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Hemispheric competence for auditory spatial representation

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Sound localization relies on the analysis of interaural time and intensity differences, as well as attenuation patterns by the outer ear. We investigated the relative contributions of interaural time and intensity difference cues to sound localization by testing 60 healthy subjects: 25 with focal left and 25 with focal right hemispheric brain damage. Group and single-case behavioural analyses, as well as anatomo-clinical correlations, confirmed that deficits were more frequent and much more severe after right than left hemispheric lesions and for the processing of interaural time than intensity difference cues. For spatial processing based on interaural time difference cues, different error types were evident in the individual data. Deficits in discriminating between neighbouring positions occurred in both hemispaces after focal right hemispheric brain damage, but were restricted to the contralesional hemispace after focal left hemispheric brain damage. Alloacusis (perceptual shifts across the midline) occurred only after focal right hemispheric brain damage and was associated with minor or severe deficits in position discrimination. During spatial processing based on interaural intensity cues, deficits were less severe in the right hemispheric brain damage than left hemispheric brain damage group and no alloacusis occurred. These results, matched to anatomical data, suggest the existence of a binaural sound localization system predominantly based on interaural time difference cues and primarily supported by the right hemisphere. More generally, our data suggest that two distinct mechanisms contribute to: (i) the precise computation of spatial coordinates allowing spatial comparison within the contralateral hemispace for the left hemisphere and the whole space for the right hemisphere; and (ii) the building up of global auditory spatial representations in right temporo-parietal cortices.

Keywords: auditory localization; auditory spatial representations; auditory cortex; hemispheric dominance; brain damage; human

Abbreviations: IID = interaural intensity difference; ITD = interaural time difference; LHD = left hemispheric damage; RHD = right hemispheric damage

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Introduction

Sound localization relies on the analysis of interaural time (ITD) and intensity (IID) differences, as well as attenuation patterns by the outer ear. In humans, auditory spatial functions have been assessed either in a free-field setting (Ruff *et al*., 1981, Poirier *et al*., 1994, Haeske-Dewick *et al*., 1996), by means of stereophonic simulation manipulating ITD (Altman *et al*., 1979, Griffiths *et al*., 1996, Tanaka *et al*., 1999), IID (Bisiach *et al*., 1984, Sterzi *et al*., 1996). These studies and others have shown sound localization impairments after focal hemispheric lesions, supporting the conclusion that auditory spatial functions involve cortical processing. Furthermore, there is now convincing evidence that the spatial dimension of sounds is processed by a specialized brain network at the cortical level. Animal data (e.g. Rauschecker and Tian, 2000) as well as human data (lesion studies: Clarke *et al*., 2000, 2002; activation studies: Alain *et al*., 2001, 2009; Maeder *et al*., 2001; Ahveninen *et al*., 2006; Murray *et al*., 2006, 2008; DeSantis *et al*., 2007; Spierer *et al*., 2007, 2008), have described a 'What' system relying on a ventral, temporo-lateral network, and a 'Where' system subserved by a dorsal, temporo-fronto-parietal network. Very little is known about the anatomo-functional organization of this 'Where' system in humans, with some, furthermore, supporting a more nuanced model wherein the dorsal system is instead functionally organized around action representations rather than spatial processing *per se* (e.g. Zatorre, 2002; Hickock and Poeppel, 2007). The variability of localization deficits described in the literature suggests that the 'Where' system is not unitary, but rather likely composed of different subsystems.

With a simulation paradigm it is possible to study separately the processing of a given localization cue (ITD, IID, spectral information). Following the duplex theory of localization (Strutt, 1907), ITD cues contribute mostly to the lateralization of low frequency tones, and IID cues to the lateralization of high frequency tones. However, this theory does not concern complex sounds. Many studies have shown that interaural time differences can be detected on the basis of the envelope of complex high frequency sounds (Scharf *et al*., 1976; Levine *et al*., 1993; Aharonson *et al*., 1998). Studies on human subjects with circumscribed lesions in the brainstem have revealed the influence of both the type of cue used to simulate spatial lateralizations (ITD versus IID), and the precise locus of the lesion. In some patients, selective spatial deficits were observed for the processing of interaural time difference cues, suggesting that interaural intensity and time discrepancies are processed by different pathways at the level of the brainstem (Levine *et al*., 1993; Griffiths, 1998). In what concerns the precise locus of lesions, damage of the trapezoid body gave rise to complete inability in spatial discrimination (all stimuli perceived at the midline), whereas lesions of the lateral lemniscus gave rise to a shift of all the stimuli (all stimuli erroneously allocated either to the left or to the right) (Furst *et al*., 1995).

Paavilainen *et al*. (1989) showed that auditory potentials evoke similar cortical responses wherever a complex sound is effectively positioned in space, or its lateralization is simulated by interaural time difference alone or interaural intensity difference alone. However, further ERP studies on healthy subjects suggest that ITD and IID binaural cues are processed by partially segregated, but interacting, pathways. For instance, Schröger (1996) showed that the amplitude of the mismatch negativity (MMN) evoked by sounds whose lateralization was simulated by both ITD and IID cues corresponded to the sum of the mismatch negativities evoked by interaural time differences or interaural intensity differences alone. This result was interpreted as an evidence for the existence of distinct neuronal populations working in parallel, one dedicated to interaural time difference and the other to interaural intensity difference processing. Recent electrophysiological studies further showed that while ITD and IID cues engage distinct superior temporal cortical networks at an early latency, supra-additive neural response interactions occur within temporo-parietal and inferior frontal cortices at later processing stages when both cues were presented simultaneously (Tardif *et al*., 2006). Collectively, these results suggest that ITD and IID cues are processed by parallel, but interacting, cortical networks.

Lesion studies are potentially useful to understand the organization of interaural time and intensity difference processing at the cortical level. Very few studies have compared ITD and IID localization in brain-damaged patients. Using a discrimination threshold paradigm, Griffiths and collaborators (1996, 1997) found no significant dissociation between ITD and IID cues in a patient with a right temporo-parietal lesion, whereas Yamada and collaborators (1996) have found more severe deficits for the processing of ITD than IID cues in patients sustaining temporal lobe lesions. In agreement with the latter observation, in an active localization task, interaural time difference simulations were found to be more sensitive than free-field testing for the demonstration of auditory spatial impairments following brain damage (Tanaka *et al*., 1999).

Different types of localization impairment have been described after unilateral cerebral lesions: imprecision in the contralesional hemispace (Sanchez-Longo and Forster, 1958; Efron *et al*., 1983; Poirier *et al*., 1994), the pericentral space (Haeske-Dewick *et al*., 1996), the whole space (Ruff *et al*., 1981; Zatorre and Penhune, 2001), and directional bias to the ipsilesional space with or without alloacusis (Altman *et al*., 1979; Bisiach *et al*., 1984; Vallar *et al*., 1995; Sterzi *et al*., 1996). Some authors emphasized the role of the temporal lobe (Sanchez-Longo and Forster, 1958; Efron *et al*., 1983), while others proposed a specialization within the parietal lobe (Ruff *et al*., 1981; Bisiach *et al*., 1984; Griffiths *et al*., 1996, 1997; Tanaka *et al*., 1999). In addition, the issue of putative hemispheric dominance for auditory localization remains unclear. Generally, authors reporting deficits after temporal lesions do not describe differences between the effects of right and left hemispheric lesions (Sanchez-Longo and Forster, 1958; Efron *et al*., 1983), while authors emphasizing the role of the parietal lobe advocate right hemispheric specialization (Ruff *et al*., 1981; Bisiach *et al*., 1984; Tanaka *et al*., 1999).

The discrepancies between studies regarding the type of errors as well as site and side of lesions may be accounted for by different factors. Most data were collected from group studies without reports of individual performance and very often without precise descriptions of the cerebral lesions. Some studies included

only patients fitting a specific criterion (e.g. temporal lobectomy, right parietal lesion with visual neglect) without contrasting these results with other sites of lesion. The diversity of testing paradigms (active localization, discrimination threshold, subjective acoustic midline) and methods (free-field setting or simulation by ITD or IID) prevents inter-study comparisons. There is, therefore, need for multiple case studies using the same range of sound localization tests and including patients with differently located lesions. On the other hand, group analysis can be useful to reveal, by summation, mild characteristics that would unlikely reach the significance threshold at the individual level.

We investigated the mechanisms and cerebral structures involved in sound localization by testing 50 patients: 25 consecutive patients with unilateral right and 25 with unilateral left hemispheric damage, with two localization tasks, one using interaural time difference and the other interaural intensity difference cues. Patients were not selected according to anatomical or symptomatic characteristics in order to avoid *a priori* selection bias.

Methods

Subjects

Patients

Consecutive patients in the rehabilitation program of the Neuropsychology and Neurorehabilitation Service at the Vaudois University Hospital Centre and University of Lausanne participated in this study. The inclusion criteria for participating in this study were: (i) a first unilateral hemispheric lesion documented by MRI, CT scan and/or radiological report; (ii) absence of previous cerebral lesions or atrophy; (iii) normal hearing, and in particular less than 10 dB HL threshold discrepancy between ears as averaged from all frequencies assessed with tonal audiometry; (iv) good cooperation and absence of major behavioural or attentional problems; and (v) good auditory verbal understanding of the instructions. Points (iv) and (v) were evaluated as part of a detailed neuropsychological assessment including language and behavioural items. Inclusion in the study was not determined by auditory spatial capacities.

Fifty patients were retained (Table 1). Twenty-five patients had right (RHD, 12 female and 13 male; mean age = 52 years, range = 23–66 years), and 25 patients had left unilateral hemispheric lesions (LHD, 13 female and 12 male; mean age = 48 years, range = 17–69 years). There was no evidence of age differences between patients with RHD and LHD ($t_{(48)} = 1.22$; $P > 0.22$). The two subgroups of patients were found to be similar with respect to the interval between the onset of illness and the present investigation: <2 months in 14 RHD and 10 LHD, 2–4 months in 5 RHD and 8 LHD and more than 10 months in 6 RHD and 5 LHD. Forty-three patients were right-handed, six left-handed (Subjects R12, R23, L10, L15, L20 and L22), and one ambidextrous (L23). Patient L15, however, had neuropsychological deficits reflecting left hemispheric dominance for language and right hemispheric dominance for visuo-spatial functions (visuo-spatial neglect in R12).

Control population

Sixty neurologically normal subjects, 30 male and 30 female, aged between 20 and 85 years (mean age ± SD: 42.5 ± 14.3 years) served as controls. Twenty subjects were aged 20–34 years (26.8 ± 3.6 years), 20 aged 35–49 years (41.7 ± 4.3 years) and 20 aged 50 years or more (60 ± 7.4 years).

Anatomo-clinical correlations

For a subgroup of 20 patients with available clinical MRI and/or CT scans (10 RHD: R16–R25; 10 LHD: L16–L25), brain lesions were reconstructed on axial slices of the standard Montreal Neurological Institute's (MNI) brain template using the MRIcro software (Rorden and Brett, 2000; Brett *et al*., 2001), according to previously described methods (e.g. Karnath *et al*., 2004). The normalized lesion regions of interest (ROIs) were then submitted to statistical mapping analyses using Voxel-based Lesion-Symptom Mapping (VLSM) algorithms using the Matlab software (The Mathworks, Natick, MA; Bates *et al*., 2003) in order to determine brain areas where damage yielded different degrees of deficit in the sound lateralization tasks. *t*-tests were performed on a voxel-by-voxel basis to compare performance in patients with versus without a lesion in each voxel. The minimal group size for analysis was set to two patients, that is, the *t*-tests were restricted to those voxels where there were at least two patients in each group (i.e. with and without a lesion). Results of the *t*-tests were then colour-coded and mapped on the MNI template brain.

Tests of auditory localization

Sound localization was assessed by means of two stereophonic tests simulating auditory lateralizations either by interaural time or intensity difference. Stereophonic rather than free-field localization tests were chosen because: (i) stereophonic spatial simulations allow separate investigations of ITD and IID cues; (ii) the use of headphones renders the perception of spatial lateralization of sounds independent of head position; this is particularly appropriate for a neurological population, which may include patients with abnormal head and trunk orientations; and (iii) ITD simulations tend to be more sensitive than free-field testing for the demonstration of auditory spatial impairments following brain damage (Tanaka *et al*., 1999). However, this approach does not allow the investigation of monaural pinna-based spectral filtering cues.

ITD lateralization

This test has been described elsewhere (Clarke *et al*., 2000; Bellmann *et al*., 2001). It was elaborated digitally on a PowerMacintosh fitted with an Audiomedia card II and the software Sound designer II and Protools Powermix. The stimulus was the sound of a bumblebee, ranging from 20 to 16 000 Hz, of 2 s duration including 100 ms rising and falling times. It was presented at the intensity level judged most comfortable by each subject. One central and four lateral intra-cranial positions, two in each hemispace, were simulated. The lateral positions were created by delaying the left or right channel by 0.3 ms (intermediate lateralization) or 1 ms (extreme lateralization). These values were chosen according to other data in the literature that showed that fused acoustic images were perceived for ITD of up to 2 or 2.5 ms, with the most lateral positions reported for ITD between 800 μs and 1 ms (Walsh, 1957; Jones *et al*., 1991). Sixty items, 12 at each position, were presented in pseudorandom order with the inter-stimulus interval adapted to each patient's response speed.

IID lateralization

The same sound stimuli were used for this task, but lateralizations were simulated by a difference in intensity level between the ears. The most lateral positions were created with a 95:5 intensity ratio

Table 1 Patients' characteristics

Case[a]	Age	Sex	Handed-ness	Educ.[b]	Aetiology[c]	Delay[d]	Site of lesion[e]	Neuropsychological deficits[f]
R1	37	F	R	I	I	9 y	Ts, Pi-sm, Fi-m, Ins	Const apr, executive, memory (VS)
R2	58	M	R	II	I	4 m	Ts, Pi-sm-psc, Fi-m-prc, Ins, Bg	Neglect, cons apr, VS, exec, VS memory
R3	41	M	L	I	H	10 w	Ins, claustrum, Bg	Neglect, const apr, exec, slowing down
R4	62	M	R	I	I	2 m	Tm-s, Pi-sm-ang-psc-s, Fi-m-prc, Om, Ins, Bg	Neglect, const apr, VS, exec
R5	63	M	R	III	H	10 w	Ts, Pi, Fi-prc, Ins, Bg	Neglect, VS, const + IM apr, exec, memory
R6	56	M	R	II	H	24 m	Fi-m, anterior Ins, Thal, Bg	VS, exec (neglect)
R7	64	F	R	I	I	2 m	Ts, Pi-sm-ang-psc, Fi-m-prc, Ins, Cc	Const apr, VS memory (neglect)
R8	59	F	R	I	I	3 m	Ts, Ppsc-i, Fi-m-prc, Thal, Bg, Ins	Neglect, const + IM apr, exec, memory
R9	65	M	R	II	I	3 w	Ts, Ppsc, Fprc, Ins	Neglect, aprosodia, exec, slowing down
R10	54	M	R	I	I	1 m	Tp-i-s, anterior Ins, Bg	Neglect, const apr, executive, VS memory
R11	54	M	R	II	CHI	40 m	Tp-i-m-fus, Hipp, para-hipp	VS, const apr, landscape rec, naming, exec, memory
R12	66	F	R	II	H	1 m	Tm-s, Ppsc-i, Ins, Bg	Neglect, visual rec, const apr, exec, memory
R13	38	F	R	II	H	1 m	Thal	Attention, slowing down
R14	48	M	R	II	I	30 m	Tm-s, Pi-sm, Fprc, Ins, Bg, ant. Thal	Singing (neglect)
R15	46	F	R	II	I	34 m	Ts, Pi-psc, Fprc, ant. Ins, Bg, Thal	Exec, attention, const apr (neglect)
R16	59	M	R	II	H	2 m	Ti-s, Pi-s, Oa	Neglect, const apr, exec, memory
R17	23	F	R	I	I	1 m	Tp-i-s, Pi-sm-ps, Oi Ins	Neglect, exec, memory, slowing down
R18	58	F	R	II	I	1 m	Tpi-s, ant. Ins, lent	Neglect, const apr
R19	53	M	R	II	H	10 w	Tp-m, Bg, lent	Neglect, VS memory, const apr, exec
R20	61	M	R	II	I	1 m	Tp, Pa, ant. Ins, lent	Exec, mem V, neglect, slowing down, attention
R21	33	M	R	III	H	3 m	Fi, Tm-s, ins, lent	Exec, neglect, constructional apr, attention, slowing down
R22	61	F	R	I	I	3 w	Fp, Ta, Par-a, Ins, lent	Neglect, memory, exec
R23	63	F	L (c)	I	I	1 m	Pre-F, Thal, Mes	Exec, memory
R24	62	F	R	II	H	2 w	Fi-m	Negl, exec, const apr.
R25	32	F	R	II	H	2 w	Tp, smg, Pi	Slowing down, const apr., memory,
L1	49	F	R	II	I	22 m	Tm-s, Pi-sm-ang-psc, Fi-m-prc, Ins	Global A, IM apr, exec, memory
L2	34	M	R	III	I	6 w	Tm-s, Tm-Om junct., Ins, Bg, Hipp	Broca A, IM apr, exec
L3	57	F	R	III	H	1 m	Ts, Pi-psc, Fprc, posterior Ins	Broca A, exec
L4	69	F	R	III	H	4 m	Caudate nucleus, cuneus, precuneus	Naming, visual rec
L5	64	F	R	I	H	18 m	Ti-m-s, Pi, Fi, Ins	Wernicke A, exec
L6	49	F	L	III	H	10 m	Tm-s, Pi-sm, Ins, Hipp	Conductional A
L7	38	M	L	II	H	12 m	Ppsc-i, Fprc	Phonetic disintegration, slowing down
L8	41	M	R	I	L	25 m	Tfus, Hipp, para-hipp, amygdale	Memory, exec, personality modifications
L9	36	M	R	II	H	6 w	Ti-m-s, Pi-sm, Ins, Hipp, Bg	Wernicke A, visual rec, const + IM apr, exec
L10	56	F	R	II	I	6 w	Tm-s, Pi-pstc-sm, Fi-m-prc, Ins, Bg, amyg, Hipp	Global A, exec
L11	36	M	R	III	H	29 m	Tm-s, Ins, Hipp, Bg	Wernicke A
L12	68	F	R	I	H	9 w	Thal, Bg, claustrum	Trans sens A, visual rec, const + IM apr, exec, memory
L13	32	F	R	I	H	2 w	Ins, Bg	Fluent A, memory
L14	63	F	R	I	H	3 m	Tm-s, Fi-prc, anterior Ins, Bg	Non-fluent A, exec
L15	59	M	R	III	I	2 m	Scattered: Tm-s, Fi-m, Bg	Broca A, IM apr
L16	41	M	R	III	I	2 w	Ti-m-s, Pi-sm	Cond A, memory,
L17	52	F	R	II	H	6 w	Ti-m-s, O, Pi	Wernicke A, const + IM apr, memory
L18	55	F	R	I	H	1 m	Fi-prc, caudate nucleus	Trans Mot A, slowing down, IM apr, exec, memory
L19	17	F	R	I	H	5 m	Fi-m-prc, Ti-m-s, Pi-sm, Putamen	Broca A, memory
L20	36	M	L	I	H	4 m	Tm-s, Pi	Neglect, exec, memory, constructional apr

(continued)

Table 1 Continued

Case[a]	Age	Sex	Handed-ness	Educ.[b]	Aetiology[c]	Delay[d]	Site of lesion[e]	Neuropsychological deficits[f]
L21	46	M	R	II	I	4 m	Tm-s, Pi-psc	Global A
L22	57	M	L	II	H	2 m	Ta, Pi	Non-fluent A, memory, exec
L23	44	M	Both	I	I	1 m	Fa, Tm-s, Pi-psc, Ins	Broca A
L24	62	M	R	I	I	3 m	Fa, P, T, Ins	Broca A, exec, memory
L25	47	F	R	III	I	2 m	Putamen, caps. Int.	Broca A

a Patients R1–R25 had a unilateral right and L1–L25 a unilateral left damage.
b Education level: (I) no professional training; (II) professional training of 3 years or more; (III) graduation from university.
c Aetiology: I = Ischaemia, H = Haemorrhage, L = Lobectomy.
d Interval between onset of illness and present investigation: w = week, m = month, y = year.
e Capital letters F, O, P, T stand for frontal, occipital, parietal and temporal lobes, respectively; Cc = corpus callosum; Bg = basal ganglia; Thal = thalamus; Ins = insula; Hipp = hippocampus; ang = angular gyrus; fus = fusiforme; i = inferior; m = middle; p = pole; prc = precentral; psc = postcentral; s = superior; sm = supramarginal.
f Neuropsychological impairment at the moment of testing: A = aphasia; const apr = constructional apraxia; exec = executive disorder; IM apr = ideomotor apraxia; neglect = visual hemineglect (at least at cancellation or bisection tasks); rec = recognition deficit; VS = visuo-spatial impairment (assessed by topographical orientation, the Hopper test or the Benton line test); () = impairment at the initial stage of illness but resorbed at the moment of testing.

favouring either the left or right ear, and the intermediate positions with a 75:25 intensity ratio. The central stimulus was perfectly identical to the central stimulus of the ITD version.

Both ITD and IID tasks used the same procedure. During the testing session, subjects sat in a quiet room and heard the stimuli through earphones (Sony MDR-CD480) directly linked to the computer. A graduated semi-circle affixed to the headphones was used to determine the angular value of the perceived position (from 0° at the vertex, to 90° at each ear). The subjects were asked to indicate the perceived position on their head with the index finger of their ipsilesional hand (same procedure as Altman *et al*., 1979; Bisiach *et al*., 1984). Half of the control subjects were instructed to use their right hand, and the other half their left hand. The two lateralization tests were administered in two different sessions not separated by more than one week. Half of the patients and controls did the interaural intensity difference version first, and the reverse order was applied for the remaining patients.

To quantify the overall performance of auditory lateralization, a relative score was computed by comparing the relative positions attributed to two consecutive stimuli. A response was counted as correct when a stimulus was correctly placed to the left or the right of the previous stimulus in correspondence with the interaural difference or within ±10° of the previous location for identical stimuli (maximal score 59). This score has proved to be a sensitive global measure of overall performance (Clarke *et al*., 2000; Bellmann *et al*., 2001). For individual analyses of patients, each result was converted into a *z*-score relative to the mean and standard deviation of the control (CTRL) population; the limit of normal performance was set 2 SD below the mean (i.e. *z*-score < –2). More specific measures were intended to reveal potential error types described in the literature. The incidence and direction of alloacusis was recorded. Discrimination between neighbouring positions was assessed at the individual level with a series of *t*-tests between reported positions of nearby lateralizations (LLvsL; LvsC; CvsR and RvsRR).

Results

Spatial processing by healthy controls

The average relative score was 57.15 (SD = 1.79) for ITD lateralization, and 56.95 (SD = 1.84) for IID lateralization (see Supplementary Fig. 1). Control subjects never exhibited alloacusis. Their pointing responses were very precise at the central position (average intra-individual variability of 5.69°, SD = 6.480 for the ITD test and of 6.73°, SD = 8.86 for the IID test), less so in the left and right hemispaces (ITD: 10.98°, SD = 5.050 and 11.59°, SD = 5.070, respectively/IID: 11.29°, SD = 5.11 and 11.91°, SD = 5.66, respectively). In the ITD test, failure to differentiate intermediate and extreme lateral stimuli, as determined by non-significant *t*-test comparisons, was found in 10% of normal subjects, either for the left or right hemifield; controls never failed to differentiate intermediate and extreme (R-RR;L-LL) stimuli in both hemifields. In the IID test, one subject did not differentiate significantly intermediate and extreme positions on the left, and another on the right. The scores of overall performance were influenced neither by age [ITD: $F(2,57) = 1.47$, $P = 0.239$/IID: $F(2,57) = 0.43$, $P = 0.958$] nor by the pointing hand [ITD: $F(1,58) = 0.417$, $P = 0.522$/IID: $F(1,58) = 1.44$, $P = 0.235$]. The average angular values attributed to each stimulus and inter-individual variability are shown in Supplementary Fig. 1. There was no statistically significant difference between the relative scores of the ITD and IID versions [$F(1,59) = 0.364$, $P = 0.547$]. Individual results on ITD and IID tasks were positively correlated [$r(58) = 0.316$, $P = 0.0134$].

Spatial processing between controls and groups of patients

Relative lateralization scores i.e. the comparison of the relative positions attributed to two consecutive stimuli, were assessed by a 3X2 ANOVA with Group (Controls, LHD, RHD) as the between subjects factor and Cue (ITD, IID) as the within subjects factor. There was a main effect of Group [$F(2,107) = 23.006$, $P < 0.001$], a main effect of Cue [$F(1,107) = 20.243$, $P < 0.001$] and a significant interaction between Group and Cue [$F(2,107) = 11.994$, $P < 0.001$]. Number of Alloacusis was assessed by a $3 \times 2 \times 2$ ANOVA with Group (Controls, LHD, RHD) as the between subject factor and Cue (ITD, IID) and Side of Alloacusis (L-to-R, R-to-L) as within subject factor. Results revealed a main effect of Group [$F(1,106) = 27.436$, $P < 0.001$], a main effect of Cue [$F(1,106) = 4.953$, $P < 0.03$] and a main effect of Side of

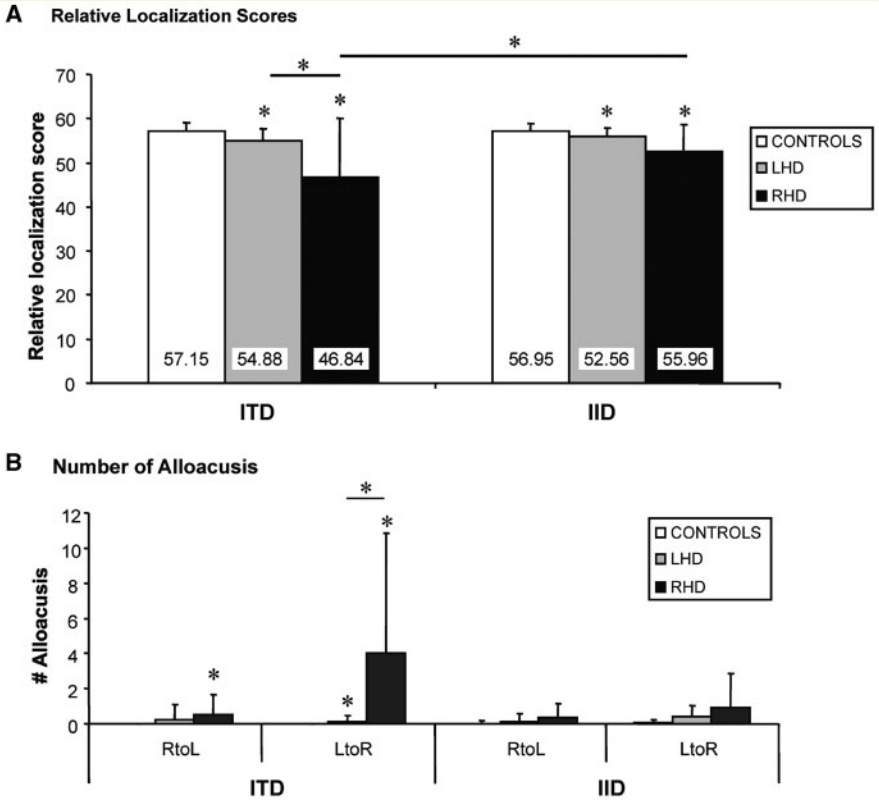

Figure 1 (**A**) Mean relative score (±SD) for RHD (black), LHD (grey) and controls (white). (**B**) Mean number of alloacusis (±SD; RtoL = right to left; LtoR = left to right). The asterisk indicates a score significantly different (at a threshold of <0.05) from the controls or difference between patient groups (when over bar).

Alloacusis [$F(1,106) = 16.344$, $P < 0.001$]. The ANOVA also showed significant interactions between Group and Cue [$F(2,106) = 5.939$, $P < 0.005$], Group and Side of Alloacusis [$F(2,106) = 13.134$, $P < 0.001$] and Group, Cue and Side of Alloacusis [$F(2,106) = 4.382$, $P < 0.02$].

Given the significant interactions between Group, Cue and performance indexes we performed separate ANOVAs for the ITD and IID test and within RHD and LHD groups.

Performance of patients on the ITD and IID lateralization tasks

ANOVAs with Group as the between subject factor and each ITD performance index as the within subject factor were performed. For the Relative score index, there was a significant main effect of Group [$F(2,107) = 21.542$, $P < 0.001$]. Follow-up *t*-tests revealed that scores of RHD and LHD were significantly more impaired than Controls and that RHD were more impaired than LHD (Fig. 1A). For Number of Alloacusis there was a main effect of Side of Alloacusis [$F(1,106) = 9.288$; $P < 0.005$], a main effect of Group [$F(1,106) = 22.778$; $P < 0.001$] and an interaction between Group and Side [$F(1,106) = 9.698$; $P < 0.001$]. Follow-up *t*-tests revealed that RHD committed significantly more R to L alloacusis than Controls and more L to R than Controls and LHD. LHD committed more L to R alloacusis than Controls (Fig. 1B).

Follow-up ANOVAs with Group as the between subject factor and each IID performance index as the within subject factor were performed. For the Relative score, there was a main effect of Group [$F(2,107) = 16.863$, $P < 0.001$]. *Post hoc t*-tests revealed that RHD and LHD were significantly more impaired than Controls (Fig. 1). For Number of Alloacusis, there was a main effect of group [$F(2,107) = 15.076$, $P < 0.001$], a main effect of factor 'side of alloacusis' (R to L; L to R) [$F(1,107) = 9.933$, $P < 0.003$] and a significant interaction between Group and Side [$F(2,107) = 4.331$, $P < 0.02$]. Given these results, follow-up ANOVAs were performed with Cue and performance indexes as the within subject factors. For the Relative score, neither main effect nor the interaction reached our significance level. For Number of Alloacusis, there was a main effect of factor Side (R to L; L to R) [$F(1,23) = 7.863$, $P < 0.02$], indicating that L to R alloacusis were more frequent than R to L in the ITD test.

Discrimination between neighbouring positions in the left- and right-hemispace in RHD and LHD

Discrimination between neighbouring positions was assessed at the individual level with a series of *t*-tests between reported positions of nearby lateralizations (LLvsL; LvsC; CvsR and RvsRR). Resulting *P*-values were then group-averaged for each pair in

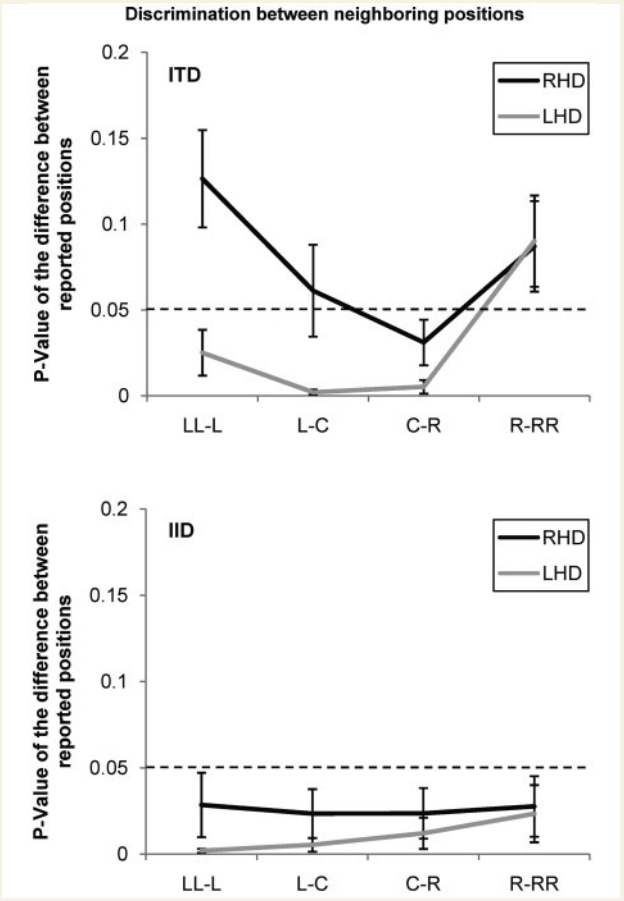

Figure 2 Mean *P*-value (±SEM) of the *t*-tests between neighbouring positions in the ITD and IID conditions (LL = extreme left, L = left, C = centre, R = right, RR = extreme right). High (>0.05) *P*-value correspond to inability to differentiate neighbouring positions. In the ITD condition, RHD is associated with imprecision in the both auditory hemispaces, whereas LHD deficits only with imprecision in the contralesional (right) hemispace.

order to examine whether precision in left and right hemispace was similarly affected in the RHD and LHD groups. Results suggest more severe deficits in the ITD than IID condition. Moreover, RHD show more severe imprecision than LHD in the whole space, with an asymmetry favouring the right hemispace in LHD but not RHD (Fig. 2). This pattern of results suggests the prominent involvement of the left hemisphere in the processing of the contralesional (right) hemispace, whereas the right hemisphere would be involved in precise computation of the whole of (frontal) auditory space.

Multiple single case analysis

Individual results for the relative score and for each of the specific dimensions assessed in our tests are shown in Table 2. The average position attributed to each lateralization is individually illustrated in Supplementary Fig. 1A (RHD) and B (LHD).

ITD test

Individual data confirmed and supplemented the group analysis.

Relative lateralization

In the ITD test, 15 out of 25 RHD patients had a deficient relative score, whereas only 6 out of 25 LHD patients were significantly impaired. Deficits were not only more frequent, but also more severe after right hemispheric lesions: *z*-scores indicating deficient performance ranged from –2.3 to –28.4, whereas they were not inferior to –5.1 among the LHD group. Three patients heard all the stimuli at the same place either near the centre (R1), or on the right (R7 and R19, see Supplementary Fig. 1). This lack of sound position discrimination was confirmed by the *t*-tests comparing locations attributed to stimuli with close ITDs: none of the adjacent simulated positions were significantly differentiated (Table 2). Although less severe, three other RHD showed inability in discriminating contiguous positions (three out of four pairs of stimuli were not differentiated in R4, R8 and R20); these deficits mainly concerned extreme lateral positions. This massive impairment can be labelled as *a complete* inability of processing ITD cues, and was found exclusively in RHD patients. The imprecision profile was quite different in the LHD patients, where it was mainly confined to the contralesional (i.e. the right) hemispace (10 out of 25 patients showed deficits in discriminating between right-lateralized stimuli only). In summary, the failure to discriminate spatial positions was principally limited to the contralesional hemispace in LHD patients, whereas it involved the whole frontal space in RHD patients.

Alloacusis to the ipsilesional hemispace were found in 14 RHD and only 3 LHD patients. In RHD, these errors were frequent (R2, R7 and R19, Fig. 1B) or occasional. Spatial bias toward the right hemispace was associated with severe spatial discrimination deficits in R2 and R19.

IID test

Performance deficits were overall less frequent and less severe in the IID than ITD test. However, as in the ITD test, RHD showed more frequent and more severe deficits than LHD for IID-lateralized stimuli.

Relative lateralization

Ten RHD were significantly impaired in relative lateralization. Only two patients showed a *z*-score below –4.3 (R1 and R22), the others had scores ranging from –4.3 to –2.1 following RHD and from –3.2 to –2.1 following three LHD. Complete inability for spatial discrimination was never found in LHD. When comparing positions attributed to neighbouring positions (Table 2, precision inter-stimuli), two RHD showed inability in discriminating three out of four pairs of stimuli (R1 and R22).

Alloacusis were also less frequent and occurred in fewer patients in the IID than ITD test.

Table 2 Individual results of the 50 patients for the ITD and IID lateralization tests

	ITD lateralization test						IID lateralization test					
Cases	Relative lateralization z-score[a]	Alloacousis[b]	Precision Inter-stimuli[c] (ns p-val)				Relative lateralization z-score[a]	Alloacousis[b]	Precision Inter-stimuli[c] (ns p-val)			
			LL-L	L-C	C-R	R-RR			LL-L	L-C	C-R	R-RR
R1	**–28.4**	0	■	■	■	■	**–15.8**	0	■	■	■	■
R2	**–12.3**	13 (R)	■				–1.6	1 (R)				
R3	–0.08	0					+0.03	0				
R4	**–16.2**	6 (R)	■	■		■	**–3.2**	0				
R5	–1.75	2 (R)	■			■	–1.6	0		■		
R6	+0.5	0					+0.03	0				
R7	**–17.9**	23 (R)	■	■	■	■	**–4.3**	1 (R)				
R8	**–5.1**	1 (R)	■		■	■	–1.6	4 (R)				
R9	**–4.5**	1 (L)	■			■	**–2.1**	2 (L)	■		■	
R10	–0.6	0					–0.5	0				
R11	+0.5	0					+1.1	0				
R12	**–4**	2 (R) 1 (L)	■			■	–1.1	2 (R)				
R13	+1	0					+1.1	0				
R14	–1.75	0					–1.6	3 (R) 1 (L)				
R15	–0.08	0				■	+0.6	2 (L)				
R16	–1.2	0					–1.1	0				
R17	**–4**	0	■				**–3.8**	0				
R18	**–2.3**	1 (R)					**–2.1**	1 (R)				
R19	**–17.9**	23(R)	■	■	■	■	**–4.3**	5 (R)			■	
R20	**–4.5**	9(R) 5 (L)	■		■	■	–1.1	2(R)		■		
R21	**–5.1**	4(R) 2(L)	■	■			**–2.1**	0				
R22	**–2.3**	2 (R)	■				**–7.1**	8 (R)	■		■	■
R23	**–4**	1(R) 2 (L)				■	**–2.7**	1 (R) 3 (L)				
R24	**–10.7**	9(R) 2(L)	■		■		**–3.2**	0				
R25	–0.6	0					–1.6	0				
L1	**–2.9**	1 (L)				■	+0.03	1 (R)				
L2	**–5.1**	0			■	■	–1.69	0				■
L3	+0.5	0					+0.6	1 (R)				
L4	–1.75	0	■				**–2.1**	0				
L5	**–4.5**	0				■	+0.03	0				
L6	–0.6	0					–0.5	0				
L7	–1.75	0					–1.1	2 (R)				
L8	+1	0					+0.06	0				
L9	+0.5	0					–1.1	0				
L10	–1.75	4 (R)					–0.5	0				
L11	–0.6	0					+0.6	0				
L12	–1.75	0				■	–1.6	1 (R)				
L13	–0.08	0					**–2.1**	0				
L14	+0.5	0					+0.6	0				
L15	+1	0					–0.5	0				
L16	–1.75	0				■	–0.5	0				
L17	–0.6	1(R)	■			■	+1.1	2(L)			■	
L18	–0.08	0					+0.6	1 (R)				
L19	**–2.3**	0					–1.6	0				
L20	**–2.3**	0				■	**–3.2**	0				■
L21	–1.75	1(R)	■			■	–0.5	0				
L22	–1.2	0					–0.5	1 (R)			■	
L23	–0.08	0	■			■	+0.6	0				
L24	**–2.3**	0					–0.5	1 (R) 1 (L)		■		
L25	–1.75	1 (R) 1 (L)				■	+0.03	2 (R)				

Relative *z*-score and other dimensions considered.
a Values >2 SD below the mean of the control population are in bold.
b No of alloacusis to the *right* hemispace (*R*) or to the *left* hemispace (*L*).
c Discrimination between the contiguous positions. Results of the *t*-tests between the extreme and intermediate left stimuli (LL-L), intermediate left and central stimuli (L-C), central and intermediate right stimuli (C-R) and intermediate and extreme right stimuli (R-RR); *P*-values above threshold of 0.05 are coloured in black; NS = non-significant.

ITD versus IID test correlations

There was a strong positive correlation between the relative scores in the ITD and IID tests by RHD, whereas LHD showed only a trend [correlation index: RHD: $r(23) = 0.78$, $P < 0.001$ and LHD: $r(23) = 0.36$, $P = 0.07$], suggesting the involvement of the right hemisphere in processing stages where both cues are integrated. However, despite this correlation, clear differences were observed between performances on the two tests. As mentioned above, in the IID test, no patient had complete inability for spatial discrimination, and none displayed systematic directional error to the ipsilesional hemispace.

Anatomo-clinical correlations

In our population, lesions tended to be smaller in the right than left hemisphere (Fig. 3A for the lesion density maps across all 20 patients). Furthermore, the parietal lobe tended to be more greatly and more often involved in the left than the right hemisphere. Thus, the more severe deficits observed after right than left hemispheric lesions cannot be ascribed to larger size of the implicated lesions or to a greater involvement of the parietal lobe.

A VLSM was performed on a subset of 20 patient's lesions (10 RHD: R16-R25, and 10 LHD: L16-L25) to explore any possible

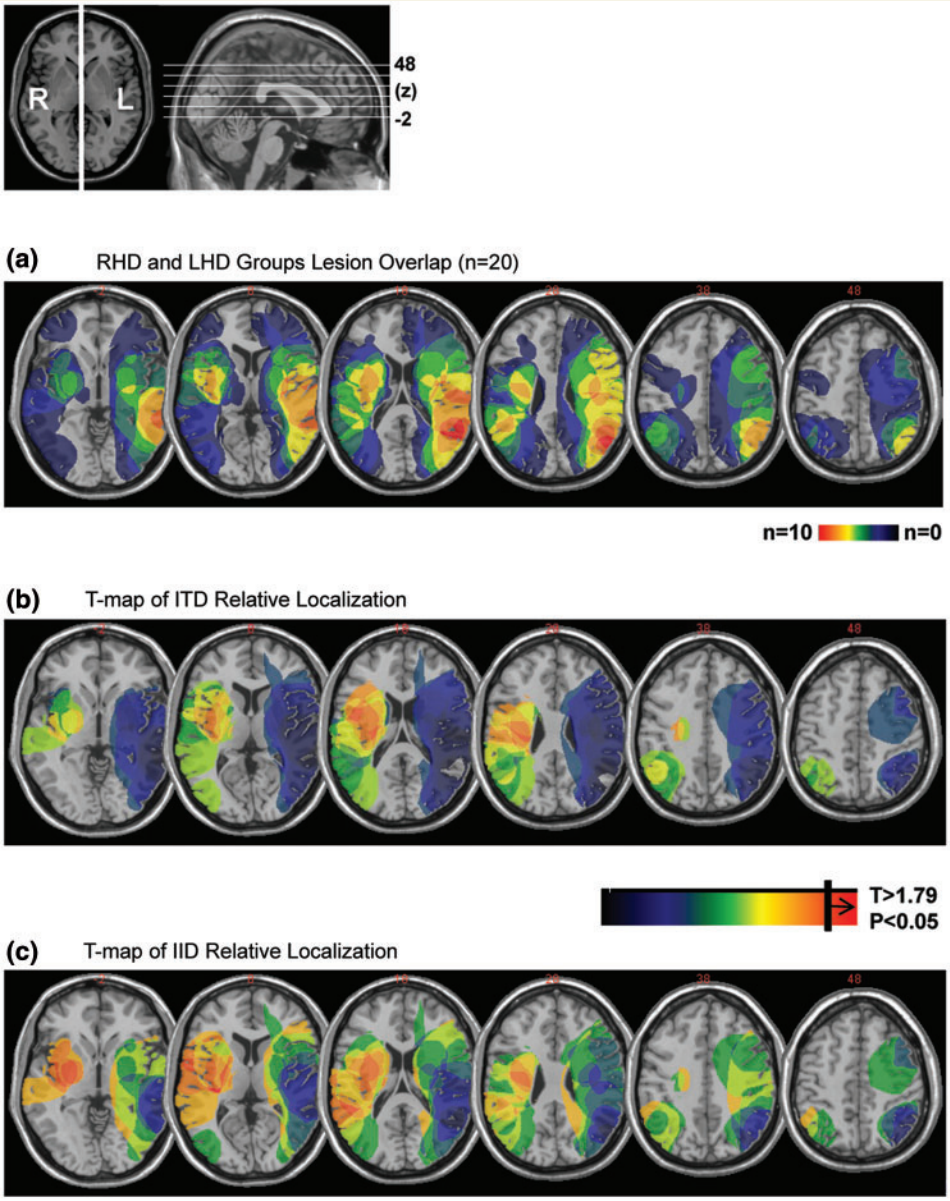

Figure 3 Voxel-based lesion-symptom mapping on the subgroup of 20 patients (L16–L25; R16–R25) show the relationship between localization performance and brain lesions; right hemisphere on the left. (**A**) RHD and LHD groups lesion overlap. (**B** and **C**) Colours displayed at each voxel are the values of the *t*-tests between patients in who the corresponding voxel is intact versus damaged. T-map of the ITD (**B**) and IID (**C**) relative localization score suggests that right hemispheric lesions yields more severe deficits than left hemispheric lesions.

relationship between behavioural performance and the sites of brain damage. *t*-tests were performed on a voxel-by-voxel basis to compare performance in patients with versus without lesion in each voxel. Figure 3A and B shows colour-coded *t*-values mapped onto the MNI template. Results revealed a more important involvement of the right than left hemisphere in ITD and IID relative lateralization. Regions of brain damage significantly associated with lateralization impairment notably include right temporal areas [$t(19) > 1.729$, $P < 0.05$, Fig. 3A and B].

Discussion

Our study documents the involvement of the cerebral hemispheres and specific cortical lesion sites in the processing of binaural spatial cues. The large sample of patients presented with the same battery of tests as well as the conjunction of group and individual analyses bring further insight into the structural and functional organization of auditory spatial processing specifically and of the 'Where' system in audition more generally. Our results are relevant to two major issues: (i) inter-hemispheric and intra-hemispheric specializations for auditory localization; and (ii) partially differential specialization of the auditory spatial system for the processing of ITD and IID cues.

Right hemispheric dominance for auditory localization

Right hemispheric dominance for auditory localization was found for both binaural cues. Group analysis of our data revealed significantly more severe impairment of auditory localization in the right hemispheric damage (RHD) than in the control or left hemispheric damage group (LHD). In the LHD, but not RHD group, imprecision, assessed by comparing localization performance between neighbouring positions, was more severe within the right (contralateral) than left hemispace. Deficits in discrimination between neighbouring positions were evident in both hemispaces in RHD and prominently restricted to the contralateral (right) hemispace in LHD (Fig. 2), suggestive of the specialization of the right hemisphere in precise computation of the whole of frontal auditory space. Moreover, the significant positive correlation between ITD and IID performance in RHD but not LHD supports the role of right hemisphere in higher-order integration of spatial cues.

Single case analysis confirmed that RHD lead to auditory localization impairments that were more frequent, more severe, and qualitatively different than those in LHD. In particular, complete failure to localize sounds and frequent occurrence of alloacusis were found only after RHD. Nevertheless, the impairment in some patients with LHD speaks in favour of a left hemisphere contribution to sound localization. It follows that the right hemispheric dominance observed here cannot be understood as an exclusive involvement of one hemisphere, but rather as differential and asymmetrical involvement of each hemisphere. Although deficits after left hemispheric lesions have also been reported (Sanchez-Longo and Forster, 1958; Efron *et al*., 1983; Pinek *et al*., 1989; Clarke *et al*., 2000), this proposition is in accordance with previous lesion and neuroimaging studies suggesting right hemispheric dominance for sound localization (Lesion data: Altman *et al*., 1979; Ruff *et al*., 1981; Bisiach *et al*., 1984; Tanaka *et al*., 1999; Zatorre and Penhune, 2001; neuroimaging data: Kaiser and Lutzenberger, 2001; Ducommun *et al*., 2002, 2004; Herrmann *et al*., 2002; Lewald *et al*., 2002; Arnott *et al*., 2004; Krumbholz *et al*., 2005; DeSantis *et al*., 2007; Spierer *et al*., 2009).

Different types of auditory localization deficits on the ITD test

The variety of deficient performance emerging from the literature on auditory localization leaves suspect the existence of local specializations within the 'Where' pathway. The finding of different error types among our population on the same ITD localization task further supports this position.

Complete inability for spatial discrimination using ITD cues was found in 3 RHD patients, who failed to perceive any spatial difference between the stimuli. Similar deficits revealed by a similar testing paradigm have been described after brainstem lesions at the level of the trapezoid body (Furst *et al*., 1995; Aharonson *et al*., 1998; Pratt *et al*., 1998) and with other testing paradigms (discrimination of lateralization thresholds) in five patients whose lesions involved the right parietal lobe and auditory pathway (Tanaka *et al*., 1999) or the right inferior parietal, superior temporal and insular cortices (Griffiths *et al*., 1996). It is worth noting that auditory motion deafness has also been found following resection of the right anterior temporal lobe and the right posterior superior temporal gyrus (e.g. Ducommun *et al*., 2004).

Alloacusis, characterized by spatial bias to the ipsilesional hemispace, was observed almost exclusively in RHD patients, sometimes in association with complete inability in spatial discrimination. Alloacusis were particularly marked and systematic in three patients (R2, R7 and R19). This type of deficit has been interpreted as a manifestation of auditory neglect due to a systematic error in the transformation of spatial coordinates into an egocentric frame of reference (Bellmann *et al*., 2001). In previous studies, alloacusis was described not only under stereophonic conditions simulated with ITD (Altman *et al*., 1979) or IID (Bisiach *et al*., 1984), but also in free-field conditions (Haeske-Dewick *et al*., 1996; Soroker *et al*., 1997). Directional bias to the ipsilesional hemispace was also described with the subjective auditory midline paradigm (Vallar *et al*., 1995; Sterzi *et al*., 1996).

Imprecision in the whole auditory spatial field was found exclusively in RHD patients. These patients categorized all the stimuli, including the central ones, into 'left' or 'right' without differentiation inside each hemispace (R8, R9, R12, R14, R20 and R24). Similar responses were described after brainstem lesions at the level of the lateral lemniscus (Furst *et al*., 1995). Group studies of RHD patients have reported difficulty localizing para-central stimuli (Haeske-Dewick *et al*., 1996) or imprecision in the whole auditory field (Ruff *et al*. 1981).

Imprecision restricted to the contralesional hemispace was present mostly in LHD patients (only 3 RHD showed this pattern). Failure to differentiate intermediate and extreme right-sided stimuli at a statistically significant level was found in 10% of normal subjects. It occurred more frequently in LHD patients (24% with a deficit restricted to the contralesional hemispace; see Table 2). Lesions associated with sound localization deficits in LHD patients were not homogeneous. Nonetheless, a common feature was a lesion of the primary auditory cortex and/or interruption of the auditory callosal pathway. The left hemisphere may be involved primarily in the processing of spatial coordinates of contralesional sound sources and their transmission to the right hemisphere, via the corpus callosum, where they are integrated into an auditory spatial framework. The fact that impaired localization in the right hemispace was not found more often in the LHD group might reflect the compensation by the intact right-hemispheric mechanisms concerned with processing in the ipsilateral as well as contralateral hemispace.

Intrinsic organization of the 'Where' system for the processing of ITD cues

The heterogeneity of localization deficits and the evidence supporting their distinct anatomical correlates speak against a single sound localization mechanism. Two broad categories of errors were demonstrated: imprecision (in the whole space after RHD and in the contralesional hemispace after LHD), and biased and/or abolished spatial representation after RHD. The present data suggest a dual mechanism of auditory spatial processing: (i) processing of precise auditory spatial coordinates, implemented in both hemispheres; and (ii) integration of this information in an auditory spatial representation in the right temporo-parietal cortex.

Processing of precise auditory spatial coordinates

Effects of lesions suggest that the right hemisphere is concerned with the whole space, and the left hemisphere with the contralateral, right hemispace (see also Krumbholz *et al*., 2005 for fMRI evidence in healthy subjects). A similar hemispheric specialization has been described for visuo-spatial attention (Heilman and Valenstein, 1979). Comparison between patient's abilities to discriminate between neighbouring positions and their lesion description (Table 2) suggests that the superior temporal gyrus, insula and basal ganglia, are critical for precise localization, but not for right-left categorization. This rough spatial categorization may be sustained by the intact parietal cortex. The fact that our patients' lesions were large and that radiological description of the lesions were only available for 20 out of 50 patients did not allow finer description of the anatomical site(s) responsible for the processing of precise spatial coordinates. In what concerns the superior temporal gyrus, while some data from non-human primates suggest that the posterior supratemporal cortex rather than the primary auditory cortex is involved in spatial processing (Rauschecker, 1998; Kaas *et al*., 1999; see also Weeks *et al*., 1999 for human PET data), numerous animal electrophysiological (Brugge *et al*., 1996, Harrington *et al*., 2008) and lesion (King *et al*., 2007) studies indicate that neurons within primary auditory cortex are ITD-sensitive. More generally, our findings as well as prior studies in humans (e.g. Zatorre and Penhune, 2001) showing that lesions along the supratemporal plane are associated with sound localization deficits, lend further support to models of sound localization proposing that interaural cues are processed by distributed neural populations (e.g. Furukawa *et al*., 2000; Stecker *et al*., 2005). These and similar findings highlight how there is unlikely to be strict anterior versus posterior functional specialization for recognition and localization of sounds within the superior temporal lobe. Rather the whole of the superior temporal cortex appears to be involved (albeit perhaps to varying degrees and at varying latencies) in the spatial analysis of sounds. It will therefore be important to determine whether and when each functional region along the supratemporal plane is playing an essential role or rather if damage to underlying white matter tracks (that perhaps originate and/or terminate elsewhere or involve specific subsets of regions) is the basis for concluding there to be involvement of distributed supratemporal cortices in sound localization.

Integration to auditory spatial representation

Complete inability in spatial discrimination and alloacusis were found after right hemisphere lesions comprising the frontal and posterior parietal cortices, but not after similar left hemisphere lesions. Moreover, patients R1, R4, R7 and R19 could not use the spatial competencies of their left hemisphere to compensate for the deficit in the right hemispace. These results suggest that the right parietal and possibly frontal cortex, are necessary for the formation of a conscious and adequate representation of sounds in space and represent the ending point and keystone of the hierarchical organization of the 'where' system. Many studies have emphasized this function of integration, and building of conscious spatial representation of the human parietal cortex (Gentilucci *et al*., 1997; Karnath, 1997; Bellmann *et al*., 2001; Krumbholz *et al*., 2005; Spierer *et al*., 2007, 2008). A recent study demonstrated this in the auditory modality using transcranial magnetic stimulation with an ITD paradigm in normal subjects. The authors reported that focal stimulation of the posterior parietal cortex induced a systematic shift in the lateralization of ITD stimuli, whereas the acuity of ITD discrimination was unaffected (Lewald *et al*., 2002, see also Lewald *et al*., 2004). Our patients, with complete inability in spatial discrimination or alloacusis, all had visuo-spatial impairments, but some other patients, either normal or with imprecision errors also had similar difficulties. Although recent evidence demonstrates positive correlations between auditory and visuo-spatial neglect (Pavani *et al*., 2002; Spierer *et al*., 2007), in the present study there was no such clear relation between visuo-spatial and auditory manifestations of neglect. Functional studies have suggested the existence of both uni-sensory and multi-sensory spatial integration regions within the parietal lobe (e.g. Bushara *et al*., 1999; Macaluso and Driver

2005; Avillac *et al*. 2007). Further investigation is necessary to address this point with lesional studies.

The proposition that a first analysis of auditory spatial information is performed in the temporo-insular region before being further processed dorsally in the parieto-frontal regions is further supported by animal data. Electrophysiological recordings in the temporal cortex of non-human primates have revealed the existence of two parallel auditory streams, one dedicated to the analysis of sound content, and the other to the spatial processing of sounds. The latter involved the posterior part of the superior temporal gyrus (Rauschecker, 1998; Kaas *et al*., 1999). This posterior region is known to project further to parietal cortex and to the posterior and dorsal part of the frontal lobe (Romanski *et al*., 1999). Prior research from our group on the spatio-temporal mechanisms of auditory spatial functions would suggest that there is extensive interplay between temporal and parietal cortices in the localization of sound sources that occurs over several parallel stages (Ducommun *et al*., 2002; DeSantis *et al*., 2007; Spierer *et al*., 2007, 2008, 2009; see also Krumbholz *et al*., 2005, Tardif *et al*., 2006). Specifically, we have proposed that parietal regions may be particularly involved in the transformation of spatial representations into coordinates and/or reference frames, whereas temporal regions would be more implicated in both relative and absolute localization of sounds sources (Spierer *et al*., 2008, 2009; see also Lewald *et al*., 2002). This conceptualization of auditory spatial processing as involving (at least) two stages between temporal and parietal regions as well as distinctions between whether auditory spatial information is being used for truly spatial or instead for more action-related purposes, would support a more nuanced understanding of the dorsal 'Where' auditory system (e.g. Middlebrooks, 2002; Zatorre *et al*., 2002; Hickok and Poeppel, 2007). That is, this system would appear to not only serve spatial functions, but also functions linked to establishing a sensory-motor capacity to interact within the surrounding environment.

Partially differential specialization of the auditory spatial system for the processing of ITD and IID cues

The results on the IID test displayed both similarities and differences with those on the ITD test. Right hemispheric dominance, though less pronounced, was also seen with IID cues, and a positive correlation linked the individual results on the two tasks in the RHD group. However, the interaction between group and cue was significant, and was found to be due essentially to better performance of the RHD group in the IID task. Individual data showed that two error types characteristic of RHD patients (complete inability to discriminate spatial positions and systematic alloacusis) were not found with IID cues. The distinction between global imprecision in RHD patients and contralesional imprecision in the LHD patients was also less clear in the IID than the ITD test. These differences between the two tasks could not be explained by differential task difficulty (relative scores were similar for ITD and IID tasks in the CTRL and LHD groups). Likewise, the order of administration of the tests could not account for the differences observed in the RHD group (no significant interaction between 'Order' and 'Condition').

Patients with lesions at the level of the brainstem have been found to have marked deficits in the processing of ITD cues, whereas the processing of IID cues was normal or at least less impaired (Levine *et al*., 1993; Griffiths *et al*., 1998). Furst and collaborators (1995) have even found that the profile of complete inability of spatial discrimination (all stimuli located at the midline) occurred only in ITD condition, whereas lateralization errors (all the stimuli either attributed to the right or to the left) could occur with ITD or IID cues. These authors concluded that at least partially distinct mechanisms might be involved for the analysis of these two types of cues. A similar conclusion can be drawn from our results at the cortical level. The 'Where' system does not seem to operate on the basis of a unique spatial code independent of the nature of the cue. We propose that the articulated system described above operates on the basis of binaural cues (ITD and perhaps also IID cues) already processed at the level of the brainstem and further analysed for precision and elaboration of a spatial representation at the cortical level. ITD cues might be particularly relevant for this processing because they are constant for a given individual (though changes during development occur as the head grows, leading to increases in interaural distance), unlike IID cues which can be altered, for example, by a clogged ear. IID cues can be treated as binaural cues, computed at the level of the brainstem and sent as 'spatial code' to each hemisphere, but also as monaural cues. Given the asymmetry of crossed and uncrossed auditory fibres, the auditory cortex contralateral to the loudest signal will be more activated. An inter-hemispheric comparison of the amount of intensity received by each hemisphere could be used for rough sound localization. We postulate that such a monaural system of auditory localization can be recruited on the basis of IID cues to complete the processing of the binaural system of localization operating essentially on ITD cues. The intervention of this inter-hemispheric comparison might explain why patients with damaged temporo-parietal regions, but preserved inter-hemispheric communication, recovered the ability to differentiate left from right targets.

In conclusion, our study documents the involvement of the cerebral hemispheres in spatial processing of sounds. Sound localization deficits were found after temporo-parieto-frontal lesions, predominantly on the right, which is congruent with the dorsal 'where' system in audition as inferred from electrophysiological recordings in animals, and from neuroimaging and previous lesion studies in humans. Furthermore, this study brings insight into the organization of this 'where' system, highlighting the interplay between supratemporal and parietal cortices. Both anatomical and psychoacoustic factors were found to influence performance on auditory localization. Deficits were more severe and frequent after right temporo-fronto-parietal lesions, and with the ITD cues. We propose the existence of a binaural system of sound localization essentially based on ITD cues, composed of two mechanisms: (i) precise computation of spatial coordinates concerning the contralateral hemispace for the left hemisphere and the whole hemispace for the right hemisphere; and (ii) building up of an auditory space representation in the right temporo-parietal cortex.

Supplementary material

Supplementary material is available at *Brain* online.

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