[1] F. Pavani, M. Husain, E. Ládavas, and J. Driver, "Auditory deficits in visuospatial neglect patients," *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, vol. 40, no. 2, pp. 347–365, 2004.

[2] K. M. Heilman and E. Valenstein, "Auditory neglect in man," *Archives of Neurology*, vol. 26, no. 1, pp. 32–35, 1972.

[3] K. Hugdahl, K. Wester, and A. Asbjørnsen, "Auditory neglect after right frontal lobe and right pulvinar thalamic lesions," *Brain and Language*, vol. 41, no. 3, pp. 465–473, 1991.

[4] D. Kimura, "Functional asymmetry of the brain in dichotic listening," *Cortex*, vol. 3, no. 2, pp. 163–178, 1967.

[5] R. Sparks and N. Geschwind, "Dichotic listening in man after section of neocortical commissures," *Cortex*, vol. 4, no. 1, pp. 3–16, 1968.

[6] S. Pollmann, M. Maertens, D. Yves, J. Lepsien, and K. Hugdahl, "Dichotic listening in patients with splenial and nonsplenial callosal lesions," *Neuropsychology*, vol. 16, no. 1, pp. 56–64, 2002.

[7] M. Sugishita, K. Otomo, K. Yamazaki, H. Shimizu, M. Yoshioka, and A. Shinohara, "Dichotic listening in patients with partial section of the corpus callosum," *Brain*, vol. 118, Part 2, pp. 417–427, 1995.

[8] E. D. Renzi, M. Gentilini, and F. Pattacini, "Auditory extinction following hemisphere damage," *Neuropsychologia*, vol. 22, no. 6, pp. 733–744, 1984.

[9] A. Bellmann, R. Meuli, and S. Clarke, "Two types of auditory neglect," *Brain: A Journal of Neurology*, vol. 124, Part 4, pp. 676–687, 2001.

[10] L. Spierer, R. Meuli, and S. Clarke, "Extinction of auditory stimuli in hemineglect: space versus ear," *Neuropsychologia*, vol. 45, no. 3, pp. 540–551, 2007.

[11] A. B. Thiran and S. Clarke, "Preserved use of spatial cues for sound segregation in a case of spatial deafness," *Neuropsychologia*, vol. 41, no. 9, pp. 1254–1261, 2003.

[12] E. Bisiach, L. Cornacchia, R. Sterzi, and G. Vallar, "Disorders of perceived auditory lateralization after lesions of the right hemisphere," *Brain: A Journal of Neurology*, vol. 107, Part 1, pp. 37–52, 1984.

[13] H. Haeske-Dewick, A. G. M. Canavan, and V. Hömberg, "Sound localization in egocentric space following hemispheric lesions," *Neuropsychologia*, vol. 34, no. 9, pp. 937–942, 1996.

[14] N. Soroker, N. Calamaro, J. Glicksohn, and M. S. Myslobodsky, "Auditory inattention in right-hemisphere-damaged patients with and without visual neglect," *Neuropsychologia*, vol. 35, no. 3, pp. 249–256, 1997.

[15] A. Farnè, Y. Rossetti, S. Toniolo, and E. Làdavas, "Ameliorating neglect with prism adaptation: visuo-manual and visuo-verbal measures," *Neuropsychologia*, vol. 40, no. 7, pp. 718–729, 2002.

[16] F. Frassinetti, V. Angeli, F. Meneghello, S. Avanzi, and E. Làdavas, "Long-lasting amelioration of visuospatial neglect by prism adaptation," *Brain*, vol. 125, no. 3, pp. 608–623, 2002.

[17] L. Pisella, G. Rode, A. Farnè, C. Tilikete, and Y. Rossetti, "Prism adaptation in the rehabilitation of patients with visuo-spatial cognitive disorders," *Current Opinion in Neurology*, vol. 19, no. 6, pp. 534–542, 2006.

[18] G. Rode, T. Klos, S. Courtois-Jacquin, Y. Rossetti, and L. Pisella, "Neglect and prism adaptation: a new therapeutic tool for spatial cognition disorders," *Restorative Neurology and Neuroscience*, vol. 24, no. 4–6, pp. 347–356, 2006.

[19] G. Rode, Y. Rossetti, and D. Boisson, "Prism adaptation improves representational neglect," *Neuropsychologia*, vol. 39, no. 11, pp. 1250–1254, 2001.

[20] Y. Rossetti, G. Rode, L. Pisella et al., "Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect," *Nature*, vol. 395, no. 6698, pp. 166–169, 1998.

[21] A. Serino, S. Bonifazi, L. Pierfederici, and E. Làdavas, "Neglect treatment by prism adaptation: what recovers and for how long," *Neuropsychological Rehabilitation*, vol. 17, no. 6, pp. 657–687, 2007.

[22] A. Serino, V. Angeli, F. Frassinetti, and E. Làdavas, "Mechanisms underlying neglect recovery after prism adaptation," *Neuropsychologia*, vol. 44, no. 7, pp. 1068–1078, 2006.

[23] H. L. Chapman, R. Eramudugolla, M. Gavrilescu et al., "Neural mechanisms underlying spatial realignment during adaptation to optical wedge prisms," *Neuropsychologia*, vol. 48, no. 9, pp. 2595–2601, 2010.

[24] D. M. Clower, J. M. Hoffman, J. R. Votaw, T. L. Faber, R. P. Woods, and G. E. Alexander, "Role of posterior parietal cortex in the recalibration of visually guided reaching," *Nature*, vol. 383, no. 6601, pp. 618–621, 1996.

[25] J. Danckert, S. Ferber, and M. A. Goodale, "Direct effects of prismatic lenses on visuomotor control: an event-related functional MRI study," *The European Journal of Neuroscience*, vol. 28, no. 8, pp. 1696–1704, 2008.

[26] M. Küper, M. J. S. Wünnemann, M. Thürling et al., "Activation of the cerebellar cortex and the dentate nucleus in a prism adaptation fMRI study," *Human Brain Mapping*, vol. 35, no. 4, pp. 1574–1586, 2014.

[27] J. Luauté, S. Schwartz, Y. Rossetti et al., "Dynamic changes in brain activity during prism adaptation," *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, vol. 29, no. 1, pp. 169–178, 2009.

[28] S. Crottaz-Herbette, E. Fornari, and S. Clarke, "Prismatic adaptation changes visuospatial representation in the inferior parietal lobule," *Journal of Neuroscience*, vol. 34, no. 35, pp. 11803–11811, 2014.

[29] S. Crottaz-Herbette, E. Fornari, M. P. Notter, C. Bindschaedler, L. Manzoni, and S. Clarke, "Reshaping the brain after stroke: the effect of prismatic adaptation in patients with right brain damage," *Neuropsychologia*, vol. 104, pp. 54–63, 2017.

[30] E. Salo, T. Rinne, O. Salonen, and K. Alho, "Brain activity during auditory and visual phonological, spatial and simple discrimination tasks," *Brain Research*, vol. 1496, pp. 55–69, 2013.

[31] D. V. Smith, B. Davis, K. Niu et al., "Spatial attention evokes similar activation patterns for visual and auditory stimuli," *Journal of Cognitive Neuroscience*, vol. 22, no. 2, pp. 347–361, 2010.

[32] W. Sturm, F. Longoni, B. Fimm et al., "Network for auditory intrinsic alertness: a PET study," *Neuropsychologia*, vol. 42, no. 5, pp. 563–568, 2004.

[33] C. M. Thiel and G. R. Fink, "Visual and auditory alertness: modality-specific and supramodal neural mechanisms and their modulation by nicotine," *Journal of Neurophysiology*, vol. 97, no. 4, pp. 2758–2768, 2007.

[34] G. Rode, C. Pagliari, L. Huchon, Y. Rossetti, and L. Pisella, "Semiology of neglect: an update," *Annals of Physical and Rehabilitation Medicine*, vol. 60, no. 3, pp. 177–185, 2017.

[35] S. Jacquin-Courtois, G. Rode, F. Pavani et al., "Effect of prism adaptation on left dichotic listening deficit in neglect patients: glasses to hear better?," *Brain*, vol. 133, no. 3, pp. 895–908, 2010.

[36] R. Eramudugolla, A. Boyce, D. R. F. Irvine, and J. B. Mattingley, "Effects of prismatic adaptation on spatial gradients in unilateral neglect: a comparison of visual and auditory target detection with central attentional load," *Neuropsychologia*, vol. 48, no. 9, pp. 2681–2692, 2010.

[37] S. Clarke and S. Crottaz-Herbette, "Modulation of visual attention by prismatic adaptation," *Neuropsychologia*, vol. 92, pp. 31–41, 2016.

[38] K. Derey, G. Valente, B. de Gelder, and E. Formisano, "Opponent coding of sound location (azimuth) in planum temporale is robust to sound-level variations," *Cerebral Cortex (New York, N.Y.: 1991)*, vol. 26, no. 1, pp. 450–464, 2016.

[39] S. A. McLaughlin, N. C. Higgins, and G. C. Stecker, "Tuning to binaural cues in human auditory cortex," *Journal of the Association for Research in Otolaryngology: JARO*, vol. 17, no. 1, pp. 37–53, 2016.

[40] G. C. Stecker, S. A. McLaughlin, and N. C. Higgins, "Monaural and binaural contributions to interaural-level-difference sensitivity in human auditory cortex," *NeuroImage*, vol. 120, pp. 456–466, 2015.

[41] S. Jacquin-Courtois, J. O'Shea, J. Luauté et al., "Rehabilitation of spatial neglect by prism adaptation: a peculiar expansion of sensorimotor after-effects to spatial cognition," *Neuroscience & Biobehavioral Reviews*, vol. 37, no. 4, pp. 594–609, 2013.

[42] G. M. Redding, Y. Rossetti, and B. Wallace, "Applications of prism adaptation: a tutorial in theory and method," *Neuroscience & Biobehavioral Reviews*, vol. 29, no. 3, pp. 431–444, 2005.

[43] J. Fernández-Ruiz and R. Díaz, "Prism adaptation and aftereffect: specifying the properties of a procedural memory system," *Learning & Memory*, vol. 6, no. 1, pp. 47–53, 1999.

[44] L. Spierer, A. Bellmann-Thiran, P. Maeder, M. M. Murray, and S. Clarke, "Hemispheric competence for auditory spatial representation," *Brain*, vol. 132, Part 7, pp. 1953–1966, 2009.

[45] M. Adriani, P. Maeder, R. Meuli et al., "Sound recognition and localization in man: specialized cortical networks and effects of acute circumscribed lesions," *Experimental Brain Research*, vol. 153, no. 4, pp. 591–604, 2003.

[46] S. Clarke, A. B. Thiran, P. Maeder et al., "What and where in human audition: selective deficits following focal hemispheric lesions," *Experimental Brain Research*, vol. 147, no. 1, pp. 8–15, 2002.

[47] S. Clarke, A. Bellmann, R. A. Meuli, G. Assal, and A. J. Steck, "Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways," *Neuropsychologia*, vol. 38, no. 6, pp. 797–807, 2000.

[48] M. Cogné, J.-F. Knebel, E. Klinger et al., "The effect of contextual auditory stimuli on virtual spatial navigation in patients with focal hemispheric lesions," *Neuropsychological Rehabilitation*, vol. 6, pp. 1–16, 2016.

[49] C. Y. Ducommun, C. M. Michel, S. Clarke et al., "Cortical motion deafness," *Neuron*, vol. 43, no. 6, pp. 765–777, 2004.

[50] C. Duffour-Nikolov, E. Tardif, P. Maeder et al., "Auditory spatial deficits following hemispheric lesions: dissociation of explicit and implicit processing," *Neuropsychological Rehabilitation*, vol. 22, no. 5, pp. 674–696, 2012.

[51] B. Rey, R. Frischknecht, P. Maeder, and S. Clarke, "Patterns of recovery following focal hemispheric lesions: relationship between lasting deficit and damage to specialized networks," *Restorative Neurology and Neuroscience*, vol. 25, no. 3-4, pp. 285–294, 2007.

[52] P. Azouvi, P. Bartolomeo, J.-M. Beis, D. Perennou, P. Pradat-Diehl, and M. Rousseaux, "A battery of tests for the quantitative assessment of unilateral neglect," *Restorative Neurology and Neuroscience*, vol. 24, no. 4–6, pp. 273–285, 2006.

[53] J.-F. Knebel, D. C. Javitt, and M. M. Murray, "Impaired early visual response modulations to spatial information in chronic schizophrenia," *Psychiatry Research: Neuroimaging*, vol. 193, no. 3, pp. 168–176, 2011.

[54] M. Corbetta, J. M. Kincade, and G. L. Shulman, "Neural systems for visual orienting and their relationships to spatial working memory," *Journal of Cognitive Neuroscience*, vol. 14, no. 3, pp. 508–523, 2002.

[55] M. A. Silver and S. Kastner, "Topographic maps in human frontal and parietal cortex," *Trends in Cognitive Sciences*, vol. 13, no. 11, pp. 488–495, 2009.

[56] M. Corbetta and G. L. Shulman, "Control of goal-directed and stimulus-driven attention in the brain," *Nature Reviews Neuroscience*, vol. 3, no. 3, pp. 201–215, 2002.

[57] G. Koch, M. Cercignani, S. Bonnì et al., "Asymmetry of parietal interhemispheric connections in humans," *Journal of Neuroscience*, vol. 31, no. 24, pp. 8967–8975, 2011.

[58] G. Koch, M. Oliveri, B. Cheeran et al., "Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect," *Brain*, vol. 131, Part 12, pp. 3147–3155, 2008.

[59] R. Westerhausen, R. Grüner, K. Specht, and K. Hugdahl, "Functional relevance of interindividual differences in temporal lobe callosal pathways: a DTI tractography study," *Cerebral Cortex*, vol. 19, no. 6, pp. 1322–1329, 2009.

[60] I. A. Harrington, G. C. Stecker, E. A. Macpherson, and J. C. Middlebrooks, "Spatial sensitivity of neurons in the anterior, posterior, and primary fields of cat auditory cortex," *Hearing Research*, vol. 240, no. 1-2, pp. 22–41, 2008.

[61] G. C. Stecker, I. A. Harrington, and J. C. Middlebrooks, "Location coding by opponent neural populations in the auditory cortex," *PLoS Biology*, vol. 3, no. 3, article e78, 2005.

[62] G. C. Stecker, B. J. Mickey, E. A. Macpherson, and J. C. Middlebrooks, "Spatial sensitivity in field PAF of cat auditory cortex," *Journal of Neurophysiology*, vol. 89, no. 6, pp. 2889–2903, 2003.

[63] T. M. Woods, S. E. Lopez, J. H. Long, J. E. Rahman, and G. H. Recanzone, "Effects of stimulus azimuth and intensity on the single-neuron activity in the auditory cortex of the alert macaque monkey," *Journal of Neurophysiology*, vol. 96, no. 6, pp. 3323–3337, 2006.

[64] G. H. Recanzone, "Spatial processing in the auditory cortex of the macaque monkey," *Proceedings of the National Academy of Sciences*, vol. 97, no. 22, pp. 11829–11835, 2000.

[65] S. R. Arnott, M. A. Binns, C. L. Grady, and C. Alain, "Assessing the auditory dual-pathway model in humans," *NeuroImage*, vol. 22, no. 1, pp. 401–408, 2004.

[66] K. O. Bushara, R. A. Weeks, K. Ishii et al., "Modality-specific frontal and parietal areas for auditory and visual spatial localization in humans," *Nature Neuroscience*, vol. 2, no. 8, pp. 759–766, 1999.

[67] L. De Santis, S. Clarke, and M. M. Murray, "Automatic and intrinsic auditory "what"and "where"processing in humans revealed by electrical neuroimaging," *Cerebral Cortex (New York, N.Y.: 1991)*, vol. 17, no. 1, pp. 9–17, 2007.

[68] P. P. Maeder, R. A. Meuli, M. Adriani et al., "Distinct pathways involved in sound recognition and localization: a human fMRI study," *NeuroImage*, vol. 14, no. 4, pp. 802–816, 2001.

[69] J. Kaiser, W. Lutzenberger, H. Preissl, H. Ackermann, and N. Birbaumer, "Right-hemisphere dominance for the processing of sound-source lateralization," *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, vol. 20, no. 17, pp. 6631–6639, 2000.

[70] A. At, L. Spierer, and S. Clarke, "The role of the right parietal cortex in sound localization: a chronometric single pulse transcranial magnetic stimulation study," *Neuropsychologia*, vol. 49, no. 9, pp. 2794–2797, 2011.

[71] J. Lewald, I. G. Meister, J. Weidemann, and R. Töpper, "Involvement of the superior temporal cortex and the occipital cortex in spatial hearing: evidence from repetitive transcranial magnetic stimulation," *Journal of Cognitive Neuroscience*, vol. 16, no. 5, pp. 828–838, 2004.

[72] L. Cammoun, J. P. Thiran, A. Griffa, R. Meuli, P. Hagmann, and S. Clarke, "Intrahemispheric cortico-cortical connections of the human auditory cortex," *Brain Structure & Function*, vol. 220, no. 6, pp. 3537–3553, 2015.

[73] M. J. Dietz, K. J. Friston, J. B. Mattingley, A. Roepstorff, and M. I. Garrido, "Effective connectivity reveals right-hemisphere dominance in audiospatial perception: implications for models of spatial neglect," *Journal of Neuroscience*, vol. 34, no. 14, pp. 5003–5011, 2014.

[74] G. H. Recanzone, "Rapidly induced auditory plasticity: the ventriloquism aftereffect," *Proceedings of the National Academy of Sciences*, vol. 95, no. 3, pp. 869–875, 1998.

[75] B. Bonath, T. Noesselt, A. Martinez et al., "Neural basis of the ventriloquist illusion," *Current Biology*, vol. 17, no. 19, pp. 1697–1703, 2007.

[76] B. Bonath, T. Noesselt, K. Krauel, S. Tyll, C. Tempelmann, and S. A. Hillyard, "Audio-visual synchrony modulates the ventriloquist illusion and its neural/spatial representation in the auditory cortex," *NeuroImage*, vol. 98, pp. 425–434, 2014.

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ORIGINAL ARTICLE

Supramodal effect of rightward prismatic adaptation on spatial representations within the ventral attentional system

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Abstract

Rightward prismatic adaptation (R-PA) was shown to alleviate not only visuo-spatial but also auditory symptoms in neglect. The neural mechanisms underlying the effect of R-PA have been previously investigated in visual tasks, demonstrating a shift of hemispheric dominance for visuo-spatial attention from the right to the left hemisphere both in normal subjects and in patients. We have investigated whether the same neural mechanisms underlie the supramodal effect of R-PA on auditory attention. Normal subjects underwent a brief session of R-PA, which was preceded and followed by an fMRI evaluation during which subjects detected targets within the left, central and right space in the auditory or visual modality. R-PA-related changes in activation patterns were found bilaterally in the inferior parietal lobule. In either modality, the representation of the left, central and right space increased in the left IPL, whereas the representation of the right space decreased in the right IPL. Thus, a brief exposure to R-PA modulated the representation of the auditory and visual space within the ventral attentional system. This shift in hemispheric dominance for auditory spatial attention offers a parsimonious explanation for the previously reported effects of R-PA on auditory symptoms in neglect.

Keywords Supramodal · Prismatic adaptation · Functional MRI · Ventral attentional system · Inferior parietal lobule

Abbreviations

AG	Angular gyrus
PSC	Percent signal changes
fMRI	Functional magnetic resonance imaging
IPL	Inferior parietal lobule
R-PA	Rightward prismatic adaptation
L-PA	Leftward prismatic adaptation
SMG	Supramarginal gyrus

Introduction

Rightward prismatic adaptation (R-PA) was repeatedly shown to alleviate visuo-spatial symptoms in neglect (Rossetti et al. 1998; Redding and Wallace 2006; Pisella et al. 2006; Rode et al. 2007; Danckert et al. 2008; Fortis et al. 2011; Yang et al. 2013; Jacquin-Courtois et al. 2013). In addition, it was reported to lessen auditory symptoms by reducing left ear extinction in dichotic listening (Jacquin-Courtois et al. 2010; Tissieres et al. 2017) and by improving the detection of auditory targets (Eramudugolla et al. 2010). These latter observations suggest that R-PA may have a supramodal effect. The mechanism by which R-PA affects spatial attention is partially understood in the visual but not in the auditory modality (e.g., Clarke and Crottaz-Herbette 2016).

Prismatic adaptation is a visuo-motor training task during which subjects point to visual targets while wearing glasses mounted with prisms. In neglect rehabilitation, the prisms deviate the visual field to the right. During the initial trials, subjects show pointing errors in the direction of the prism deviation, then they adapt their movement and point correctly to the target. When the prisms are removed, the first trials show pointing errors in the opposite direction to the

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prism deviation (Rossetti et al. 1998). The neural mechanisms underlying the effect of R-PA have been investigated in visual tasks. In normal subjects, several studies revealed the involvement of the right posterior parietal cortex and in the right cerebellum during the stages of the visuo-motor adaptation (Clower et al. 1996; Danckert et al. 2008; Luauté et al. 2009; Chapman et al. 2010; Küper et al. 2014). By comparing task-related brain activations before and after prismatic adaptation in normal subjects, Crottaz-Herbette and colleagues have shown that R-PA modulates visuo-spatial representations bilaterally in the inferior parietal lobules (IPL) by increasing the representation of the left, center and right visual field in the left IPL and decreasing the representation of the right visual field in the right IPL (Crottaz-Herbette et al. 2014). Using the same paradigm in neglect, R-PA was found to enhance the representation of left and central visual space within the left hemisphere in IPL and in parts of the temporal and prefrontal convexities (Crottaz-Herbette et al. 2017a). Thus, R-PA shifts the hemispheric dominance for visuo-spatial attention from the right to the left hemisphere (Clarke and Crottaz-Herbette 2016). In contrast, L-PA was found to enhance the representation of the right visual space within the right IPL (Crottaz-Herbette et al. 2017b); this change offers a partial explanation for the attentional bias towards the right space, which is characteristic of the pseudo-neglect induced by L-PA in normal subjects (Colent et al. 2000; Michel 2003; Martín-Arévalo et al. 2016).

Auditory spatial processing relies heavily on the dorsal auditory pathway and more particularly on IPL (Maeder et al. 2001; Arnott et al. 2004; Brunetti et al. 2005; Deouell et al. 2007; Häkkinen et al. 2015). Several lines of evidence support right-hemispheric dominance for auditory spatial functions. In particular, the right IPL was shown to be competent for the whole auditory space, as demonstrated in activation (Bushara et al. 1999; Kaiser et al. 2000; Itoh et al. 2000; De Santis et al. 2007) and lesion studies (Tanaka et al. 1999; Spierer et al. 2009). In contrast, the left IPL is limited to the representation of the contralateral, right auditory hemispace, as reported in EEG (Kaiser et al. 2000; Spierer et al. 2008), transcranial magnetic stimulation (Lewald et al. 2002) and lesion studies (Clarke et al. 2000; Spierer et al. 2009). The regions, which are involved in auditory spatial processing, are partially co-extensive with regions involved in visuo-spatial functions; this is the case of parts of the right IPL, this latter has been proposed to be involved in multimodal spatial processing (Bushara et al. 1999).

The contiguity of visual and auditory spatial processing units within the right IPL suggests that similar neural mechanisms may underlie the effect of R-PA in both modalities. If so, R-PA is likely to switch hemispheric dominance not only of visual but also of auditory spatial representation from the right to the left IPL. We have tested this hypothesis by comparing pre- and post-R-PA activation patterns elicited by auditory or visual stimuli presented in the left, central or right space in a between-subjects design. Activation data were analyzed with a mixed-design ANOVA, with Session (pre, post R-PA) and Stimulus position (left, center, right) as within-subject factors and Modality (visual, auditory) as between-subjects factor. Four specific issues were investigated. First, we have expected that R-PA has a general impact on the processing within the left and right IPL, independently of the modality. This was indeed demonstrated by a massive main effect of Session. Second, R-PA was expected to increase the representation of the ipsilateral space within the left IPL and to decrease it within the right IPL. This change was revealed by the interaction of the factors Stimulus position and Session, independently of the modality. Third, the modulation by R-PA in the IPL may differ between modalities. If so, we would expect a significant interaction between the factor Modality and Session, which in fact did not occur within the IPL on either side. Fourth, we have expected that R-PA modulates spatial representations in either modality in the IPL. This was demonstrated by a significant main effect of Session in the IPL for each modality separately.

Materials and methods

Participants

Thirty healthy right-handed (Oldfield 1971) subjects participated in this study (16 in the auditory task: 8 men, mean age = 27.7 years, standard deviation (SD) = 4.3 years; and 14 in the visual task: 7 men, mean age = 26 years, SD = 5 years). None of the subjects had a history of psychiatric or neurological disorder; all reported normal or corrected-to-normal vision and normal hearing. The study has been approved by the Ethic Committee of the Canton de Vaud, Switzerland and all subjects provided written informed consent according to the procedures.

Experimental design

The experiment consisted of three parts: (1) the pre R-PA MRI session; (2) R-PA; and (3) the post R-PA MRI Session. Subjects started the experiment by anatomical MRI sequences and fMRI acquisitions of the auditory or the visual detection task. Other anatomical and functional sequences were acquired for the purpose of another study, but are not reported here. Then subjects underwent a R-PA session outside the scanner room. After the R-PA session, subjects had a second fMRI session, repeating the same task as before the R-PA (i.e., the visual or auditory detection task). As in the previous study (Crottaz-Herbette et al.

2014), the order of tasks within the pre- and post-PA fMRI sessions was counterbalanced across subjects. In addition, the same time schedule was used, for which the adaptation effects where shown to be preserved throughout the time span of the post-PA fMRI acquisition (Crottaz-Herbette et al. 2014).

Auditory detection task

The design of the auditory task was similar to the design used in our previous visual task (Crottaz-Herbette et al. 2014). It was used to reveal changes in the spatiotopic representation of sounds and hence it was important that performance remained as constant as possible before and after the R-PA session. Auditory stimuli were bursts of pink noise presented for 500 ms. Sounds onset and offset were ramped with 10 ms of a linear slope. Broadband noise was chosen because it was proven to be better for localization tasks than tones (Recanzone 2000). Three different positions were used: 30° to the left of the medio-sagittal plane, the medio-sagittal plane (0°) or 30° to the right of the medio-sagittal plane; the three positions were easily discriminated by all subjects. Sounds were elaborated using interaural level differences (ILD): a difference of 4 dB between left and right channels was used to create stimuli at 30° to the left or to the right. A sound without intensity difference between the two channels was used to create central stimuli. Sounds were created using Audacity 2.1.0 (http://audacity.sourceforge.net/). Positions of the stimuli were pseudo-randomized; each sound was presented 20 times. The inter-event intervals were jittered and lasted up to 20 s with a step of 1 s. The total task length was 6 min 44 s. During the task, subjects had to maintain their gaze straight-ahead by looking at a red cross in the center of the screen. Subjects were asked to press on a button with their right index when a target was detected. The task was developed using E-Prime 2.0 (Psychology Software Tools, Inc.).

Visual detection task

The visual task and corresponding fMRI and behavioral data came from our previous study (Crottaz-Herbette et al. 2014), however, the whole set of fMRI data were reprocessed in the same way as the newly acquired auditory detection task (see data analysis below). Visual stimuli were large white stars on a black background, presented for 500 ms in three different positions: in the midsagittal plane, at 20° to the right or 20° to the left. The positions of the stimuli were pseudo-randomized and each of them was presented 20 times. The jitter of inter-event intervals was up to 20 s with a step of 1 s. The duration of the task was 6 min 44 s. A red cross in the center of the screen helped subjects to maintain their gaze straight-ahead. Subjects pressed on a button with their right index when they detected a target. E-Prime 2.0 (Psychology Software Tools, Inc.) was used to develop the task.

Prismatic adaptation

Participants underwent a R-PA session outside the scanner. The adaptation consisted of 3 min (around 150 movements) of pointing with the right index to two black dots presented at a distance of 57 cm and 14° to the left or to the right of their midsagittal plane. Their head was positioned on a chinrest and the first two-thirds of the pointing trajectories were hidden from their sight. During these movements, all participants wore prisms (http://www.optiquepeter.com) that deviated the entire visual field 10° to the right (Rossetti et al. 1998; Redding et al. 2005; Rode et al. 2006; Pisella et al. 2006; Jacquin-Courtois et al. 2013; Crottaz-Herbette et al. 2014). The aftereffect was assessed immediately after the adaptation by measuring the pointing errors. Subjects fixated a dot without prisms, then closed their eyes and pointed to the dot. The pointing error was measured twice, for the left and the right dot. Negative values corresponded to a deviation of the pointings to the left of the targets. The pointing errors to both dots were averaged and compared across experimental groups using an unpaired *t* test.

Imaging data acquisition

MRI and event-related fMRI were acquired at the Lemanic Biomedical Imaging Center (CIBM) in the CHUV, Lausanne on a 3T Siemens Prisma scanner (auditory task) with a standard 20-channel head-coil and on a 3T Siemens Trio scanner (visual task) with a standard 32-channel head-coil. Functional MR images were acquired with a single-shot echo planar imaging gradient echo sequence (repetition time = 2 s; flip angle = 90°; echo time = 30 ms; number of slices = 32; voxel size = 2 × 2 × 3 mm (auditory task), 3 × 3 × 3 mm (visual task); 10% gap). The 32 slices, were acquired in a sequential ascending order, and covered the whole head volume in the AC-PC plane. A high-resolution T1-weighted 3D gradient echo sequence was acquired for each participant (240 slices (auditory task), 160 slices (visual task), voxel size = 1 × 1 × 1 mm). These T1 images were used for the co-registration with the functional images in the subsequent processing procedure.

Data analysis

Behavioral tasks

On behavioral data acquired during fMRI, mixed three-way ANOVAs were conducted on the mean accuracy and on the mean reaction times with Modality (auditory, visual) as a between-subjects factor; and Session (pre, post) and

Stimulus position (left, center, right) as within-subject factors. Analyses were processed using R (R Development Core Team 2008, Vienna, Austria).

fMRI data

Auditory and visual imaging data were processed using Statistical Parametric Mapping (SPM12, Wellcome Department of Cognitive Neurology, London, UK). Data were first corrected for motion by applying a six-parameter rigid-body transformation minimizing the difference between each image and the first scan. Slice timing correction was performed on these realigned images. For each participant, these functional images and the anatomical image were co-registered and then normalized to the Montreal Neurological Institute (MNI) template using the deformation field calculated by SMP12. Normalized functional images were resliced to a $2\times2\times2$ mm voxel size and anatomical images to a $1\times1\times1$ mm voxel size. These functional images were finally spatially smoothed to increase the signal-to-noise ratio using an isotropic Gaussian kernel of 6 mm FWHM. Statistics at the subject-level were done across the whole brain in a voxelwise manner. The general linear model was conducted using a canonical hemodynamic response. The six realignment parameters were included in the model as regressors. Linear contrasts were specified for the two sessions in the same design matrix.

In the second-level analysis, a mixed-design ANOVA was performed with the factor Modality (auditory, visual) as a between-subject factor and the factor Stimulus position (left, center, right) and Session (pre, post) as within-subject factors. From this ANOVA, the main effect of the factor Session allowed determining which regions are modulated by R-PA independently of the Modality or Stimulus position. The interaction between the factor Session and Stimulus position revealed where R-PA's effect varies with the change in stimulus position independently of the modality. Post hoc ANOVAs on the factor Stimulus position and Session were conducted separately for each modality. The statistical maps of activation for these analyses were thresholded at $p<0.05$ and cluster extent of $k=50$ (above the expected number of voxels per cluster as provided automatically by SPM12). The interaction between the factor Modality and Session revealed where the effect of R-PA is different between modalities, independently of the stimulus position. The statistical maps of activation for this analysis were thresholded at $p<0.05$ and cluster extent of $k=36$ (above the expected number of voxels per cluster as provided automatically by SPM12).

Regions of interest

The regions of interest (ROIs) analyses were conducted on the clusters of activation in the IPL in the interaction between the factor Stimulus position and Session. They were constructed as spheres with a 3 mm diameter.

Results

Behavioral data

The visuo-motor R-PA aftereffect, i.e., the pointing error after the removal of the prisms, was observed in the group performing the auditory ($M=-7.12°$, SD = 1.4°) and the visual paradigm ($M=-8.6°$, SD = 2.6°) and did not differ significantly between the groups, $t\,(23.5)=1.96$, $p=0.06$.

The accuracy and reaction times of the visual and of the auditory detection tasks performed during the fMRI paradigm were analyzed using mixed-design ANOVAs with the factor Modality (auditory, visual) as a between-subjects factor and the factors Stimulus position (left, center, right) and Session (pre, post) as within-subject factors (Table 1). Subjects showed high accuracy for all conditions, ranging between 90 and 100%. The ANOVA on accuracy data

Table 1 Behavioral results for the detection tasks. Mean and standard deviation (SD) for the accuracy and the reaction time (RT), by Session and Stimulus position

Pre					Post				
	Left	Center	Right	Mean		Left	Center	Right	Mean
Auditory					Auditory				
Mean RT (ms)	403.0	411.0	411.0	408.3	Mean RT (ms)	391.0	383.0	400.0	391.3
SD of RT	105.3	100.7	95.3	100.5	SD of RT	101.5	107.5	105.9	105.0
Mean accuracy (%)	98.9	97.5	99.3	98.6	Mean accuracy (%)	98.6	98.6	99.6	98.9
SD of accuracy	2.1	4.3	2.7	3.0	SD of accuracy	3.06	2.34	1.3	2.3
Visual					Visual				
Mean RT (ms)	408.0	400.0	405.0	404.3	Mean RT (ms)	424.0	409.0	420.0	417.7
SD of RT	54.8	53.3	49.3	52.5	SD of RT	71.2	55.4	56.4	61.0
Mean accuracy (%)	97.9	100.0	96.8	98.2	Mean accuracy (%)	99.3	98.9	99.6	99.3
SD of accuracy	3.8	0.0	6.1	3.3	SD of accuracy	1.8	2.9	1.3	20.0

showed a significant interaction between the factor Modality and Stimulus position [F (2, 52) = 4.202, p = 0.02], which was driven by a lower accuracy for right targets in the visual modality and for central targets in the auditory modality. The other interactions and all main effects were not significant.

For the reaction times, the ANOVA showed a significant main effect of the factor Stimulus position [F (2, 26) = 3.25, p = 0.047], subjects had shorter reaction times for central stimuli and longer reaction times for right stimuli. Results also showed a significant interaction between the factor Session and Modality [F (2, 52) = 4.609, p = 0.041]. This interaction was driven by longer reaction times after R-PA compared to before R-PA in the visual task, and vice-versa for the auditory task.

In summary, behavioral results confirmed that the tasks at hand were fit for the use of a spatiotopic analysis. First, both the auditory and the visual detection tasks were performed at a high level of accuracy, which was not modulated by R-PA. Second, although reaction times were modulated by R-PA, the effect did not differ in a given modality between the three positions.

Intervention-related changes in activation patterns

Activation patterns elicited by the target detection tasks were analyzed by a general mixed-design ANOVA including the between-subject factor Modality (auditory, visual) and the within-subject factor Stimulus position (left, center, right) and Session (pre, post). The following analyses addressed our specific hypotheses.

General impact of R-PA on spatial processing

The main effects of the factor Session (Fig. 1a) involved a large activation in the left angular gyrus and, to smaller extents, bilateral activations in the insula, supramarginal gyrus, superior temporal gyrus, and prefrontal regions; left activations in the cerebellum and right activations in the middle temporal gyrus and the precuneus. These effects did not depend on the modality or on the stimulus position.

Modulation of the representation of the ipsilateral space within IPL

The interaction between the factor Stimulus position and Session, independently of the modality, was significant in the left and right IPL, the left Heschl's gyrus, the right fusiform gyrus and to a smaller extent, in the middle frontal gyrus, precuneus and insula on both hemispheres (Fig. 1b; Table 2 for more details). ROIs analyses (Fig. 1c; Table 2) showed that within the left and right IPL, this interaction was driven by an increase in activation after R-PA when targets were on the left and center and a decrease in activation after R-PA when targets were on the right. Thus, R-PA induced greater activation for ipsilateral targets within the left hemisphere and a decrease in activation for ipsilateral targets in the right IPL, independently of the target modality.

Modality-specific effects of R-PA

Putative differences in the effect of R-PA on either modality were assessed by the interaction Modality × Session. No significant interaction was present in IPL on either side. Small significant clusters were observed in the left postcentral gyrus, insula and cerebellum, in the right middle temporal sulcus and bilaterally in the middle and inferior frontal gyri (Fig. 1d).

The modality-specific effect of R-PA was assessed for each modality with two-way ANOVAs including the within-subject factor Stimulus position (left, center, right) and Session (pre, post). In the left IPL, more precisely in the angular gyrus, the cluster showing a significant main effect of Session for the auditory modality overlapped with the cluster showing a significant main effect of Session for the visual modality (Fig. 2top, Table 3). In the right hemisphere, auditory and visual tasks also led to a main effect of Session in the IPL, but in the supramarginal gyrus. These activations in the right SMG in each modality were adjacent, not overlapping. In addition to the angular and supramarginal gyri, significant main effect of Session included in the auditory modality bilaterally prefrontal regions, the cerebellum, the precuneus and superior temporal gyri; the left inferior parietal lobule and postcentral gyrus and the right middle temporal gyrus; and in the visual modality bilaterally prefrontal regions, and the right middle temporal gyrus (Fig. 2top, Table 3).

The effect of R-PA on spatial representations in each modality was assessed in ROIs centered on peaks of activation in the IPL (for coordinates see Table 3). In the auditory modality, the increased activity observed on the left hemisphere and the decreased activity observed on the right hemisphere corresponded respectively to the enhancement of the representation of the left, central and right space within the left angular gyrus and to the decreased representation of the right space (and partially of the central and left space) in the right supramarginal gyrus (Fig. 2bottom part). Similarly, in the visual modality, the representation of the left, central and right space was enhanced within the left angular gyrus, whereas the representation of the right space decreased in the right supramarginal gyrus.

Post hoc analyses (t tests) on the activation related to the effect of R-PA on each stimulus position and on each modality separately confirmed these changes (Supplementary Information). In particular, surface renderings of the activation showed that R-PA yielded a significant increase in the representation of the left, central and right space within

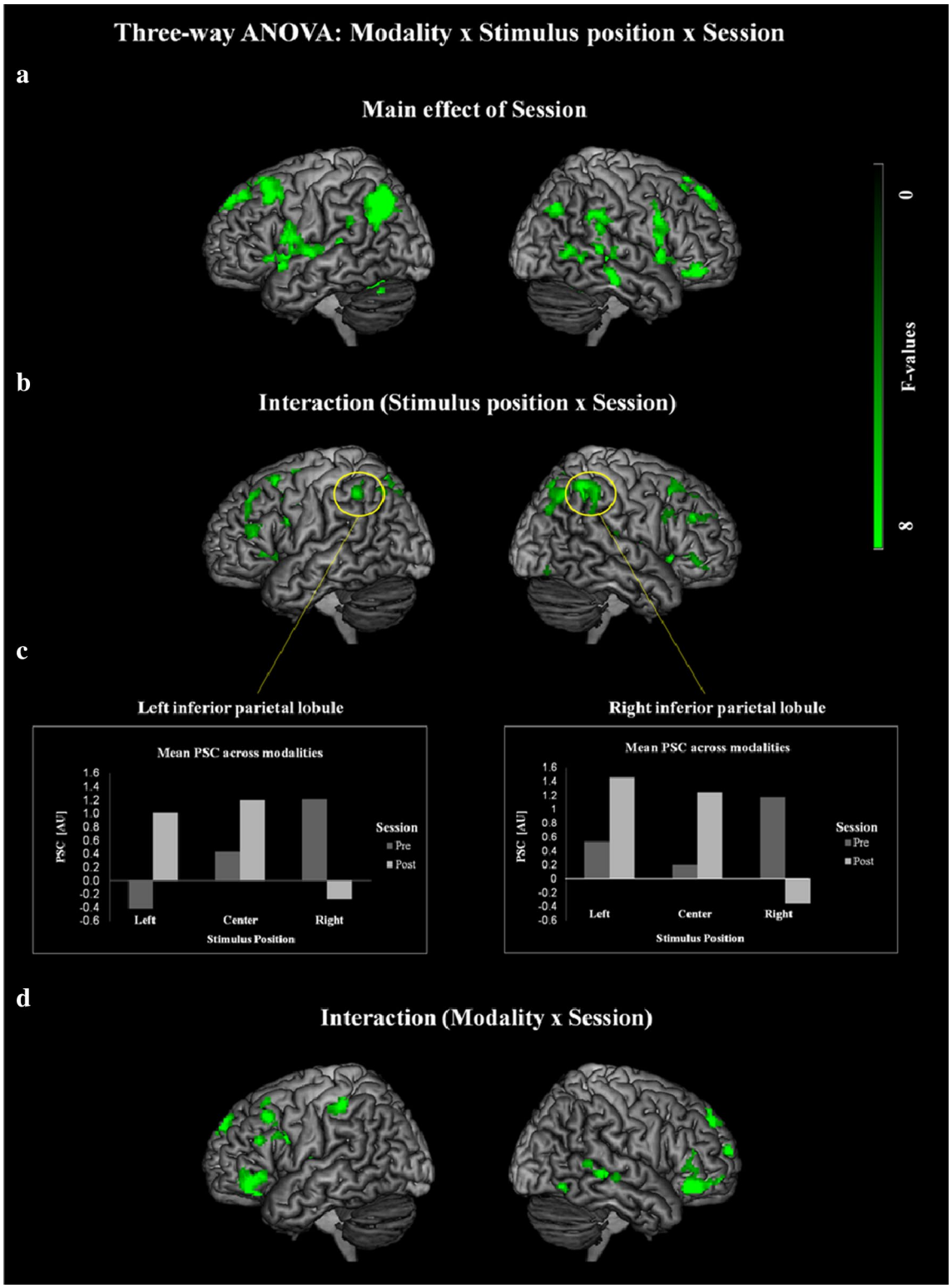

Fig. 1 Surface renderings of significant brain activations during the auditory and visual detection tasks in the mixed-design ANOVA, for **a** the main effect of Session, **b** the interaction Stimulus position × Session and **d** the interaction Modality × Session. **c** Barplots illustrating the percent signal changes (PSC) for the left (coordinates: −48/−46/46) and right IPL (coordinates: −42/−50/52) for both tasks at each stimulus position. All maps are thresholded at $p < 0.05$, $k = 50$

Table 2 Coordinates of the main clusters, listed in MNI atlas space with their local maxima and anatomical details of their extend, showing significant effects for the interaction (Stimulus position × Session) in the general ANOVA

Anatomical region	H	BA	MNI coordinates	Peak intensity	Nb of voxels
Interaction (Stimulus position × Session)					
Inferior parietal lobule, supramarginal gyrus	R	40	42/−50/52	8.83	501
Inferior parietal lobule	L	40	−48/−46/46	7.35	204
Middle frontal gyrus, superior frontal gyrus	R	8/9	32/18/46	7.33	135
Fusiform gyrus, lingual gyrus and middle occipital gyrus	R	37/18/19	32/−66/−12	5.51	152
Fusiform gyrus, parahippocampal gyrus	L	37	−36/−50/−16	5.83	50
Inferior frontal gyrus, middle frontal gyrus	L	45/46	−40/30/20	7.97	138
Insula, inferior frontal gyrus	R	13/14/47/45	36/20−4	7.44	104
Insula, inferior frontal gyrus	L	13/14/45/47	−38/22/0	6.63	129
Precuneus, superior and inferior parietal lobules, cuneus, superior occipital lobe	L	7/5/40/17	−6/−72/46	8.31	789
Precuneus, superior and inferior parietal lobules, angular gyrus, superior occipital lobe	R	7/5/40/39/17	4/−64/54	7.93	805
Hippocampus	R		28/−8/−20	12.55	76

the left IPL and a significant decrease of right space in the right IPL for the auditory modality. For the visual modality surface renderings of R-PA-related activation showed that R-PA yielded a significant increase in the representation of the left, central and right space within the left IPL and a significant decrease of right auditory space in the right IPL.

In summary, these results demonstrate that R-PA modulates within the right and left IPL not only visuo-spatial but also auditory spatial representations. Furthermore, they provide the following answers to our hypotheses. First, R-PA has an impact on visual and auditory attentional processing within the left and right IPL, as demonstrated by a massive main effect of Session, independently of the modality. Second, the significant interaction between the factor Stimulus position and Session, independently of the modality, confirmed that R-PA enhances the representation of the ipsilateral space within the left IPL and decreases it within the right IPL. Third, the modulation by R-PA within the IPL did not differ between the modalities, as indicated by the lack of significant interaction in the IPL between the factor Modality and Session. Fourth, R-PA-modulated spatial representations within the IPL in either modality, as demonstrated by modality-specific ANOVA analysis. In particular, in either modality, the representation of the left, central and right space increased in the left IPL, whereas the representation of the right space decreased in the right IPL.

Discussion

Our results demonstrate that a brief exposure to R-PA modulates the processing of auditory stimuli within the inferior parietal cortex. It enhances the involvement of the left angular gyrus in the detection of left, central and right targets and decreases the involvement of the right supramarginal gyrus for right targets. Thus, R-PA shifts hemispheric dominance for auditory spatial attention from the right to the left IPL. This effect of R-PA is similar to the previously described hemispheric shift for visuo-spatial attention (Crottaz-Herbette et al. 2014; Clarke and Crottaz-Herbette 2016).

The above described changes occur very rapidly, following a brief exposure to R-PA. The underlying neural mechanisms may, therefore, rely on pre-existing ipsilateral representations of the auditory space within the left hemisphere and on supramodal effects of PA. Furthermore, the R-PA-induced shift in hemispheric dominance for auditory spatial attention offers a parsimonious explanation for the previously reported effects on dichotic listening (Jacquin-Courtois et al. 2010; Tissieres et al. 2017) and auditory target detection in neglect (Eramudugolla et al. 2010).

Networks underlying auditory spatial representations and auditory attention

Studies in non-human primates indicate that auditory areas encode auditory space in a distributed fashion, without an orderly topographical map (Stecker et al. 2003, 2005; Harrington et al. 2008). Single neurons tend to have large receptive fields which are centered on locations within the contralateral space (Recanzone 2000; Stecker et al. 2003; Woods et al. 2006). Human auditory areas on the supratemporal plane are organized very similarly, but with hemispheric differences. FMRI studies reported preferential responses to contralateral locations with broad spatial tuning (Derey et al. 2016; McLaughlin et al. 2016). Activation patterns revealed greater bilaterality of responses on the right and stricter contralaterality on the left supratemporal side (Stecker et al. 2015).

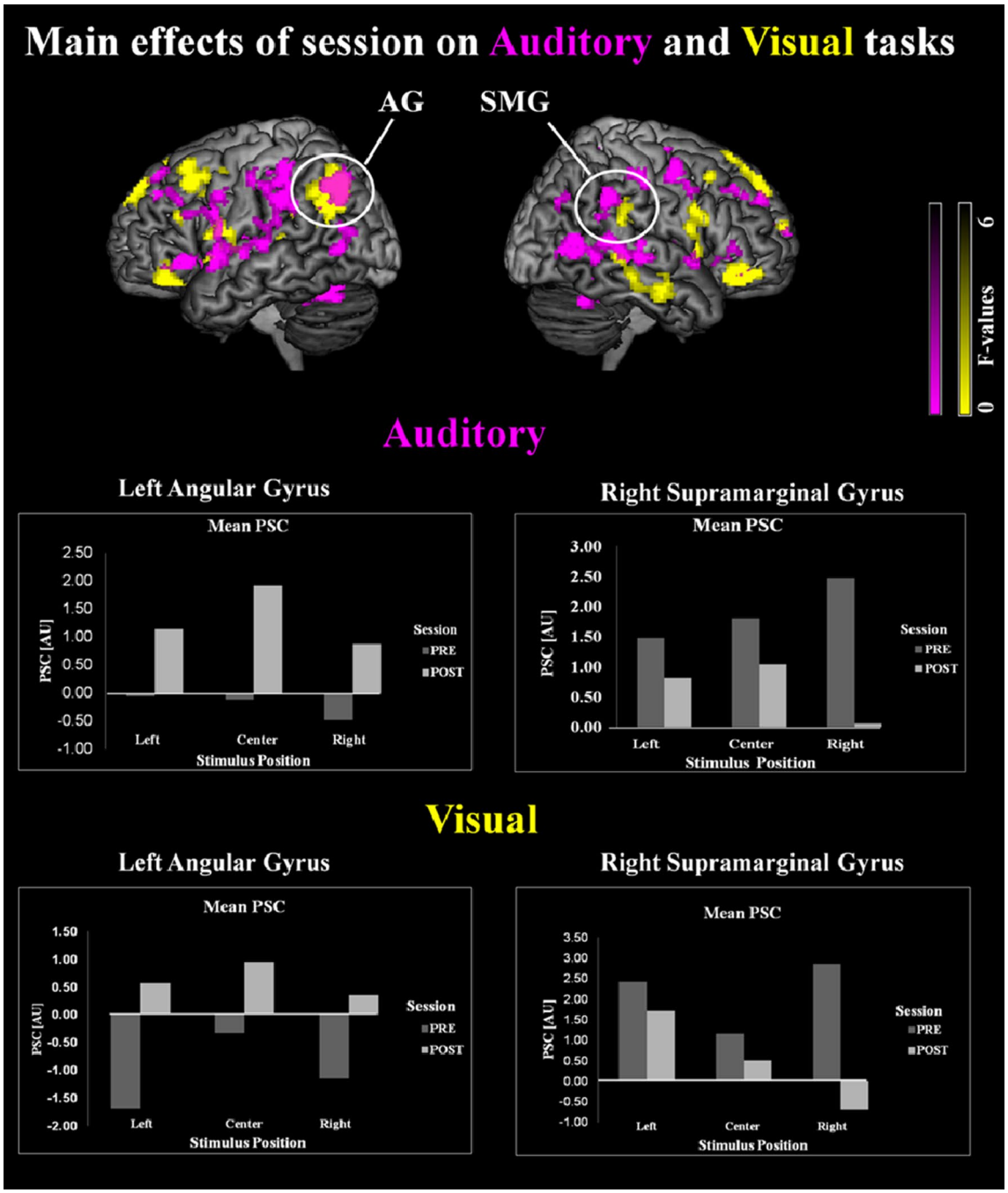

Fig. 2 Surface renderings of brain activations for the main effect of Session during the auditory and visual tasks separately (in the two-way ANOVA Stimulus position × Session). Activations for the auditory task in purple and for the visual task in yellow. Barplots illustrating the percent signal changes (PSC) in the left AG and right SMG for each task at each stimulus position. All maps are thresholded at $p < 0.05$, $k = 36$

The representation of the auditory space outside the supratemporal plane is largely asymmetrical, with a right-hemispheric dominance. A series of fMRI (Bushara et al. 1999; Maeder et al. 2001; Arnott et al. 2004; De Santis et al. 2007), magnetoencephalography (Kaiser et al. 2000), transcranial magnetic stimulation (At et al. 2011; Lewald and Getzmann 2011) and lesion studies (Spierer et al. 2009) reported the involvement of the right fronto-parietal cortex in the representation of the whole auditory space, whereas the left fronto-parietal cortex was focused on the contralateral, right space. Comparing activation patterns elicited by auditory stimuli in left, central or right failed to

Table 3 Main effect of Session for each Modality separately. Coordinates of the main clusters, listed in MNI atlas space with their local maxima and anatomical details of their extent, showing significant activation for the main effect of Session on the two-way ANOVAs

Anatomical region	H	BA	MNI coordinates	Peak intensity	Nb of voxels
Auditory task					
Angular gyrus: cluster extending to inferior parietal lobule, superior parietal lobule, precuneus	L	39/40/7	−44/−60/40	11.39	516
Angular gyrus	R	39	48/−74/32	7.47	36
Supramarginal gyrus: cluster extending to inferior parietal lobule	R	40	58/−42/34	13.45	179
Supramarginal gyrus: cluster extending to postcentral gyrus, superior temporal gyrus and inferior temporal gyrus	L	40/38/5	−62/−32/34	15.02	727
Visual task					
Angular gyrus: cluster extending to inferior parietal lobule, supramarginal gyrus, middle and superior temporal gyri	L	39/40/42	−44/−62/30	18.82	788
Supramarginal gyrus: cluster extending to inferior parietal lobule, superior temporal gyrus	R	40/42/21	60/−32/28	7.75	127

reveal topographic representations of the auditory space; however, stronger activation were reported by central auditory stimuli in the right IPL and by left stimuli in the posterior part of the left middle temporal gyrus (Zimmer et al. 2006).

Electrophysiological studies suggest two stages of auditory spatial processing; at short post-stimulus latencies, each hemispace appears to involve preferentially the contralateral temporoparietal cortex, while at latter latencies both hemispaces implicate the right parietal cortex, reflecting the right-hemispheric dominance for auditory spatial representation (Kaiser and Lutzenberger 2001; Tardif et al. 2006; De Santis et al. 2007; Spierer et al. 2009; At et al. 2011). Patterns of structural and functional connectivity further support this fronto-parietal asymmetry and the right-hemispheric dominance model for auditory spatial perception (Dietz et al. 2014; Cammoun et al. 2015).

Auditory spatial representations are malleable and can be modulated by auditory manipulations. In a behavioral study, subjects were exposed to long-term monaural distortions of the perceived spectrum, which lead to deficits in sound localization with subsequent recalibration of the percept (Wanrooij and Opstal 2005). A later imaging study demonstrated that behavioral recalibration due to shifted interaural time differences was associated with shifts of spatial representation within both hemispheres (Trapeau and Schönwiesner 2015).

The simultaneous presentation of auditory and visual stimuli at different locations can introduce a bias to the auditory spatial perception. Referred to as the ventriloquism effect, this phenomenon appears rapidly and can last for over 20 min (Recanzone 1998). EEG and fMRI studies reported changes in auditory spatial representations and highlighted the role of the left–right balance within the planum temporale as putative neural mechanism (Bonath et al. 2007, 2014).

The effect of R-PA is not the only example of supramodal effect of visuo-motor adaptation on auditory spatial functions. A previous behavioral study reported the effects of a visuo-motor adaptation through exposure to a rotated screen cursor–hand relationship. A brief exposure yielded visuo-motor and similar auditory-motor after effects. This adaptation effect did not require active cross-modal experience (Kagerer and Contreras-Vidal 2009).

Attending to auditory stimuli involves a wide range of regions in either hemisphere. Non-spatial auditory alertness was shown to rely on an extended, predominantly right-hemispheric network including frontal, cingular, inferior parietal, temporal and thalamic regions (Sturm et al. 2004). Comparing regions involved in auditory and in visual alertness revealed modality-specific regions within posterior parietal and frontal cortices; the only region involved in both modalities was the right superior temporal gyrus (Thiel and Fink 2007).

Auditory spatial attention was investigated with different paradigms, which highlighted the contribution of different neural networks. Selective attention to stimuli presented in one ear was found to activate the supplementary motor area, the left postcentral cortex and precentral regions bilaterally; in addition the superior temporal gyrus was activated, with a preference for attending to the contralateral ear (Tzourio et al. 1997; Alho et al. 1999). A later study reported an overall right-hemispheric dominance for auditory attention, which was modulated by eye position (Petit et al. 2007).

Selective attention to auditory or visual stimuli, which were presented in simultaneous streams, activated, in addition to the modality-specific cortices, overlapping regions in the inferior parietal cortex, more on the right than the left side (Salo et al. 2013). Smith and colleagues (Smith et al. 2010), with an orthogonal-cueing paradigm, investigated in a within-subject design the similarities between the patterns of activations for visual and auditory stimuli during a

spatial attentional task. Results showed that visual and auditory tasks recruit similar networks. The regions common to the two spatial tasks highlighted by their study are the supplementary motor area, the posterior parietal cortex and the frontal eye fields. The authors suggest that these three areas might be representative of a supramodal attentional network.

In summary, the above-quoted evidence shows that representation of the auditory space and auditory attention depends to a great extent on a right-dominant parieto-frontal network. There are, however, indications that the left hemisphere may comprise discrete representations of the ipsilateral auditory space. An fMRI study reported that the left middle temporal gyrus, but not the IPL was strongly activated by left-sided auditory stimuli (Zimmer et al. 2006). A later EEG study has shown that a left temporo-prefrontal network supported a position-linked representation of sound objects across the whole auditory space (Bourquin et al. 2013; Clarke and Geiser 2015). It is currently unclear, how far these left-hemispheric representations contribute to the effect of R-PA. Alternatively, the left-lateralized motor attentional system (Rushworth et al. 2001, 2003) may be at the origin of the bilateral spatial representation within the left IPL.

The supramodal effect of R-PA on auditory space representation is in line with the previously described examples of auditory–visual spatial interactions, such as the ventriloquism effect (e.g., Bonath et al. 2014, 2007; Recanzone 1998) or auditory-motor after effects following visuo-motor adaptation (Kagerer and Contreras-Vidal 2009).

Auditory neglect and rightward prismatic adaptation

Auditory neglect is characterized by impaired attention to left-sided stimuli. Most commonly, this is observed in paradigms where auditory stimuli are presented from the right and left side simultaneously, to either ear (dichotic listening: Heilman and Valenstein 1972; Hugdahl et al. 1991) or lateralized to the left or right space by means of interaural cues (diotic listening: Bellmann et al. 2001; Thiran and Clarke 2003; Spierer et al. 2007). Neglect phenomena have been also proposed to play a role in alloacousia, i.e., systematic left to right bias in sound localization (Bisiach et al. 1984). Left-sided extinction on dichotic or diotic listening and the distortion of auditory space perception can occur independently of each other and define most likely different types of auditory neglect (Bellmann et al. 2001; Thiran and Clarke 2003; Spierer et al. 2007).

Two previous studies demonstrated an effect of R-PA on auditory neglect. In both instances, the shift in hemispheric dominance for auditory spatial attention from the right to the left IPL, which we have described here, offers a parsimonious explanation of the underlying neural mechanisms. The ventral attentional system is known to be involved in the detection of unexpected stimuli, and therefore, in the reorienting of attention (Corbetta and Shulman 2002; Igelström and Graziano 2017; Shulman et al. 2003, 2010; Todd et al. 2005). In neglect, it is generally damaged and can no longer support the detection of targets (Corbetta and Shulman 2002). The shift of the ventral attentional system to left IPL is likely to restore the alerting input to the dorsal attentional system on either sides, both for auditory and visual targets (Crottaz-Herbette et al. 2014, 2017a; Clarke and Crottaz-Herbette 2016).

In the first study, R-PA was shown to improve overall performance on auditory target detection without, however, restoring the spatial gradient of attention (Eramudugolla et al. 2010). The overall improvement may be related to our observation that R-PA enhances left IPL activation by auditory stimuli independently of whether they occur in left, central or right space. Two other studies demonstrated R-PA-induced alleviation of left ear extinction on dichotic listening; this effect was specific to the detection asymmetry between the two ears and did not affect general arousal (Jacquin-Courtois et al. 2010; Tissieres et al. 2017). The side-specific effect in this study may be due to the nature of stimuli which were used. Both studies used a verbal dichotic listening paradigm, in which pairs of phonological similar bisyllabic words were presented and the task consisted in repeating the words. The repetition task depends critically on left-hemispheric speech networks. It is likely that the restoration of the left ear input to the left IPL had in this configuration a greater functional impact than the enhancement of the right ear input.

Direction-specific effects of PA

Several lines of evidence suggest that partially different neural mechanisms underlie the effects of R-PA and L-PA. R-PA was shown to induce a shift in hemispheric dominance of the ventral attentional system from the right to the left hemisphere in the visual modality, both in normal subjects and in neglect patients (Crottaz-Herbette et al. 2014, 2017a), and in the auditory modality (here). This shift offers a parsimonious explanation of behavioral effects of R-PA. In normal subjects, only few such changes were reported and they can be attributed to the changes in information flow between early-stage visual areas and the right and left IPL (for detailed discussion see (Clarke and Crottaz-Herbette 2016): (1) the rightward shift in visual midpoint judgments in extrapersonal, but not in peripersonal space (Berberovic and Mattingley 2003); speeding of exogeneous reorienting of attention from invalid cues for targets on the right side (Striemer et al. 2006); and (2) the modulation of oculomotor performance in a double-step saccade paradigm (Bultitude et al. 2013). In neglect, R-PA was reported to reduce the

visuo-spatial bias in tasks which involve the dorsal attentional system (Striemer and Danckert 2010); this effect is likely to be mediated by the left IPL, which after R-PA relays stimulus-driven input to the right dorsal attentional system (for detailed discussion see Clarke and Crottaz-Herbette 2016). R-PA was also found to alleviate left ear extinction in dichotic listening tasks (Jacquin-Courtois et al. 2010; Tissieres et al. 2017). The shift of left auditory space representation to the left IPL offers a likely explanation for this effect.

L-PA was shown to strengthen right-hemispheric dominance of the ventral attentional system by enhancing the representation of the right visual space within the right IPL (Crottaz-Herbette et al. 2017b). The resulting overemphasis of the right visual space within the right IPL offers a parsimonious explanation of neglect-like effects induced by L-PA in normal subject performances (Colent et al. 2000; Martín-Arévalo et al. 2016; Crottaz-Herbette et al. 2017b).

Conclusions

A brief exposure to R-PA modulated the representation of the auditory and of the visual space within the ventral attentional system by enhancing, in either modality, the representation of the left, central and right space in the left IPL, and reducing the representation of the right space in the right IPL. The effect of R-PA occurred very rapidly and may, therefore, rely on pre-existing ipsilateral spatial representations within the left hemisphere. Previous studies suggest that discrete parts of the left hemisphere may encode ipsilateral auditory space. The left middle temporal gyrus, but not the IPL, was reported to be strongly activated by left-sided auditory stimuli (Zimmer et al. 2006). A left temporo-prefrontal network was shown to support a position-linked representation of sound objects across the whole auditory space (Bourquin et al. 2013; Clarke and Geiser 2015). Alternatively, the bilateral spatial representations within the left IPL may be related to the left-lateralized motor attentional system (Rushworth et al. 2001, 2003).

The modulation of auditory spatial representations by R-PA is a further example of auditory–visual interactions, such as those involved in the ventriloquism effect (e.g., Bonath et al. 2014, 2007; Recanzone 1998) or auditory-motor after effects following visuo-motor adaptation (Kagerer and Contreras-Vidal 2009).

The shift in hemispheric dominance for auditory spatial attention from the right to the left IPL offers a parsimonious explanation for the effect of R-PA on dichotic listening and target detection in neglect (Jacquin-Courtois et al. 2010; Eramudugolla et al. 2010). It is currently unknown, whether R-PA affects similarly other auditory symptoms of neglect, such as the shift in auditory spatial attention and alloacousia.

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Compliance with ethical standards

Conflict of interest The authors reported no conflict of interest.

References

Alho K, Medvedev SV, Pakhomov SV et al (1999) Selective tuning of the left and right auditory cortices during spatially directed attention. Cogn Brain Res 7:335–341. https://doi.org/10.1016/S0926-6410(98)00036-6

Arnott SR, Binns MA, Grady CL, Alain C (2004) Assessing the auditory dual-pathway model in humans. NeuroImage 22:401–408. https://doi.org/10.1016/j.neuroimage.2004.01.014

At A, Spierer L, Clarke S (2011) The role of the right parietal cortex in sound localization: a chronometric single pulse transcranial magnetic stimulation study. Neuropsychologia 49:2794–2797. https://doi.org/10.1016/j.neuropsychologia.2011.05.024

Bellmann A, Meuli R, Clarke S (2001) Two types of auditory neglect. Brain J Neurol 124:676–687

Berberovic N, Mattingley JB (2003) Effects of prismatic adaptation on judgements of spatial extent in peripersonal and extrapersonal space. Neuropsychologia 41:493–503. https://doi.org/10.1016/S0028-3932(02)00090-8

Bisiach E, Cornacchia L, Sterzi R, Vallar G (1984) Disorders of perceived auditory lateralization after lesions of the right hemisphere. Brain J Neurol 107(Pt 1):37–52

Bonath B, Noesselt T, Martinez A et al (2007) Neural basis of the ventriloquist illusion. Curr Biol 17:1697–1703. https://doi.org/10.1016/j.cub.2007.08.050

Bonath B, Noesselt T, Krauel K et al (2014) Audio-visual synchrony modulates the ventriloquist illusion and its neural/spatial representation in the auditory cortex. NeuroImage 98:425–434. https://doi.org/10.1016/j.neuroimage.2014.04.077

Bourquin NM-P, Murray MM, Clarke S (2013) Location-independent and location-linked representations of sound objects. NeuroImage 73:40–49. https://doi.org/10.1016/j.neuroimage.2013.01.026

Brunetti M, Belardinelli P, Caulo M et al (2005) Human brain activation during passive listening to sounds from different locations: an fMRI and MEG study. Hum Brain Mapp 26:251–261. https://doi.org/10.1002/hbm.20164

Bultitude JH, Van der Stigchel S, Nijboer TCW (2013) Prism adaptation alters spatial remapping in healthy individuals: evidence from double-step saccades. Cortex 49:759–770. https://doi.org/10.1016/j.cortex.2012.01.008

Bushara KO, Weeks RA, Ishii K et al (1999) Modality-specific frontal and parietal areas for auditory and visual spatial localization in humans. Nat Neurosci 2:759–766. https://doi.org/10.1038/11239

Cammoun L, Thiran JP, Griffa A et al (2015) Intrahemispheric cortico-cortical connections of the human auditory cortex. Brain Struct Funct 220:3537–3553. https://doi.org/10.1007/s00429-014-0872-z

Chapman HL, Eramudugolla R, Gavrilescu M et al (2010) Neural mechanisms underlying spatial realignment during adaptation to optical wedge prisms. Neuropsychologia 48:2595–2601. https://doi.org/10.1016/j.neuropsychologia.2010.05.006

Clarke S, Crottaz-Herbette S (2016) Modulation of visual attention by prismatic adaptation. Neuropsychologia 92:31–41. https://doi.org/10.1016/j.neuropsychologia.2016.06.022

Clarke S, Geiser E (2015) Roaring lions and chirruping lemurs: how the brain encodes sound objects in space. Neuropsychologia 75:304–313. https://doi.org/10.1016/j.neuropsychologia.2015.06.012

Clarke S, Bellmann A, Meuli RA et al (2000) Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. Neuropsychologia 38:797–807. https://doi.org/10.1016/S0028-3932(99)00141-4

Clower DM, Hoffman JM, Votaw JR et al (1996) Role of posterior parietal cortex in the recalibration of visually guided reaching. Nature 383:618–621. https://doi.org/10.1038/383618a0

Colent C, Pisella L, Bernieri C et al (2000) Cognitive bias induced by visuo-motor adaptation to prisms: a simulation of unilateral neglect in normal individuals? NeuroReport 11:1899

Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215. https://doi.org/10.1038/nrn755

Crottaz-Herbette S, Fornari E, Clarke S (2014) Prismatic adaptation changes visuospatial representation in the inferior parietal lobule. J Neurosci 34:11803–11811. https://doi.org/10.1523/JNEUROSCI.3184-13.2014

Crottaz-Herbette S, Fornari E, Notter MP et al (2017a) Reshaping the brain after stroke: the effect of prismatic adaptation in patients with right brain damage. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2017.08.005

Crottaz-Herbette S, Fornari E, Tissieres I, Clarke S (2017b) A brief exposure to leftward prismatic adaptation enhances the representation of the ipsilateral, right visual field in the right inferior parietal lobule. eNeuro ENEURO.0310–17.2017. https://doi.org/10.1523/ENEURO.0310-17.2017

Danckert J, Ferber S, Goodale MA (2008) Direct effects of prismatic lenses on visuomotor control: an event-related functional MRI study. Eur J Neurosci 28:1696–1704. https://doi.org/10.1111/j.1460-9568.2008.06460.x

De Santis L, Clarke S, Murray MM (2007) Automatic and intrinsic auditory "what" and "where" processing in humans revealed by electrical neuroimaging. Cereb Cortex 17:9–17. https://doi.org/10.1093/cercor/bhj119

Deouell LY, Heller AS, Malach R et al (2007) Cerebral responses to change in spatial location of unattended sounds. Neuron 55:985–996. https://doi.org/10.1016/j.neuron.2007.08.019

Derey K, Valente G, de Gelder B, Formisano E (2016) Opponent coding of sound location (azimuth) in planum temporale is robust to sound-level variations. Cereb Cortex N Y 26:450–464. https://doi.org/10.1093/cercor/bhv269

Dietz MJ, Friston KJ, Mattingley JB et al (2014) Effective connectivity reveals right-hemisphere dominance in audiospatial perception: implications for models of spatial neglect. J Neurosci 34:5003–5011. https://doi.org/10.1523/JNEUROSCI.3765-13.2014

Eramudugolla R, Boyce A, Irvine DRF, Mattingley JB (2010) Effects of prismatic adaptation on spatial gradients in unilateral neglect: a comparison of visual and auditory target detection with central attentional load. Neuropsychologia 48:2681–2692. https://doi.org/10.1016/j.neuropsychologia.2010.05.015

Fortis P, Goedert KM, Barrett AM (2011) Prism adaptation differently affects motor-intentional and perceptual-attentional biases in healthy individuals. Neuropsychologia 49:2718–2727. https://doi.org/10.1016/j.neuropsychologia.2011.05.020

Häkkinen S, Ovaska N, Rinne T (2015) Processing of pitch and location in human auditory cortex during visual and auditory tasks. Front Psychol 6. https://doi.org/10.3389/fpsyg.2015.01678

Harrington IA, Stecker GC, Macpherson EA, Middlebrooks JC (2008) Spatial sensitivity of neurons in the anterior, posterior, and primary fields of cat auditory cortex. Hear Res 240:22–41. https://doi.org/10.1016/j.heares.2008.02.004

Heilman KM, Valenstein E (1972) Auditory neglect in man. Arch Neurol 26:32–35. https://doi.org/10.1001/archneur.1972.00490070050007

Hugdahl K, Wester K, Asbjørnsen A (1991) Auditory neglect after right frontal lobe and right pulvinar thalamic lesions. Brain Lang 41:465–473. https://doi.org/10.1016/0093-934X(91)90167-Y

Igelström KM, Graziano MSA (2017) The inferior parietal lobule and temporoparietal junction: a network perspective. Neuropsychologia. https://doi.org/10.1016/j.neuropsychologia.2017.01.001

Itoh K, Yumoto M, Uno A et al (2000) Temporal stream of cortical representation for auditory spatial localization in human hemispheres. Neurosci Lett 292:215–219. https://doi.org/10.1016/S0304-3940(00)01465-8

Jacquin-Courtois S, Rode G, Pavani F et al (2010) Effect of prism adaptation on left dichotic listening deficit in neglect patients: glasses to hear better? Brain 133:895–908. https://doi.org/10.1093/brain/awp327

Jacquin-Courtois S, O'Shea J, Luauté J et al (2013) Rehabilitation of spatial neglect by prism adaptation: a peculiar expansion of sensorimotor after-effects to spatial cognition. Neurosci Biobehav Rev 37:594–609. https://doi.org/10.1016/j.neubiorev.2013.02.007

Kagerer FA, Contreras-Vidal JL (2009) Adaptation of sound localization induced by rotated visual feedback in reaching movements. Exp Brain Res 193:315–321. https://doi.org/10.1007/s00221-008-1630-3

Kaiser J, Lutzenberger W (2001) Location changes enhance hemispheric asymmetry of magnetic fields evoked by lateralized sounds in humans. Neurosci Lett 314:17–20. https://doi.org/10.1016/S0304-3940(01)02248-0

Kaiser J, Lutzenberger W, Preissl H et al (2000) Right-hemisphere dominance for the processing of sound-source lateralization. J Neurosci Off J Soc Neurosci 20:6631–6639

Küper M, Wünnemann MJS, Thürling M et al (2014) Activation of the cerebellar cortex and the dentate nucleus in a prism adaptation fMRI study. Hum Brain Mapp 35:1574–1586. https://doi.org/10.1002/hbm.22274

Lewald J, Getzmann S (2011) When and where of auditory spatial processing in cortex: a novel approach using electrotomography. PLoS One 6:e25146. https://doi.org/10.1371/journal.pone.0025146

Lewald J, Foltys H, Töpper R (2002) Role of the posterior parietal cortex in spatial hearing. J Neurosci Off J Soc Neurosci 22:RC207

Luauté J, Schwartz S, Rossetti Y et al (2009) Dynamic changes in brain activity during prism adaptation. J Neurosci Off J Soc Neurosci 29:169–178. https://doi.org/10.1523/JNEUROSCI.3054-08.2009

Maeder PP, Meuli RA, Adriani M et al (2001) Distinct pathways involved in sound recognition and localization: a human fMRI study. NeuroImage 14:802–816. https://doi.org/10.1006/nimg.2001.0888

Martín-Arévalo E, Schintu S, Farnè A et al (2016) Adaptation to leftward shifting prisms alters motor interhemispheric inhibition. Cereb Cortex. https://doi.org/10.1093/cercor/bhw386

McLaughlin SA, Higgins NC, Stecker GC (2016) Tuning to binaural cues in human auditory cortex. J Assoc Res Otolaryngol 17:37–53. https://doi.org/10.1007/s10162-015-0546-4

Michel C (2003) Simulating unilateral neglect in normals using prism adaptation: implications for theory. ScienceDirect. http://www.sciencedirect.com/science/article/pii/S0028393202001355. Accessed 9 Nov 2017

Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113

Petit L, Simon G, Joliot M et al (2007) Right hemisphere dominance for auditory attention and its modulation by eye position: an event related fMRI study. Restor Neurol Neurosci 25:211–225

Pisella L, Rode G, Farnè A et al (2006) Prism adaptation in the rehabilitation of patients with visuo-spatial cognitive disorders. Curr Opin Neurol 19:534–542. https://doi.org/10.1097/WCO.0b013e328010924b

Recanzone GH (1998) Rapidly induced auditory plasticity: the ventriloquism aftereffect. Proc Natl Acad Sci 95:869–875

Recanzone GH (2000) Spatial processing in the auditory cortex of the macaque monkey. Proc Natl Acad Sci 97:11829–11835. https://doi.org/10.1073/pnas.97.22.11829

Redding GM, Wallace B (2006) Prism adaptation and unilateral neglect: review and analysis. Neuropsychologia 44:1–20. https://doi.org/10.1016/j.neuropsychologia.2005.04.009

Redding GM, Rossetti Y, Wallace B (2005) Applications of prism adaptation: a tutorial in theory and method. Neurosci Biobehav Rev 29:431–444. https://doi.org/10.1016/j.neubiorev.2004.12.004

Rode G, Klos T, Courtois-Jacquin S et al (2006) Neglect and prism adaptation: a new therapeutic tool for spatial cognition disorders. Restor Neurol Neurosci 24:347–356

Rode G, Revol P, Rossetti Y et al (2007) Looking while imagining: the influence of visual input on representational neglect. Neurology 68:432–437. https://doi.org/10.1212/01.wnl.0000252936.54063.b0

Rossetti Y, Rode G, Pisella L et al (1998) Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 395:166–169. https://doi.org/10.1038/25988

Rushworth MFS, Krams M, Passingham RE (2001) The attentional role of the left parietal cortex: the distinct lateralization and localization of motor attention in the human brain. J Cogn Neurosci 13:698–710. https://doi.org/10.1162/089892901750363244

Rushworth MFS, Johansen-Berg H, Göbel SM, Devlin JT (2003) The left parietal and premotor cortices: motor attention and selection. NeuroImage 20(Suppl 1):S89–S100. https://doi.org/10.1016/j.neuroimage.2003.09.011

Salo E, Rinne T, Salonen O, Alho K (2013) Brain activity during auditory and visual phonological, spatial and simple discrimination tasks. Brain Res 1496:55–69. https://doi.org/10.1016/j.brainres.2012.12.013

Shulman GL, McAvoy MP, Cowan MC et al (2003) Quantitative analysis of attention and detection signals during visual search. J Neurophysiol 90:3384–3397. https://doi.org/10.1152/jn.00343.2003

Shulman GL, Pope DLW, Astafiev SV et al (2010) Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. J Neurosci 30:3640–3651. https://doi.org/10.1523/JNEUROSCI.4085-09.2010

Smith DV, Davis B, Niu K et al (2010) Spatial attention evokes similar activation patterns for visual and auditory stimuli. J Cogn Neurosci 22:347–361. https://doi.org/10.1162/jocn.2009.21241

Spierer L, Meuli R, Clarke S (2007) Extinction of auditory stimuli in hemineglect: space versus ear. Neuropsychologia 45:540–551. https://doi.org/10.1016/j.neuropsychologia.2006.04.012

Spierer L, Murray MM, Tardif E, Clarke S (2008) The path to success in auditory spatial discrimination: electrical neuroimaging responses within the supratemporal plane predict performance outcome. NeuroImage 41:493–503. https://doi.org/10.1016/j.neuroimage.2008.02.038

Spierer L, Bellmann-Thiran A, Maeder P et al (2009) Hemispheric competence for auditory spatial representation. Brain 132:1953–1966. https://doi.org/10.1093/brain/awp127

Stecker GC, Mickey BJ, Macpherson EA, Middlebrooks JC (2003) Spatial sensitivity in field PAF of cat auditory cortex. J Neurophysiol 89:2889–2903. https://doi.org/10.1152/jn.00980.2002

Stecker GC, Harrington IA, Middlebrooks JC (2005) Location coding by opponent neural populations in the auditory cortex. PLoS Biol 3:e78. https://doi.org/10.1371/journal.pbio.0030078

Stecker GC, McLaughlin SA, Higgins NC (2015) Monaural and binaural contributions to interaural-level-difference sensitivity in human auditory cortex. NeuroImage 120:456–466. https://doi.org/10.1016/j.neuroimage.2015.07.007

Striemer CL, Danckert J (2010) Dissociating perceptual and motor effects of prism adaptation in neglect. Neuroreport 21:436–441. https://doi.org/10.1097/WNR.0b013e328338592f

Striemer C, Sablatnig J, Danckert J (2006) Differential influences of prism adaptation on reflexive and voluntary covert attention. J Int Neuropsychol Soc 12:337–349. https://doi.org/10.1017/S1355617706060553

Sturm W, Longoni F, Fimm B et al (2004) Network for auditory intrinsic alertness: a PET study. Neuropsychologia 42:563–568. https://doi.org/10.1016/j.neuropsychologia.2003.11.004

Tanaka H, Hachisuka K, Ogata H (1999) Sound lateralisation in patients with left or right cerebral hemispheric lesions: relation with unilateral visuospatial neglect. J Neurol Neurosurg Psychiatry 67:481–486

Tardif E, Murray MM, Meylan R et al (2006) The spatio-temporal brain dynamics of processing and integrating sound localization cues in humans. Brain Res 1092:161–176. https://doi.org/10.1016/j.brainres.2006.03.095

Thiel CM, Fink GR (2007) Visual and auditory alertness: modality-specific and supramodal neural mechanisms and their modulation by nicotine. J Neurophysiol 97:2758–2768. https://doi.org/10.1152/jn.00017.2007

Thiran AB, Clarke S (2003) Preserved use of spatial cues for sound segregation in a case of spatial deafness. Neuropsychologia 41:1254–1261. https://doi.org/10.1016/S0028-3932(03)00014-9

Tissieres I, Elamly M, Clarke S, Crottaz-Herbette S (2017) For better or worse: the effect of prismatic adaptation on auditory neglect. In: Neural plast. https://www.hindawi.com/journals/np/2017/8721240/abs/. Accessed 1 Nov 2017

Todd JJ, Fougnie D, Marois R (2005) Visual short-term memory load suppresses temporo-parietal junction activity and induces inattentional blindness. Psychol Sci 16:965–972. https://doi.org/10.1111/j.1467-9280.2005.01645.x

Trapeau R, Schönwiesner M (2015) Adaptation to shifted interaural time differences changes encoding of sound location in human auditory cortex. NeuroImage 118:26–38. https://doi.org/10.1016/j.neuroimage.2015.06.006

Tzourio N, El Massioui F, Crivello F et al (1997) Functional anatomy of human auditory attention studied with PET. NeuroImage 5:63–77. https://doi.org/10.1006/nimg.1996.0252

Wanrooij MMV, Opstal AJV (2005) Relearning sound localization with a new ear. J Neurosci 25:5413–5424. https://doi.org/10.1523/JNEUROSCI.0850-05.2005

Woods TM, Lopez SE, Long JH et al (2006) Effects of stimulus azimuth and intensity on the single-neuron activity in the auditory cortex of the alert macaque monkey. J Neurophysiol 96:3323–3337. https://doi.org/10.1152/jn.00392.2006

Yang NYH, Zhou D, Chung RCK et al (2013) Rehabilitation interventions for unilateral neglect after stroke: a systematic review from 1997 through 2012. Front Hum Neurosci 7:187. https://doi.org/10.3389/fnhum.2013.00187

Zimmer U, Lewald J, Erb M, Karnath H-O (2006) Processing of auditory spatial cues in human cortex: an fMRI study. Neuropsychologia 44:454–461. https://doi.org/10.1016/j.neuropsychologia.2005.05.021

Cognition and Behavior

A Brief Exposure to Leftward Prismatic Adaptation Enhances the Representation of the Ipsilateral, Right Visual Field in the Right Inferior Parietal Lobule

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Abstract

A brief exposure to rightward prismatic adaptation (PA) was shown to shift visual field representation within the inferior parietal lobule (IPL) from the right to the left hemisphere. This change in hemispheric dominance could be interpreted as (1) a general effect of discrepancy in visuomotor alignment caused by PA or (2) a direction-specific effect of rightward PA. To test these hypotheses, we compared the effects of rightward and leftward PA on visual representation in normal human subjects. Three groups of normal subjects underwent an fMRI evaluation using a simple visual detection task before and after brief PA exposure using leftward- or rightward-deviating prisms or no prisms (L-PA, R-PA, neutral groups). A two-way ANOVA group × session revealed a significant interaction suggesting that PA-induced modulation is direction specific. *Post hoc* analysis showed that L-PA enhanced the representation of the right visual field within the right IPL. Thus, a brief exposure to L-PA enhanced right hemispheric dominance within the ventral attentional system, which is the opposite effect of the previously described shift in hemispheric dominance following R-PA. The direction-specific effects suggest that the underlying neural mechanisms involve the fine-tuning of specific visuomotor networks. The enhancement of right hemispheric dominance following L-PA offers a parsimonious explanation for neglect-like symptoms described previously in normal subjects.

Key words: fMRI; inferior parietal lobule; prismatic adaptation; visual field

Significance Statement

Leftward-deviating prisms (L-PA) increased the representation of the right visual field within the right inferior parietal lobule (IPL). This enhancement of the right hemispheric dominance within the ventral attentional system contradicts the dominance shift, from right to left hemisphere, which is induced by rightward-deviating prisms (R-PA). Thus, the PA-induced modulation of hemispheric dominance within the ventral attentional system is sensitive to the direction of prismatic deviation and is likely to depend on fine-tuning of specific visuomotor networks. The overemphasis of right visual field representation within the (right) ventral attentional system offers a parsimonious explanation for neglect-like effects following L-PA.

Introduction

Prismatic adaptation (PA) consists of a brief session during which subjects point to targets under visual control while wearing goggles with prisms that deviate the visual field to the right or to the left. First pointings are characterized by errors that disappear after 10–15 trials. The adaptation is typically measured once the prisms are removed by the so-called "aftereffect" that corresponds

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to the pointing errors opposite to the deviation and that reflects the prism-induced sensorimotor realignment (Weiner et al., 1983). Adaptation to rightward-deviating prisms (R-PA) yields a systematic leftward deviation of visuomotor and proprioceptive responses, whereas adaptation to leftward-deviating prisms (L-PA) yields a systematic rightward deviation (Rossetti et al., 1998; Redding et al., 2005; Jacquin-Courtois et al., 2013).

The neural processes underlying ongoing PA have been studied in normal subjects during different stages of PA. These studies showed primary activation within the parieto-temporal cortex and the cerebellum, suggesting a visual and proprioceptive spatial realignment during L-PA (Luauté et al., 2009; Chapman et al., 2010) and R-PA (Danckert et al., 2008); alternating L-PA and R-PA was used in an early study and provided evidence for the involvement of parietal cortex in adaptation (Clower et al., 1996). The effects after the adaptation have been investigated in normal subjects using rightward deviating prisms (Crottaz-Herbette et al., 2014). By comparing task-related activations acquired pre and post-PA, this study showed that R-PA bilaterally modulated the activation in the inferior parietal lobule (IPL) during visual target detection by increasing the representation of left, central, and right visual fields in the left IPL and by decreasing the representation of right and central visual fields in the right IPL. Thus, R-PA shifted hemispheric dominance for visuospatial representation within the ventral attentional system from the right to the left hemisphere; this shift is most likely one of the key mechanisms which underlies therapeutic effect of R-PA in neglect (Clarke and Crottaz-Herbette, 2016).

This rapid change in hemispheric dominance could be interpreted in two different ways. First, it may be induced by any discrepancy in sensorimotor realignment, possibly by uncovering pre-existing bilateral visual representations within the left IPL (de Haan et al., 2015) or by tapping into the left-dominant motor attentional system (Rushworth et al., 2001, 2003). If this is the case, then adaptations to leftward or rightward prisms should lead to similar modulations of the ventral attentional system with an increased activation of the left IPL and a decreased activation of the right IPL during a visual detection task after both adaptations. Second, the change in hemispheric dominance may be specific to the direction of PA, suggesting that fine-tuning of visuospatial representations in response to specific visuomotor adaptation plays a critical role. In the case of direction specificity, L-PA could be expected to yield the opposite effect to R-PA, namely, to increase activation in the right IPL in response to ipsilateral, right targets. If present, the effect of L-PA may offer a highly interesting therapeutic option for the treatment of attentional disorders, which can occur in left hemispheric stroke (Murakami et al., 2014). To test the two hypotheses, we compared the effects of L-PA and R-PA on visual representation. The current study involved three groups of normal subjects who underwent functional MRI during a simple visual detection task before and after a brief adaptation session wearing leftward- or rightward-deviating prisms or plain glasses (L-PA, R-PA, neutral groups).

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Materials and Methods

Participants

Forty-two participants were included in this study, with 14 participants (seven men, mean age = 24.1, SD = 3.0 years) undergoing L-PA, 14 participants (seven men, mean age = 26.0 years, SD = 5.0 years) undergoing R-PA, and 14 participants (seven men, mean age = 25.8 years, SD = 5.1 years) in the control group (neutral). A one-way ANOVA comparing the mean age between the three groups did not show a significant difference between the groups ($F_{(2,39)} = 0.85$, $p = 0.44$). All participants were right handed (Oldfield, 1971) and had a normal or corrected-to-normal vision. None of the subjects had a neurological or psychiatric illnesses. All participants gave written informed consent according to procedures approved by the Ethics Committee of the Faculty of Biology and Medicine, University of Lausanne.

Experimental design

The same procedure was used for the L-PA, R-PA, and neutral groups, comprising two MRI blocks that were separated by an intervention using visuomotor adaptation. MRI blocks consisted of anatomical sequences (only before the adaptation) and event-related fMRI acquisitions (before and after the adaptation). The R-PA and neutral groups did two other tasks that were analyzed elsewhere (Crottaz-Herbette et al., 2014). The delay between the adaptation and the detection task was the same for the three groups.

Visual detection task

During the fMRI acquisitions, all participants had to press the response button when they detected a large white star on black background. These visual stimuli were presented for 500 ms in three different locations: in the midsagittal plane, at 20° to the right or 20° to the left. The locations were pseudorandomized and each location was presented 20 times. The interevent intervals were jittered, between 1 and 20 s with steps of 1 s. During this task, participants were asked to fixate on a central fixation point. Participants responded by pressing a button with their right hand as soon as they detected the visual stimulus. The tasks were programmed using the software E-Prime (Psychology Software Tools). The duration of the task was 6 min 44 s.

Visuomotor adaptation

The visuomotor adaptation was performed outside the scanner and consisted of pointing with the one index finger to visual targets presented 14° to the left or to the right of the midsagittal plane. The prisms (www.optiquepeter.com) deviated the visual field 10° to the left for the L-PA group and to the right for the R-PA group (Rossetti et al., 1998; Redding et al., 2005; Rode et al., 2006); goggles without deviation were used for the neutral group. During the pointing movements, participants in the R-PA and neutral groups used their right index finger whereas participants in the L-PA group used their left index finger. With the exception of the hand used during the adaptation, the procedure for PA, including the positioning of the participants, was similar across our three groups.

The choice of the left hand for pointing in the L-PA group was motivated by putative clinical implications. If L-PA enhances right hemispheric dominance within the ventral attentional system, as postulated in our hypothesis, it may offer an interesting therapeutic approach for attentional disorders in left hemispheric stroke (which is often associated with motor deficits of the right upper limb). Each participant's head was immobilized in a head rest and the first two thirds of the pointing trajectories were hidden from his/her view. The visuomotor adaptation involved 3 min of pointing movements. The pointing was paced by the experimenter, who indicated verbally which of the two points should be targeted next. To avoid automatic pointing, the intertrial interval varied (1.0–1.5 s) and the order of targets was pseudorandomized. The total number of pointing movements was on average 150 (range = 145–155). The time for pointing was kept constant across subjects, as was the time between the two fMRI sessions.

During the first trials, participants showed initial errors in the direction of the prisms' deviation, and then they all pointed correctly to the targets. Immediately after the goggles were removed, the aftereffect was assessed by asking the participants to look at one of the visual targets and then to close their eyes and to reach for the target with the index finger used during the adaptation. A similar procedure was used twice for the left target and twice for the right target in a pseudorandom order; the number of measures was limited in order to minimize de-adaptation before the second fMRI session. For each participant and each target position, we put a mark on the table where the participant pointed, and we measured, in mm, the deviation between the pointing and the actual target, with positive values representing a deviation to the right of the targets and negative values representing a deviation to the left of the targets. We averaged the two pointings for each target location. A mixed design ANOVA with group (R-PA, L-PA, neutral) as a between-subjects factor and side of target (left, right) as a within-subjects factor was conducted on these data.

Data acquisition

Imaging acquisitions, structural MRI and event-related fMRI were conducted at the Lemanic Biomedical Imaging Center (Centre d'Imagerie Biomédicale) in the Centre Hospitalier Universitaire Vaudois, Lausanne on a 3T Siemens Magnetom Trio scanner with a 32-channel head-coil. A single-shot echo planar imaging gradient echo sequence (repetition time = 2 s; flip angle = 90°; echo time = 30 ms; number of slices = 32; voxel size = 3 × 3 × 3 mm; 10% gap) was used for fMRI acquisitions. A total of 32 slices were acquired in the AC-PC plane in a sequential ascending order and covered the whole head volume. For each participant, a high-resolution T1-weighted 3D gradient-echo sequence was acquired (160 slices, voxel size = 1 × 1 × 1 mm). We put padding around each participant's head to prevent head movements in the coil.

Data analysis

Behavioral performances (reaction time and number of correct responses) recorded during the task were analyzed with a mixed design ANOVA with group (R-PA, L-PA, neutral) as the between-subjects factor and session (1, 2) as the within-subjects factor. The software Statistical Parametric Mapping (SPM8, Wellcome Department of Cognitive Neurology, London, United Kingdom) was used to process imaging data. For the functional acquisition, a motion correction was performed by applying a 6-parameter rigid-body transformation minimizing the difference between each image and the first scan. These realigned images were co-registered with the participants' anatomic images and then normalized to the Montreal Neurological Institute (MNI) template using a twelve parameters affine transformation. Finally, these images were resliced to obtain a 2 × 2 × 2 mm voxel size and spatially smoothed using an isotropic Gaussian kernel of 6-mm FWHM to increase signal-to-noise ratio.

For each participant, the general linear model, as implemented in SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), was used for the first level statistics. The parameters of the realignment were included in the model as regressors. For all participants, contrasts of interests were specified for both sessions. The maps generated from these contrasts were used as the second-level (group-level) statistics based on the random field theory. All group analyses were restricted to voxels with the probability of belonging to gray matter greater than 50%, as defined in the a priori template available in SPM.

Statistical analyses on the activation maps were conducted on a general mixed design ANOVA that included the factors group (R-PA, L-PA, neutral) as the between-subjects factor and session (1, 2) and stimulus position (left, center, right) as the within-subjects factors. From this general ANOVA, the first analysis was on the interaction between the three factors (group × stimulus position × session) to determine the effects of our factors globally. Then, the interaction between the factors group and session was analyzed to determine the relationship between these two factors independent of the stimulus positions. The generated statistical maps of activation for these interactions were set at a threshold of $p < 0.05$ and a cluster extent of $k > 100$ (above the expected number of voxels per cluster as automatically calculated by SPM). The effects of each intervention were further investigated by directly comparing ses-

Table 1. Average accuracy (mean ± SEM; top) and average reaction times (bottom) for the visual detection task for the L-PA, R-PA, and neutral groups for both sessions (1 and 2) and for all stimulus positions (left, central, and right targets)

	Left targets		Central targets		Right targets	
Session	1	2	1	2	1	2
	Accuracy (%)					
L-PA	99.64 ± 0.36	98.93 ± 1.07	98.93 ± 0.57	99.29 ± 0.49	99.64 ± 0.36	100.00 ± 0.00
R-PA	98.21 ± 1.00	99.29 ± 0.49	100.00 ± 0.00	99.29 ± 0.71	96.79 ± 1.62	99.64 ± 0.36
Neutral	100.00 ± 0.00	98.21 ± 1.79	99.64 ± 0.36	99.29 ± 0.49	99.64 ± 0.36	98.57 ± 1.10
Reaction time (ms)						
L-PA	388 ± 24	399 ± 17	383 ± 24	385 ± 17	379 ± 23	403 ± 19
R-PA	408 ± 15	416 ± 19	397 ± 15	403 ± 15	401 ± 13	414 ± 15
Neutral	375 ± 10	404 ± 14	360 ± 10	383 ± 14	365 ± 9	396 ± 10

sion 1 to session 2 (*post hoc t* tests) for each stimulus position and each group separately. The generated statistical maps of activation for these *t* tests were set at a threshold of $p < 0.05$ and a cluster extent of $k > 150$ (above the expected number of voxels per cluster as automatically calculated by SPM).

Results

Aftereffects of the visuomotor adaptation

The aftereffects of PA occurring after the removal of the prismatic goggles were assessed as pointing errors to the right or left of the actual target (expressed in positive and negative values, respectively). For the L-PA group, the pointing errors were always to the right of the left and right targets; the means of the pointing errors were +5.1 ± 2.4 cm for the left target and +5.9 ± 2.4 mm for the right target. For the R-PA group, the pointing errors were always to the left of the left and right targets. For this group, the means of the pointing errors were −66 ± 16 mm (mean ± SD) for the left target and −5.6 ± 1.9 mm for the right target. For the neutral group, pointing errors were to the right or to the left of the targets; mean pointing errors were +7.0 ± 1.1 cm for the left target and +6 ± 8 mm for the right target. A two-way mixed design ANOVA with group (L-PA, R-PA, neutral) as the between-subjects factor and side of target (left, right) as the within-subjects factor revealed a significant main effect of group ($F_{(2,39)} = 314.9$; $p < 0.001$) but no significant effect for the side of the target or interaction. The aftereffects were globally larger for the L-PA and R-PA than for the neutral group, with the R-PA group showing errors to the left of the targets and the L-PA group showing errors to the right of the targets.

Behavioral results of the visual detection task

For accuracy (Table 1), an ANOVA including the factors groups (L-PA, R-PA, neutral), sessions (1, 2) and stimulus positions (left, center, right) did not show a significant effect. For the reaction times (Table 1), the ANOVA including the factors group (L-PA, R-PA, neutral), session (1, 2), and stimulus position (left, center, right) showed only one significant main effect for the factor stimulus position ($F_{(2,38)} = 14.73$, $p < 0.01$), with the subjects being globally faster for the central position.

Modulation of activation patterns by interventions

The overall modulations were analyzed with a mixed design ANOVA with group (L-PA, R-PA, neutral) as the between-subjects factor and session (1, 2) and stimulus position (left, center, right) as the within-subjects factors. The triple interaction between the factors group, session, and stimulus position yielded a significant effect in the right angular gyrus, the left anterior superior and the middle temporal gyri and bilaterally in the superior (medial) parietal regions, the precuneus, medial and middle frontal gyri, SMA and the middle cingulate areas (Fig. 1*A*). The interaction between the factors group and session yielded a significant effect on the left hemisphere in the angular gyrus, the middle temporal gyrus and the middle occipital gyrus, on the right hemisphere in the supramarginal gyrus, and bilaterally in the superior temporal gyrus and the orbito-frontal cortex (Fig. 1*B*). These results indicate that the direction of prismatic deviation impacts the PA-induced modulation of activity within the left and the right IPL.

To gain insight into the direction-specific changes of the PA intervention, the effects were analyzed separately for each of the three intervention groups and stimulus position with paired *t* tests comparing activation pre- and postintervention. L-PA enhanced the response to right visual targets within the ipsilateral, right angular gyrus (Fig. 1*C*). R-PA enhanced the response to right, central, and left targets within the left IPL as described previously (Crottaz-Herbette et al., 2014), as well as in parts of the prefrontal and temporal cortexes for the central and right targets (Fig. 1*D*). Exposure to plain goggles increased the response to right targets bilaterally in the superior temporal gyrus and to left targets within the right supramarginal gyrus and bilaterally within the occipital cortex (Fig. 1*E*). Thus, there is a striking but opposing effect of PA depending on the direction of prismatic deviation. L-PA enhanced right hemispheric dominance within the ventral attentional system by increasing the representation of the right visual field within the ipsilateral, right IPL. R-PA shifted this hemispheric dominance from the right to the left IPL by increasing the representation of right, central, and left visual field within the left IPL (see also Crottaz-Herbette et al., 2014; Clarke and Crottaz-Herbette, 2016).

Direction-specific effects of PA on hemispheric dominance within the ventral attentional system

IPL is classically subdivided into angular and supramarginal gyri, each of which comprises several subdivisions defined by cytoarchitectonic and connectivity criteria (Caspers et al., 2008; Mars et al., 2011). The effects which we report here involved mostly the angular and less so the

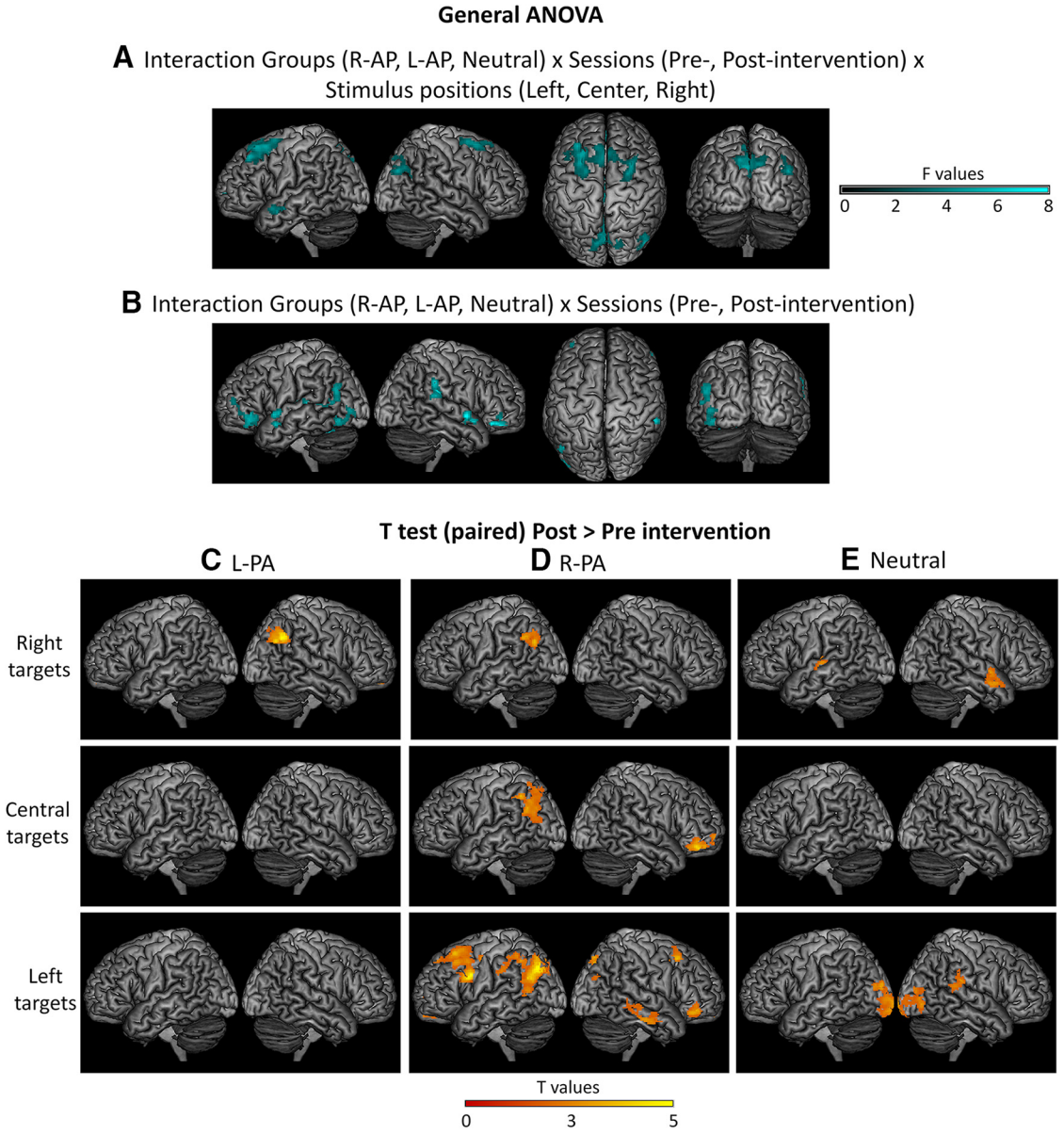

Figure 1. Surface renderings of the brain activation showing significant activation in the general mixed design ANOVA for the interaction between all three factors, group as the between-subjects factor and session and stimulus position as the within-subjects factors (***A***); and for the interaction between the factors group and session (***B***). ***C–E***, Surface renderings of *post hoc* paired *t* tests (post > pre-intervention) for the L-PA (***C***), R-PA (***D***), and neutral groups (***E***) for each stimulus position separately. All maps are set at a threshold of $p < 0.05$ and $k > 100$ for the interactions and $k > 150$ for the *t* tests.

supramarginal gyrus. The right angular gyrus showed a significant interaction between the factors group × session × stimulus position, which was driven by a strong increase in activation by right targets following L-PA (Fig. 1*A*,*C*). The left angular gyrus showed a significant interaction between the factors group × session, which was driven by a strong increase in activation by left, central, and right targets following R-PA (Fig. 1*B*,*D*; Crottaz-Herbette et al., 2014). In both hemispheres these clusters were within the cytoarchitectonic areas PGa and PGp of the angular gyrus (Caspers et al., 2008), known for their role in redirecting of visuospatial attention (Mort et al., 2003; Thiel et al., 2004). The supramarginal gyrus was highlighted on the right side by a significant interaction between the factors group × session, which appeared to be driven by an increase in activation in the control condition (Fig. 1*B*,*E*). This part of the supramarginal gyrus corresponds to the cytoarchitectonic areas PF and PFt (Caspers et al., 2008), which plays a role in visuomotor coordination (Binkofski et al., 1999; Frey et al., 2005; Grol et al., 2007). In summary, PA appears to affect the attentional module within the angular gyrus: L-PA increases the representation of right targets on the right side, whereas R-PA increases the representation of left, central, and right

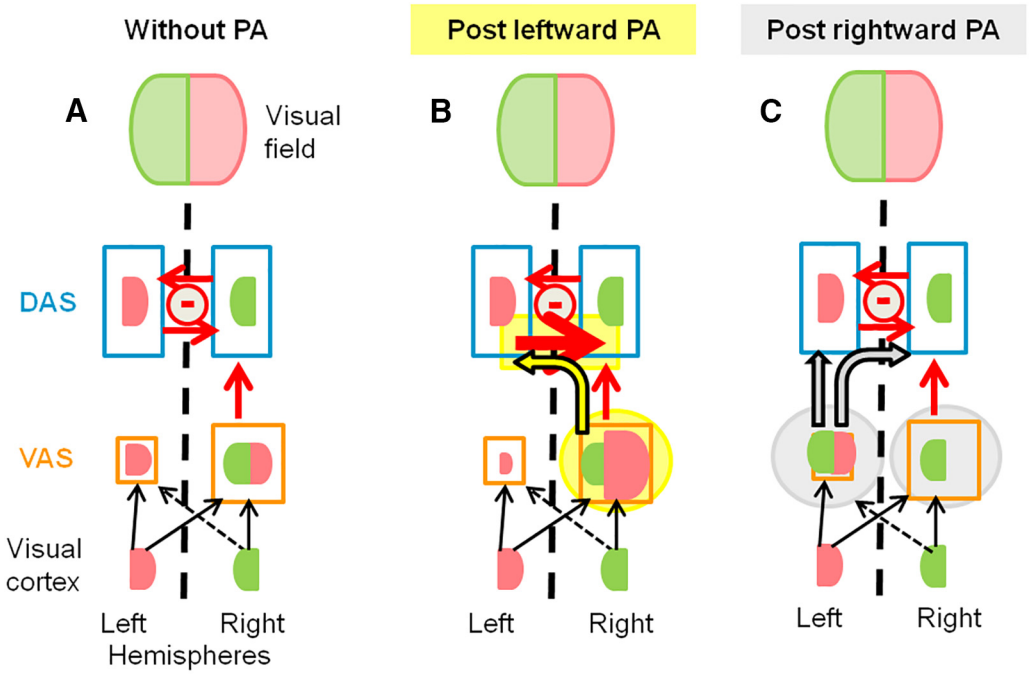

Figure 2. Schematic representation of the dorsal and ventral attentional systems (DAS, VAS, outlined in blue and orange, respectively), the visual areas, and their interactions (based on Koch et al., 2008; Corbetta and Shulman, 2011). Situations without PA (***A***) as well as after L-PA (***B***) and R-PA (***C***) are represented. L-PA-induced changes are highlighted in yellow: enhancement of right visual field representation in the right VAS (as reported in our current findings) and the increased inhibition from left to right DAS (resulting from change in respective excitability as in Schintu et al., 2016). R-PA-induced changes (***C***) are highlighted in gray (based on Crottaz-Herbette et al., 2014 and discussed in Clarke and Crottaz-Herbette, 2016).

targets on the left side. The effect in right supramarginal gyrus appears to be driven by the control condition and may represent a modulation of visuomotor coordination.

As reported in a previous study, a brief exposure to R-PA increased the representation of the left, central, and right visual fields in the left IPL and shifted the hemispheric dominance within the ventral attentional system from the right to the left hemisphere (Crottaz-Herbette et al., 2014). This shift in hemispheric dominance offers a parsimonious explanation for behavioral effects of R-PA observed both in normal subjects and neglect patients (Clarke and Crottaz-Herbette, 2016). Our new results contrast with this effect as we found that a brief exposure to L-PA increases the representation of the right visual field in the right IPL, enhancing the right hemispheric dominance within the ventral attentional system (Fig. 2). This overemphasis of the right visual field within the (right-dominant) ventral attentional system offers an explanation for the behavioral effects of L-PA reported in several previous studies, including neglect-like performance. It also offers insight into the putative neural mechanisms that underlie the effect of L-PA.

Discussion

Behavioral effects of leftward PA

Neglect-like performance in normal subjects

Several studies in normal subjects have shown that L-PA induces neglect-like performance in some, but not all visuospatial tests (Michel, 2016). L-PA yielded a rightward bias on the perceptual variant of the line bisection task (Colent et al., 2000), including striking similarities with neglect symptoms, such as effect of line length and modulation of the rightward deviation by the position of the lines (Michel et al., 2003). This rightward bias in perceptual line bisection is long-lasting yet fluctuating, suggesting that the visuospatial shift needs time to build up (Schintu et al., 2014). L-PA also induced a rightward shift in visual midpoint judgments occurring both in peri- and extrapersonal spaces (Berberovic and Mattingley, 2003).

In the present study L-PA did not induce a lateral bias in the target detection task performed during the fMRI acquisition. The use of more complex tasks during the fMRI acquisition would be of interest in further studies for two reasons. First, more difficult detection tasks would allow us to assess a putative lateral bias in performance, possibly a neglect-like effect. It is to be noted, however, that in several studies L-PA failed to yield behavioral effects with the Posner paradigm (Morris et al., 2004; Bultitude et al., 2013a).This lack of behavioral effects contrasts with the results of event-related potentials to different components of the endogenous variants of the Posner task, which revealed attentional asymmetries that were reminiscent of neglect (Martín-Arévalo et al., 2016). With L-PA, but not with R-PA or neutral goggles, two measures stood out. The L-PA induced reduction of the N1 amplitude elicited by the cue was greater for leftward than rightward cues, suggesting an L-PA-induced asymmetry in attentional orienting. The L-PA-induced reduction of the P1 amplitude was greater for the invalidly cued left than right target, suggesting an asymmetry in attentional disen-

gagement. Second, the use of bisection tasks, which have been shown to be modulated by L-PA (Michel and Cruz, 2015; Striemer et al., 2016), may help to explore the effect of L-PA beyond that on the ventral attentional system.

Our results offer a parsimonious explanation for neglect-like performance described above.

L-PA overemphasizes the responsiveness of the right IPL to stimuli presented within the right visual field. This stronger representation of the right visual field within the right-dominant ventral attentional system may facilitate the access of right stimuli to the dorsal system and drive the left dorsal attentional system more forcefully. An overactive left dorsal attentional system is bound to create a right attentional bias in behavioral tasks. In addition, it may increase the interhemispheric inhibition of the contralateral, right dorsal system and decrease its activity (Koch et al., 2011). This interpretation is supported by a recent study that has indeed demonstrated that L-PA increased the excitability of the parietal circuitry in the left and decreased it in the right hemisphere (Schintu et al., 2016).

Modulation of global *vs.* local processing bias by L-PA Tasks that implicate attention to global vs. local features of stimuli rely on complex cortical networks (Fink et al., 1996, 1997). Although sustained attention to either level was shown to activate a right hemispheric temporo-parieto-prefrontal network, directing attention to global aspects highlighted specifically the role of the right lingual gyrus while attending to local aspects activated the left inferior occipital cortex. Performance in tasks such as Navon figures, with incongruent global and local features, are characterized in normal subjects by greater interference from global rather than local features. L-PA was shown to reduce the global processing bias (Bultitude and Woods, 2010). A later study using different paradigms, the rod-and-frame illusion and the simultaneous-tilt illusion, demonstrated that L-PA enhanced local processing bias (Reed and Dassonville, 2014). Thus, in normal subjects, L-PA shifted the processing bias from global to local features, as often found in neglect (Robertson et al., 1988; Marshall and Halligan, 1995). Our results offer only a partial explanation for these findings. After L-PA, the increased activation to ipsilateral targets within the right ventral attentional system (shown here) and the ensuing enhanced activity within the left dorsal attentional system (Schintu et al., 2016) may change the encoding within the left early-stage visual areas, including the inferior occipital cortex, and may thus favor the processing of local features.

Visuospatial remapping

Spatial remapping ensures the integration of visual information as gaze moves across a scene, resulting in a stable representation of the visual environment despite constantly changing retinal images. It depends critically on the right posterior parietal cortex (Heide et al., 1995; van Koningsbruggen et al., 2010). Using the double-step saccade paradigm, Bultitude and colleagues (Bultitude et al., 2013b) have shown that L-PA impairs spatial remapping in the left visual field. The authors proposed that the temporary realignment of spatial representations with L-PA altered right hemispheric remapping processes. Our results demonstrated right hemispheric remapping within the (right) ventral attentional system, but it concerns the right and not left visual space.

Behavioral effects of rightward PA

In normal subjects R-PA appears to yield behavioral effects only rarely. R-PA increase the speed of reflexive reorienting from invalid cues on the left to targets on the right side in a subgroup of subjects, who had large cueing effects before R-PA; no effect was reported on voluntary reorienting (Striemer et al., 2006). Another study found rightward shift in visual midpoint judgment in extrapersonal, but not in peripersonal space (Berberovic and Mattingley, 2003). A third study investigated spatial remapping with a double-step saccade paradigm (Bultitude et al., 2013b). R-PA affected oculomotor performance, most likely by low-level adaptation aftereffects, but did not yield any spatial remapping. The explanation for these three observations in terms of the shift of hemispheric dominance of the ventral attentional system from the right to the left hemisphere, which is induced by R-PA, were discussed in a recent review (Clarke and Crottaz-Herbette, 2016).

Putative mechanisms of leftward PA

The effect of L-PA relies most likely on several functional systems, as suggested by a series of studies. Spatial realignment during the actual adaptation to prisms was shown to involve the parieto-temporal cortex and the cerebellum (Luauté et al., 2009; Chapman et al., 2010), with a critical contribution of the latter (Panico et al., 2016). At the level of the posterior parietal and primary motor cortices L-PA was found to induce hemispheric-specific changes in excitability: an increase in motor evoked potentials in the left and a decrease in the right hemisphere (Schintu et al., 2016). Here, we show that L-PA enhances the representation of the right visual field within the right IPL.

Taken together, the above quoted evidence suggests neural mechanisms which may underlie the effect of L-PA, and provides ground for new hypotheses and further studies. While the subject is wearing leftward-deviating prisms, targets appear to the left of their actual position. In Figure 3, we represent a simplified situation where the target is in the right visual field near the vertical meridian and L-PA shifts it into the left visual field so that the target activates the corresponding left visual field representation within the retinotopically organized visual areas of the right hemisphere. To point successfully towards the target, the movement has to be directed towards the actual site within the right hemispace; attention-driven movements towards the right hemispace are represented in the left superior parietal lobule (Leonards et al., 2000; Corbetta et al., 2002; Silver and Kastner, 2009). Thus, successful adaptation to leftward deviating prisms can be expected to involve several steps, including a modulation of salience of particular spatial representations within each hemisphere. Learning to associate a target which appears on the left side with a pointing movement oriented towards the right space is very likely to result in the strengthening of the link between the left visual field

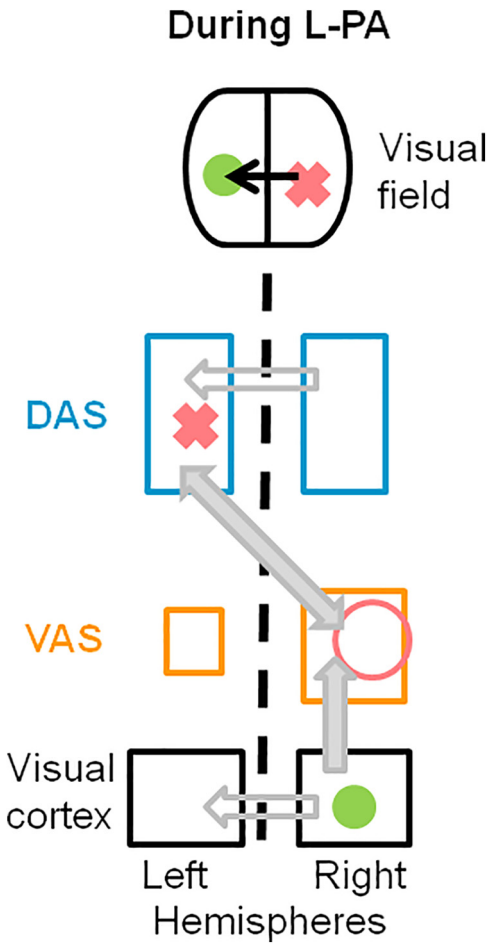

Figure 3. Schematic representation summarizing putative neural mechanisms that underlie the effects of L-PA. Same conventions as in Figure 2. The pink cross designates the actual position of the target and highlights the contralateral DAS, which is involved in pointing towards this target position. The green circle designates the position of the same target as perceived within the (left) visual space when wearing leftward deviating prisms, its representation in the right visual cortex and DAS. The pink circle highlights the L-PA-enhanced representation of the (right) visual field within the (right) DAS. Exposure to L-PA is likely to strengthen the link between the representation of the perceived target within the (right) visual cortex and the left DAS. The most likely link involves heterotopic interhemispheric connections between the (right) VAS and left DAS (full gray arrow). The homotopic interhemispheric connections between visual areas and those between DAS are unlikely to contribute (outlined gray arrows).

representations in the right occipital cortex and the dorsal attentional system in the left hemisphere. This link can be mediated by several pathways. First, the most likely pathway proceeds from visual areas in the right hemisphere to the (right) ventral attentional system and then via an interhemispheric connection to the left dorsal attentional system. Such heterotopic-crossed connections can be monosynaptic, as demonstrated histologically in the human occipito-parieto-temporal cortex (Di Virgilio and Clarke, 1997). The key observation of our study, namely, the reorganization within the (right) ventral attentional system, further supports this interpretation. Second, it is very unlikely that a functional link between the representations of the perceived and the actual position occur at the level of early-stage visual areas since the interhemispheric connections between these areas concern only a narrow part of the cortex along the representation of the vertical meridian (Clarke and Miklossy, 1990) and the intrahemispheric connections are retinotopically organized (Clarke, 1994). Third, the link is also unlikely to be mediated by afferents from the right to the left dorsal attentional system. A recent study has shown that right-to-left connections are lessened following L-PA, most likely as a result of an increase in parietal excitability in the left and a decrease in the right hemisphere (Schintu et al., 2016).

Conclusion

L-PA increased the representation of the right visual field within the right IPL. This enhancement of the right hemispheric dominance within the ventral attentional system contrasts with the dominance shift, from right to left hemisphere, which is induced by R-PA (Crottaz-Herbette et al., 2014). Thus, the PA-induced modulation of hemispheric dominance within the ventral attentional system is sensitive to the direction of the prismatic deviation and is likely to depend on fine-tuning of specific visuomotor networks.

The overemphasis of the right visual field representation within the (right) ventral attentional system offers a parsimonious explanation of neglect-like effects following L-PA. It is bound to more forcefully drive the left dorsal attentional system, creating an attentional bias towards the right space. The underlying neural mechanisms most likely involve a strengthened link between the (right) ventral attentional system and the left dorsal attentional system.

The effect of L-PA, which we report in this study, is likely to be of considerable interest for the rehabilitation of attentional deficit in left hemispheric stroke. These deficits are frequent and often preclude the return to work and/or driving (Murakami et al., 2014). They may be the result of the re-organization which takes place within the intact hemisphere after unilateral focal lesions (Adriani et al., 2003). We have shown here that adaptation to left-deviating prisms by means of left-hand pointing enhances right hemispheric dominance within the ventral attentional system and may thus constitute a very useful therapeutic intervention in left hemispheric stroke.

References

Adriani M, Bellmann A, Meuli R, Fornari E, Frischknecht R, Bindschaedler C, Rivier F, Thiran J-P, Maeder P, Clarke S (2003) Unilateral hemispheric lesions disrupt parallel processing within the contralateral intact hemisphere: an auditory fMRI study. Neuroimage 20 [Suppl 1]:S66-S74. CrossRef

Berberovic N, Mattingley JB (2003) Effects of prismatic adaptation on judgements of spatial extent in peripersonal and extrapersonal space. Neuropsychologia 41:493–503. Medline

Binkofski F, Buccino G, Stephan KM, Rizzolatti G, Seitz RJ, Freund HJ (1999) A parieto-premotor network for object manipulation: evidence from neuroimaging. Exp Brain Res 128:210–213. Medline

Bultitude JH, Woods JM (2010) Adaptation to leftward-shifting prisms reduces the global processing bias of healthy individuals. Neuropsychologia 48:1750–1756. CrossRef Medline
Bultitude JH, Downing PE, Rafal RD (2013a) Prism adaptation does not alter configural processing of faces. F1000Res 2:215.
Bultitude JH, Van der Stigchel S, Nijboer TCW (2013b) Prism adaptation alters spatial remapping in healthy individuals: evidence from double-step saccades. Cortex 49:759–770.
Caspers S, Eickhoff SB, Geyer S, Scheperjans F, Mohlberg H, Zilles K, Amunts K (2008) The human inferior parietal lobule in stereotaxic space. Brain Struct Funct 212:481–495. CrossRef Medline
Chapman HL, Eramudugolla R, Gavrilescu M, Strudwick MW, Loftus A, Cunnington R, Mattingley JB (2010) Neural mechanisms underlying spatial realignment during adaptation to optical wedge prisms. Neuropsychologia 48:2595–2601. CrossRef Medline
Clarke S (1994) Association and intrinsic connections of human extrastriate visual cortex. Proc Biol Sci 257:87–92. CrossRef Medline
Clarke S, Crottaz-Herbette S (2016) Modulation of visual attention by prismatic adaptation. Neuropsychologia 92:31-41.
Clarke S, Miklossy J (1990) Occipital cortex in man: organization of callosal connections, related myelo- and cytoarchitecture, and putative boundaries of functional visual areas. J Comp Neurol 298:188–214. CrossRef
Clower DM, Hoffman JM, Votaw JR, Faber TL, Woods RP, Alexander GE (1996) Role of posterior parietal cortex in the recalibration of visually guided reaching. Nature 383:618–621. CrossRef Medline
Colent C, Pisella L, Bernieri C, Rode G, Rossetti Y (2000) Cognitive bias induced by visuo-motor adaptation to prisms: a simulation of unilateral neglect in normal individuals? Neuroreport 11:1899–1902. Medline
Corbetta M, Shulman GL (2011) Spatial neglect and attention networks. Annu Rev Neurosci 34:569–599. CrossRef Medline
Corbetta M, Kincade JM, Shulman GL (2002) Neural systems for visual orienting and their relationships to spatial working memory. J Cogn Neurosci 14:508–523. CrossRef Medline
Crottaz-Herbette S, Fornari E, Clarke S (2014) Prismatic adaptation changes visuospatial representation in the inferior parietal lobule. J Neurosci 34:11803–11811. CrossRef Medline
Danckert J, Ferber S, Goodale MA (2008) Direct effects of prismatic lenses on visuomotor control: an event-related functional MRI study. Eur J Neurosci 28:1696–1704. CrossRef Medline
de Haan B, Bither M, Brauer A, Karnath H-O (2015) Neural correlates of spatial attention and target detection in a multi-target environment. Cereb Cortex 25:2321–2331. CrossRef
Di Virgilio G, Clarke S (1997) Direct interhemispheric visual input to human speech areas. Hum Brain Mapp 5:347–354. CrossRef Medline
Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, Dolan RJ (1996) Where in the brain does visual attention select the forest and the trees? Nature 382:626–628. CrossRef Medline
Fink GR, Halligan PW, Marshall JC, Frith CD, Frackowiak RS, Dolan RJ (1997) Neural mechanisms involved in the processing of global and local aspects of hierarchically organized visual stimuli. Brain 120:1779–1791. CrossRef
Frey SH, Vinton D, Norlund R, Grafton ST (2005) Cortical topography of human anterior intraparietal cortex active during visually guided grasping. Brain Res Cogn Brain Res 23:397–405. CrossRef Medline
Grol MJ, Majdandzi J, Stephan KE, Verhagen L, Dijkerman HC, Bekkering H, Verstraten FAJ, Toni I (2007) Parieto-frontal connectivity during visually guided grasping. J Neurosci 27:11877–11887. CrossRef Medline
Heide W, Blankenburg M, Zimmermann E, Kömpf D (1995) Cortical control of double-step saccades: implications for spatial orientation. Ann Neurol 38:739–748. CrossRef Medline
Jacquin-Courtois S, O'Shea J, Luauté J, Pisella L, Revol P, Mizuno K, Rode G, Rossetti Y (2013) Rehabilitation of spatial neglect by prism adaptation: a peculiar expansion of sensorimotor after-effects to spatial cognition. Neurosci Biobehav Rev 37:594–609. CrossRef Medline
Koch G, Oliveri M, Cheeran B, Ruge D, Lo Gerfo E, Salerno S, Torriero S, Marconi B, Mori F, Driver J, Rothwell JC, Caltagirone C (2008) Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain 131:3147–3155. CrossRef Medline
Koch G, Cercignani M, Bonnì S, Giacobbe V, Bucchi G, Versace V, Caltagirone C, Bozzali M (2011) Asymmetry of parietal interhemispheric connections in humans. J Neurosci 31:8967–8975. CrossRef Medline
Leonards U, Sunaert S, Van Hecke P, Orban GA (2000) Attention mechanisms in visual search – an fMRI study. J Cogn Neurosci 12[Suppl2]:61–75. CrossRef Medline
Luauté J, Schwartz S, Rossetti Y, Spiridon M, Rode G, Boisson D, Vuilleumier P (2009) Dynamic changes in brain activity during prism adaptation. J Neurosci 29:169–178. CrossRef Medline
Mars RB, Jbabdi S, Sallet J, O'Reilly JX, Croxson PL, Olivier E, Noonan MP, Bergmann C, Mitchell AS, Baxter MG, Behrens TEJ, Johansen-Berg H, Tomassini V, Miller KL, Rushworth MFS (2011) Diffusion-weighted imaging tractography-based parcellation of the human parietal cortex and comparison with human and macaque resting-state functional connectivity. J Neurosci 31:4087–4100. CrossRef
Marshall JC, Halligan PW (1995) Seeing the forest but only half the trees? Nature 373:521–523. CrossRef Medline
Martín-Arévalo E, Laube I, Koun E, Farnè A, Reilly KT, Pisella L (2016) Prism adaptation alters electrophysiological markers of attentional processes in the healthy brain. J Neurosci 36:1019–1030. CrossRef
Michel C (2016) Beyond the sensorimotor plasticity: cognitive expansion of prism adaptation in healthy individuals. Front Psychol 6:1979.
Michel C, Cruz R (2015) Prism adaptation power on spatial cognition: adaptation to different optical deviations in healthy individuals. Neurosci Lett 590:145–149.
Michel C, Pisella L, Halligan PW, Luauté J, Rode G, Boisson D, Rossetti Y (2003) Simulating unilateral neglect in normals using prism adaptation: implications for theory. Neuropsychologia 41:25–39. Medline
Morris AP, Kritikos A, Berberovic N, Pisella L, Chambers CD, Mattingley JB (2004) Prism adaptation and spatial attention: a study of visual search in normals and patients with unilateral neglect. Cortex 40:703–721. Medline
Mort DJ, Perry RJ, Mannan SK, Hodgson TL, Anderson E, Quest R, McRobbie D, McBride A, Husain M, Kennard C (2003) Differential cortical activation during voluntary and reflexive saccades in man. Neuroimage 18:231–246.
Murakami T, Hama S, Yamashita H, Onoda K, Hibino S, Sato H, Ogawa S, Yamawaki S, Kurisu K (2014) Neuroanatomic pathway associated with attentional deficits after stroke. Brain Res 1544:25–32. CrossRef Medline
Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97–113. Medline
Panico F, Sagliano L, Grossi D, Trojano L (2016) Cerebellar cathodal tDCS interferes with recalibration and spatial realignment during prism adaptation procedure in healthy subjects. Brain Cogn 105:1–8. CrossRef Medline
Redding GM, Rossetti Y, Wallace B (2005) Applications of prism adaptation: a tutorial in theory and method. Neurosci Biobehav Rev 29:431–444. CrossRef Medline
Reed SA, Dassonville P (2014) Adaptation to leftward-shifting prisms enhances local processing in healthy individuals. Neuropsychologia 56:418–427. CrossRef Medline
Robertson LC, Lamb MR, Knight RT (1988) Effects of lesions of temporal-parietal junction on perceptual and attentional processing in humans. J Neurosci 8:3757–3769. Medline
Rode G, Pisella L, Marsal L, Mercier S, Rossetti Y, Boisson D (2006) Prism adaptation improves spatial dysgraphia following right brain damage. Neuropsychologia 44:2487–2493. CrossRef Medline

Rossetti Y, Rode G, Pisella L, Farné A, Li L, Boisson D, Perenin MT (1998) Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. Nature 395:166–169. CrossRef Medline

Rushworth MFS, Krams M, Passingham RE (2001) The attentional role of the left parietal cortex: the distinct lateralization and localization of motor attention in the human brain. J Cogn Neurosci 13:698–710. CrossRef

Rushworth MFS, Johansen-Berg H, Göbel SM, Devlin JT (2003) The left parietal and premotor cortices: motor attention and selection. Neuroimage 20 [Suppl 1]:S89-100. Medline

Schintu S, Martín-Arévalo E, Vesia M, Rossetti Y, Salemme R, Pisella L, Farnè A, Reilly KT (2016) Paired-pulse parietal-motor stimulation differentially modulates corticospinal excitability across hemispheres when combined with prism adaptation. Neural Plast 2016: 5716179. CrossRef Medline

Schintu S, Pisella L, Jacobs S, Salemme R, Reilly KT, Farnè A (2014) Prism adaptation in the healthy brain: the shift in line bisection judgments is long lasting and fluctuates. Neuropsychologia 53: 165–170. CrossRef Medline

Silver MA, Kastner S (2009) Topographic maps in human frontal and parietal cortex. Trends Cogn Sci (Regul Ed) 13:488–495. CrossRef Medline

Striemer C, Sablatniq J, Danckert J (2006) Differential influences of prism adapation on reflexive and voluntary covert attention. J Int Neuropsychol Soc 12(3):337–349.

Striemer C, Russel K, Nath P (2016) Prism adaptation magnitude has differential influences on perceptual versus manual responses. Exp Brain Res 234:2761–2772.

Thiel CM, Zilles K, Fink GR (2004) Cerebral correlates of alerting, orienting and reorienting of visuospatial attention: an event-related fMRI study. Neuroimage 21:318–328. Medline

van Koningsbruggen MG, Gabay S, Sapir A, Henik A, Rafal RD (2010) Hemispheric asymmetry in the remapping and maintenance of visual saliency maps: a TMS study. J Cogn Neurosci 22:1730–1738. CrossRef Medline

Weiner MJ, Hallett M, Funkenstein HH (1983) Adaptation to lateral displacement of vision in patients with lesions of the central nervous system. Neurology 33:766–772. Medline