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Patterns of recovery following focal hemispheric lesions: Relationship between lasting deficit and damage to specialized networks

THESE

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Rapport de synthèse

Patterns de récupération auditive au décours de lésions hémisphériques focales: relation entre déficit durable et dommage à des réseaux spécialisés

Objectif :

Les déficits cognitifs présents dans la phase aiguë d'une lésion hémisphérique focale ont tendance à être de nature plus importante et plus générale que les déficits résiduels qui persistent dans la phase chronique de récupération. Nous avons investigué, dans le cadre de ce travail, les modèles de récupération auditive et la relation qui se dessine entre les déficits et les dommages relatifs à des réseaux spécifiques, pris comme modèle cognitif des fonctions auditives.

De nombreuses études humaines dans les domaines de la neuropsychologie, de la psychophysique ainsi que des études d'activation suggèrent que les processus de reconnaissance et de localisation sonores sont effectués par l'intermédiaire de réseaux distincts tant sur le plan anatomique que fonctionnel : il s'agit des zones de traitement du « What » et du « Where », qui sont toutes deux présentes dans les deux hémisphères. Des études ont démontré que des lésions hémisphériques focales gauches ou droites, centrées sur ces réseaux, sont associées dans la phase chronique de récupération à des déficits correspondant en ce qui concerne la reconnaissance et/ou la localisation sonore.

Méthode :

Dans le cadre de ce travail, nous avons analysé les résultats concernant les performances auditives chez 24 patients ayant subi des lésions hémisphériques focales avec déficits secondaires dans des tâches de reconnaissance, de localisation et/ou de perception du mouvement sonore lors d'un premier testing effectué en phase aiguë (9 patients), en phase subaiguë (6 patients) ou en phase chronique précoce (9 patients). La totalité de ces patients ont bénéficié d'un second testing en phase chronique. Les observations effectuées ont servi à l'élaboration de patterns de récupération auditive.

Résultats :

Tous les 24 patients avaient initialement un déficit dans le domaine de la localisation et/ou de la perception du mouvement sonore. Dans la phase aiguë, ce déficit survenait sans atteinte spécifique du réseau « Where » chez presque la moitié des patients ; en revanche, cette situation n'était jamais observée chez les patients testés en phase chronique précoce.

Une absence de récupération avait tendance à être associée à un dommage spécifique au réseau concerné ainsi qu'à la persistance d'un déficit au-delà de la phase aiguë. Les déficits résiduels n'étaient par ailleurs pas strictement en lien avec la taille lésionnelle ou l'étendue de l'atteinte du réseau spécifique.

Conclusion :

Nos résultats suggèrent que des mécanismes distincts sous-tendent la récupération et la plasticité à différentes périodes temporelles post-lésionnelles.

Mots-clefs :

Cortex auditif ; phase aiguë, subaiguë et chronique de récupération ; plasticité ; « What » et « Where »

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Patterns of recovery following focal hemispheric lesions: Relationship between lasting deficit and damage to specialized networks

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Abstract. *Purpose*: Cognitive deficits that are present in the acute stage of a focal hemispheric lesion tend to be greater and more general than residual deficits, which persist into the chronic stage. We have investigated the patterns of recovery and the relationship between deficits and damage to specialized networks taking as model auditory cognitive functions. Evidence from human psychophysical, activation and neuropsychological studies suggests that sound recognition and sound localization are processed in anatomically and functionally distinct cortical networks, the auditory "What" and "Where" processing streams, that are each present in both hemispheres. Focal left or right hemispheric lesions centred on these networks were found to be associated, in the chronic stage, with the corresponding deficits in sound recognition and/or sound localization.
Methods: We report here on recovery patterns in 24 patients who sustained focal hemispheric lesions and were deficient in sound recognition, sound localization and/or sound motion perception at a first evaluation in the acute ($n = 9$), subacute ($n = 6$) or early chronic stages ($n = 9$).
Results: All 24 patients had initially a deficit in sound localization and/or sound motion perception. In the acute stage this deficit occurred without damage to the auditory "Where" stream in almost half of the patients, a situation which was never observed in the early chronic stage. Lack of recovery tended to be associated with damage to the specialized stream plus the persistence of deficits beyond the acute stage, and was only loosely related to the size of the lesion and to the extent of damage to a specialized network.
Conclusions: Our results suggest that different mechanisms underlie deficits and recovery at different time points.

Keywords: Auditory cortex, acute stage, subacute stage, chronic stage, plasticity, "What" and "Where"

1. Introduction

Increasing amount of evidence suggests that recovery from cognitive or motor deficits following focal hemispheric lesions relies on the recruitment of cortical areas that sustain these functions in normal subjects plus areas that do not (Rijntjes, 2006). Recovery from aphasia was shown to be associated with enhanced speech-related activity in the left and the right hemisphere. Enhanced activity within the left hemisphere tended to be associated with better outcome, but the activation of specific right hemispheric foci was also correlated with recovery of specific language tasks (for recent reviews see e.g. Heiss & Thiel, 2006; Jordan & Hillis, 2006; Price & Crinion, 2005; Rijntjes, 2006).

The interpretation of activation data from aphasia recovery studies is difficult, partially because relatively the functional organisation of cortical areas involved in

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language in normal subjects are not fully understood. As in sensory systems, language appears to involve parallel processing streams, such as those for semantic and syntactic processing (e.g. Friederici, Ruschemeyer, Hahne & Fiebach, 2003; Pulvermuller, Assadollahi & Elbert, 2001; Viceic et al., 2006), but their precise anatomical substrate, including intra- and interareal organisation, and their contribution to recovery after lesions remain unknown. For this reason, we propose to investigate postlesional plasticity in a system that is closely related to language, audition, and for which more detailed anatomical and functional data are available.

Converging evidence from anatomical, physiological and lesion studies suggests that different attributes of sound, and in particular sound recognition and sound localization, are processed in at least partially independent cortical networks. The existence of separate processing streams for sound recognition and sound localization was initially proposed in non-human primate studies (for reviews see Kaas, Hackett & Tramo, 1999; Rauschecker & Tian, 2000). A similar organisation was shown to exist in man. Short-term memory tasks for sound content and sound localization revealed specific interference, suggesting that each aspect was supported by a distinct neural population (Anourova et al., 1999; Clarke, Adriani & Bellmann, 1998). Direct anatomical comparison of these processing streams was demonstrated in fMRI studies of normal subjects: sound recognition was shown to activate specifically a subset of non-primary auditory areas (Warren, Zielinski, Green, Rauschecker & Griffiths, 2002) and, on the convexity, the middle temporal gyrus and precuneus bilaterally and the posterior part of the left inferior frontal gyrus, while sound localization activated the lower part of inferior parietal lobule and posterior parts of the middle and inferior frontal gyri (Alain, Arnott, Hevenor, Graham & Grady, 2001; Maeder et al., 2001). These findings were further confirmed electrophysiologically (Alain et al., 2001; Anourova et al., 2001; De Santis, Clarke & Murray, 2007) and by other sound recognition (Engelien et al., 1995) or auditory spatial studies (Bushara et al., 1999; Griffiths, Buchel, Frackowiak & Patterson, 1998; Weeks et al., 1999; Zatorre, Bouffard, Ahad & Belin, 2002; Ziemann, Hallet & Cohen, 1998). Further evidence for separate neural networks for sound recognition and sound localization comes from patient studies. Relatively large lesions centred on the sound recognition or sound localization networks were found to be associated in the chronic stage with the corresponding deficits following right or left hemispheric lesions (Clarke, Bellmann, Meuli, Assal & Steck, 2000; Clarke et al., 2002; Fujii et al., 1990; Griffiths et al., 1997; Griffiths et al., 1996; Jerger, Lovering & Wertz, 1972; Rosati et al., 1982; Spreen, Benton & Fincham, 1965).

Although auditory cognitive deficits may persist into the chronic stage, some patients recover normal performance. We report here on patterns of recovery in three specific auditory cognitive functions – sound recognition, sound localization and sound motion perception – and explore the relationship between persistence of deficits and damage to specific auditory networks. We postulated two main hypotheses that we investigated here. First, lasting deficits in a given domain would not occur without damage to major parts of the corresponding specialized networks. Second, the persistence of deficits into subacute and early chronic stages would decrease the probability of recovery.

2. Methods

2.1. Subjects

Twenty-four patients who sustained focal hemispheric lesions were included in this study (see Table 1); 15 were male and 9 female; the mean age was 47.4 years (SD = 12.1 years) for the whole patient population, 50.1 years (SD = 7.1 years) for the female and 45.7 years (SD = 14.3 years) for the male patients. Fifteen patients sustained right hemispheric lesions (8 male and 7 female; mean age 47.7 years, SD = 12.3 years); 8 a left hemispheric damage (6 male and 2 female; mean age 44.1 years, SD = 10.5 years) and 1 a left and right hemispheric damage. Auditory cognitive performance was first evaluated in the acute stage (i.e., 4 to 13 days postlesion) in 9 patients, (4 male and 5 female, mean age 42.3 years, SD = 10.1 years); in the subacute stage (14 days to 1 month postlesion) in 6 other patients (3 male and 3 female, mean age 47.2 years, SD = 13.4 years); or in the early chronic stage (> 1 month postlesion) in 9 other patients (8 male and 1 female, mean age 52.6 years, SD = 12.2 years). It is to be noted that in the acute stage the condition of patients who were included in the subacute and early chronic stages did not allow them to be tested with our complete and rather demanding battery. All patients had a second evaluation 9 to 55 months later. These patients were recruited from in-patients of the University Hospital in Lausanne and met the following criteria: i) deficit in sound recognition, sound localization and/or

sound motion perception in the initial testing; ii) no prior neurological or psychiatric illness; iii) no history of cranio-cerebral traumatism; iv) normal hearing threshold in tonal audiometry; v) delimited lesion on MRI and/or CT; vi) absence of major cognitive deficits; vii) absence of drug therapy which influence GABAergic inhibition and viii) satisfactory collaboration at testing. The 9 patients included in the acute stage were already part of a previous study; as stated there they were tested at a time when the penumbra was dissolved (Adriani et al., 2003). The study was approved by the Ethics Committee for Clinical Research, Faculty of Biology and Medicine, University of Lausanne, and informed consent was obtained from all patients.

Sound recognition, sound localization and sound motion perception were investigated with tests, which were digitally constructed on a Power Macintosh 8100 equipped with an audiomedia card and the software Protocols Powermix and Sound Designer II. During the testing session the patients sat in a quiet room, hearing the stimuli through earphones linked to the computer.

2.2. *Recognition of environmental sounds*

Semantic recognition of environmental sounds was tested by presenting the patient with 50 samples of environmental sounds from different semantic categories, each of which lasted 7 seconds. Each of these samples was accompanied with a multiple choice display of 5 drawing with the corresponding words: the target and 4 distractors which were acoustically and semantically related to the sound; only semantically related; only acoustically related, or neither semantically or acoustically related. The patient had to point out the correct drawing or word. A detailed description of the test and normative data on 60 normal subjects were published previously (Clarke, Bellmann, DeRibaupierre & Assal, 1996).

2.3. *Sound localization*

Localization of stationary sounds was tested by stimulating different azimuthal positions of a sound source by varying interaural time difference (ITD). The stimulus was a 2 s broadband bumblebee sound, shaped with 100 ms rising and falling times, and presented through earphones. Four lateral positions, 2 in each hemisphere, were simulated by delaying the left or right channel by 0.3 ms or 1 ms. The central position was created by absence of interaural time difference. The task consisted of 60 items, 12 in each position, presented in pseudorandom order. The patient had to point the perceived position on the graduated half-circle on the headphones. An angular value of the position (from 0° at the vertex, to 90° at each ear) was determined as a measure of overall performance, the relative position attributed to two consecutive stimuli was compared. 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 difference in ITD or within ± 15° of the previous location for identical ITD. The individual scores were converted into z scores relative to the mean and the standard deviation of the control population (see Fig. 1). Detailed descriptions of normative data on 60 subjects were published previously (Clarke et al., 2000).

2.4. *Sound motion perception*

Sound motion perception was tested by creating an illusion of sound motion in the azimuthal plane by changing ITD progressively. The stimulus was a 2.3 s motorcycle sound shaped with 100 ms rising and falling times. Six different motions were simulated: extreme left to extreme right, extreme left to midsagittal place, extreme right to midsagittal plane and their reverse. The patient had to indicate the trajectory with his/her hand on the graduated half-circle on the headphones. detailed description of this test and normative data on 60 subjects have been previously reported (Clarke et al., 2000).

2.5. *Anatomical evaluation*

Anatomical evaluation was obtained by using the normalized coordinate system of Talairach and Tournaux (1988) for the comparison of sites of lesion. Lesions were delineated on MRI and/or CT by superimposing the Talairach grid on the images based on a manual selection of the anterior and posterior commissures and of the anterior, posterior, top, bottom and lateral limit of the brain (same procedures as in Adriani et al., 2003; Clarke et al., 2000; Clarke et al., 2002). For each lesion the implicated cuboïds of the Talairach grid were identified.

The lesions then discribed in terms of damage to i) the auditory "What" stream; ii) the auditory "Where" stream; and iii) the auditory structures shared by both. The shared auditory structures included the auditory thalamus, the acoustic radiation and Heschl's gyrus, the auditory callosal pathways and areas that were equally activated by the sound recognition and sound local-

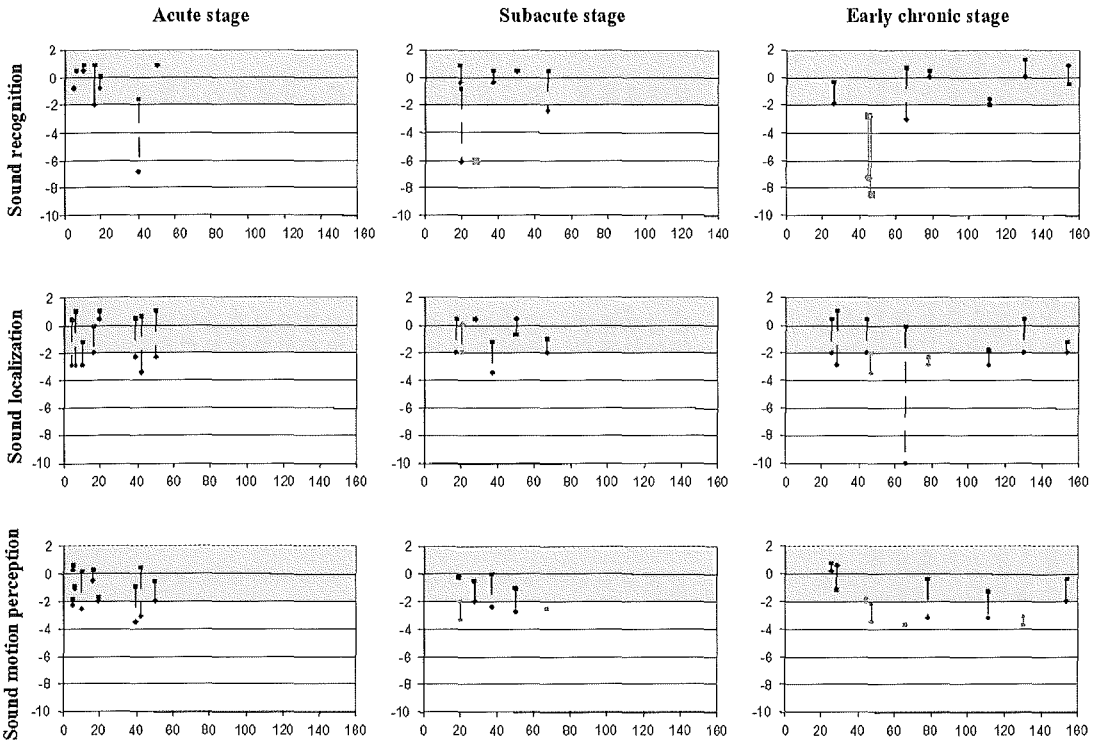

Fig. 1. Recovery pattern in sound recognition (top), sound localization (middle row) or sound motion perception (bottom) and lesion size in patients included in the acute (left), subacute (middle column) or early chronic stages (right). The number of damaged Talairach cuboids is on the x-axis, the z-score of performance in a given function on the y-axis (grey hatching indicates normal performance). Diamonds denote performance at the first, squares at the second testing; interrupted lines mark normalization of performance, grey symbols persistence of deficits or deterioration.

ization tasks (Maeder et al., 2001) on the supratemporal plane or on the middle prefrontal gyrus (for details and the list of the involved Talarach cuboids, see Adriani et al., 2003). The sound recognition network (the "What" network) and the sound localization network (the "Where" network) included clusters identified in our previous study (Maeder et al., 2001) and the list of the corresponding cuboids was published in a previous study (Adriani et al., 2003). The shared auditory structures includes 51 cuboïds in the right hemisphere and 45 in the left; the "What" network 29 cuboïds in the right hemisphere and 44 in the left; and the "Where" network 34 cuboïds in the right hemisphere and 18 in the left.

3. Results

3.1. Selective and combined deficits

From the 9 patients included in the acute stage 3 had a selective deficit in sound localization and 2 in sound motion perception; 3 a combined deficit in sound localization plus sound motion perception; and 1 a triple deficit in sound recognition, sound localization plus sound motion perception (see Table 1). From the 6 patients included in the subacute stage 1 had a selective deficit in sound localization and 1 in sound motion perception; 1 a combined deficit in sound localization plus sound motion perception and 2 a combined deficit in sound recognition plus sound motion perception; and 1 a triple deficit in sound recognition, sound localization plus sound motion perception. From the 9 patients included in the early chronic stage 2 had a selective deficit in sound localization; 1 a combined deficit in sound recognition plus sound localization, 4 in sound localization plus sound motion perception; and 2 a triple deficit in sound recognition, sound localization plus sound motion perception.

3.2. Patterns of recovery

All patients with a selective or combined deficit in the auditory spatial domain (sound localization and/or

Table 1

Case	Age (y)	Sex	Site of lesion	Damage (cuboids)			Test 1			Test 2		
				Total	"What"	"Where"	R	L	M	R	L	M
			Test 1 in acute stage									
K.E.	43	M	Right: Ci, FLI, FLS, FOF, GFi, GP, GPrC, GTs, GTT, HI, Ro, Pu	40	15	1	**−6.89**	**−2.32**	**−3.52**	−1.59	0.47	−0.94
M.B.	31	M	Left: Ci, FLS, GFi, GFm, GPoC, GPrC, GTs, GTT, INS, LPi, Pu	50	14	6	0.86	**−2.32**	**−2.00***	0.86	1.03	−0.61
P.A.	45	M	Right: FLS, FOF, GFi, GPoC, GTi, GTm, GTs, LPi, INS	41	7	3	−1.59	**−3.43**	**−3.07**	–	0.57	0.40
S.D.	23	M	Right: GTs	10	1	0	0.46	**−2.87**	**−2.51**	0.86	−1.20	0.18
B.O.	48	M	Right: GF, GTi, GTm	16	8	0	−1.99	**−2.00***	−0.50	0.86	−0.08	0.29
B.G.	57	F	Right: GPoC, Lpi	6	2	1	0.46	**−2.87**	−1.06	0.46	1.03	−0.94
P.T.	43	F	Right: Ci, GPrC, GTm, GTs	5	1	0	−0.77	**−2.87**	0.29	−0.77	0.42	0.63
M.M.	50	F	Left: GTm	5	3	0	−0.77	−0.64	**−2.29**	–	–	−1.84
R.A.	41	F	Left: FLS, GPoC, GPrC, GSm, LPi, LPs	19	2	8	−0.80	0.47	**−2.00***	0.05	1.03	−1.73
			Test 1 in subacute stage									
J.J.	51	F	Right: CA, CE, Ci, FLS, FU,GF, GFi, GPoC, GPrC, GTm, GTs, GTT, Hi, INS, LPi, Pu, Ro	67	12	8	**−2.40**	**−2.00***	**−2.51**	0.46	−1.03	**−2.51**
T.T.	51	F	Right: FLI, FLS, GSm, GTi, GTm, GTs, Hi, INS, LPi, Ro	28	6	4	**−6.08**	0.47	**−2.00***	**−6.08**	0.47	−0.49
E.B.	64	F	Right: GFi, GFm, GPoC, GPrC	20	0	2	**−6.07**	0.08	**−2.00***	−0.77	**−2.00***	**−3.30**
C.R.	55	M	Left: FLI, FLS, FOF, GF, GH, GL, GOi, GOm, GTi, Hi, Ro, Th	37	7	0	−0.36	**−3.43**	**−2.40**	0.50	−1.20	−0.05
B.J.	32	M	Right: GFi, GPrC, GTs, GTT	19	5	4	−0.36	**−2.00***	−0.15	0.86	0.47	−0.27
B.C.	30	M	Left: Ci, FLS, GFi, GPoC, GPrC, GTm, GTs, GTT, INS, Pu	50	8	8	0.46	0.47	**−2.74**	0.46	−0.64	−1.10
			Test 1 in early chronic stage									
A.R.	68	M	Right: FLS, GOm, GPoC, GTi, GTm, GTs, INS, LPi ; Left: GFi, GFm, GPrC	46	6	4	**−7.30**	**−3.45**	**−3.41**	**−2.81**	**−2.00***	**−2.06**
P.V.	49	F	Right: GC, GFO, GFL, GFm, GFs, GPoC; GPrC; GTs, INS, NC	66	4	10	**−3.03**	**−10.00**	**−3.63**	0.77	−0.08	**−3.63**
M.P.	56	M	Left: Ca, CC, Ce, Ci, FLS, FOF, FU, GP2, GP1, Hi, NC, Pu, T, Th	46	4	1	**−2.81**	**−2.00***	**−1.84**	**−8.45**	0.47	**−2.18**
L.C.	34	M	Right: Ce,Ci, FLI, FLS, Gf, GPoC, GPrC, GSm, GTs, GTT, LPi, Pu, Ro	78	15	7	0.05	**−2.87**	**−3.18**	0.46	**−2.31**	−0.38
G.R.	48	M	Right:CE, FLS, FU, GF, GH, GOm, Gos, GPoC, GPrC; GSm, GTm, GTi, GTs, GTT, INS, LPi, Pu, Ro	130	20	15	0.04	**−2.00***	**−3.07**	1.27	0.47	**−3.74**
B.F.	71	M	Right: CE, CI, Ci, FLS, FO, FOF, FU, GFi, GFm, GPoC, GPrC; GTm, GTs, GTT, INS, LPi, Pu, Th	111	12	10	−1.58	**−2.87**	**−3.18**	−1.99	−1.75	−1.27
S.J.	57	M	Right: CA, CC, CE, CI, Ci, FLI, FLS, FOF, Fu, Ga, GF, GFi, GFm, GH, Gos, GPoC, GPrC; GSm, GTi, GTm, GT, Hi, INS, LPi, LPs, NC, Pu, Ro, Th	154	12	18	0.86	**−2.00***	**−2.00***	−0.46	−1.20	−0.38
P.M.	52	M	Left: Ci, FLI, FLS, FOF, GTi, GTm, GTs, GPoC, GPrC, Ro	27	8	1	1.09	**−2.87**	0.63	–	1.03	−1.17
T.O.	38	M	Left: CA, GTi, GTm, Gts, Na	26	8	1	−1.99	**−2.00***	0.18	−0.36	0.47	0.74

Patients participating in this study and their performances in sound recognition (R), sound localization (L) and sound motion perception (M). All patients were right-handed except C.R. and T.O; all had suffered stroke with the exception of P.V. and T.O. who had ruptured anevrysma. Lesions were analysed on MRI except for T.T., E.B., B.C., M.P., G.R., B.F. and T.O., where CT were used. Performance is expressed in z-scores relative to control population (N = 60); deficient performance (defined by z equal or smaller than-2) is in bold. M = male; F = female; y = years. Anatomical abbreviations: CA = Commissura anterior cerebri, CC = Corpus callosum, Ci = Cingulum, CI = Capsulae interna, Cu = Cuneus, FLI = Fasciculus longitudinalis inferior, FLS = Fasciculus longitudinalis superior , FOF = Fasciculus occipito-frontalis, Fu = Fasciculus uncinatus, Ga = Gyrus angularis, GC = Gyrus cinguli, GF = Gyrus fusiformis, GFi = Gyrus frontalis inferior, GFm = Gyrus frontalis medius, GFs = Gyrus frontalis superioir, Gh = Gyrus parahippocampi, GL = Gyrus lingualis, GOi = Gyrus occipitalis inferior, GOm = Gyrus occipitalis medius, GOs = Gyrus occipitalis superior, GP = Globus pallidus, GPoC = Gyrus postcentralis, GPrC = Gyrus precentralis, Gsm = Gyrus supramarginalis, GTi = Gyrus temporalis inferior, GTm = Gyrus temporalis medius, GTs = Gyrus temporalis superior, GTT = Gyrus temporales transversi, Hi = Hippocampus, INS = Insula, LPi = Lobulus parietalis inferior, LPs = Lobulus parietalis superior, Na = Corpus amygdaloideum, NC = Nucleus caudatus, Pcu = Precuneus, Pu = Putamen, Ro = Radiatio optica, T = Tapetum, Th = Thalamus. * = deficient performance additionally characterized by a deviation and/or a high variability to attribute one position to a given ITD, inability to discriminate two positions within one hemispace and disturbance in motion's detection; neither of these errors was observed in the normal subjects.

sound motion perception), but without a deficit in sound recognition, recovered completely (15 patients) or partially (2 patients). Five of 7 patients with a combined deficit in the auditory spatial domain and sound recognition recovered completely (1 patient) or partially (4 patients); 2 remained stationary.

Recovery differed between groups. All patients included in the acute stage had normal performance in sound recognition , sound localization and sound motion perception by the time of the second evaluation in the chronic stage (see Table 1). They tended to have small lesions, on the whole smaller than those of patients who were included in the early chronic stage (Fig. 1).

From the patients, who were included in the subacute stage, 50% had a normal performance in all the domains by the time of the second evaluation. From the remaining patients, one normalized her performance in two domains and one in one domain; and one normalized her performance in one domain and worsened in another (see Table 1). Globally, 64% of deficient domains were normalized by the time of the second evaluation and 36% remained deficient. The range of lesion sizes in this population was roughly similar to that of the acute group and the lack of recovery was observe also in patients with small lesions.

From the patients, who were included in the early chronic stage, 44% had normal performance in all the domains by the time of the second evaluation. From the remaining patients, one normalized her performance in two domains, two normalized their performance in one domain and one normalized his performance in one domain and worsened it in another (see Table 1). Globally, 56% of deficient domains were normalized by the time of the second evaluation and 44% remained deficient. The lesions of this group were within the range of the subacute group and beyond it; absence of recovery was observed in patients whose lesions were of comparable sizes to those of the acute and subacute groups.

In summary, in our population recovery was observed in i) all patients who were included in the acute stage; and ii) most patients who were included in the subacute and early chronic stages and who had a deficit limited to the auditory spatial domain. Conversely, the co-occurrence of deficits in the auditory spatial domain plus in sound recognition in the subacute or chronic stages was associated with lasting deficits in one or the other or in both aspects.

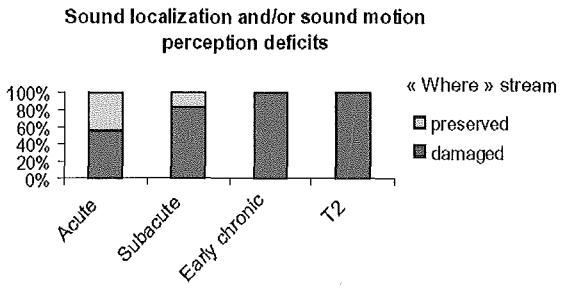

Fig. 2. Occurrence of sound localization and/or sound motion perception deficits in cases of preserved or damaged auditory "Where" stream. Note that almost half of the cases in the acute stage did not sustain damage to the "Where" stream (4 out of 9 cases), while this was never the case in the early chronic (9 cases) or chronic stages (i.e., at the time of the second testing; 7 cases).

3.3. Auditory spatial deficits and damage to the auditory "Where" stream

All 24 patients who participated in this study had, at the initial testing, a deficit in sound localization and/or sound motion perception (Table 1). In the acute stage this deficit occurred without specific damage to the "Where" stream in 44% and in the subacute stage in 16% of the cases (Table 1; Fig. 2). In the early chronic stage and at the time of the second testing a deficit in sound localization and/or sound motion perception was always accompanied with damage to the auditory "Where" stream.

The superposition of right-hemispheric lesions which were found in association with selective deficits of sound localization and/or sound motion perception (i.e., with preserved sound recognition) showed different patterns in the acute, early chronic or chronic stages (Fig. 3). In the acute stage 5 patients had this profile and their, rather smallish lesions superposed over the temporal convexity, i.e., over the auditory "What" stream. In the early chronic stage 4 patients had this profile and their lesions superposed over insula and temporo-parietal cortex, involving both the "What" and "Where" streams. At the time of the second testing, i.e. in the chronic stage, 4 patients had this profile and their lesions had a maximum superposition over the insula and parietal cortex, including the "Where" stream.

Patients who had deficits in sound localization and/or sound motion perception at the initial testing without damage to the specialized stream recovered normal performance by the time of the second testing (Fig. 4). When damage to the "Where" stream was present, part of the patients still recovered. This was the case of all patients who were included in the acute stage and

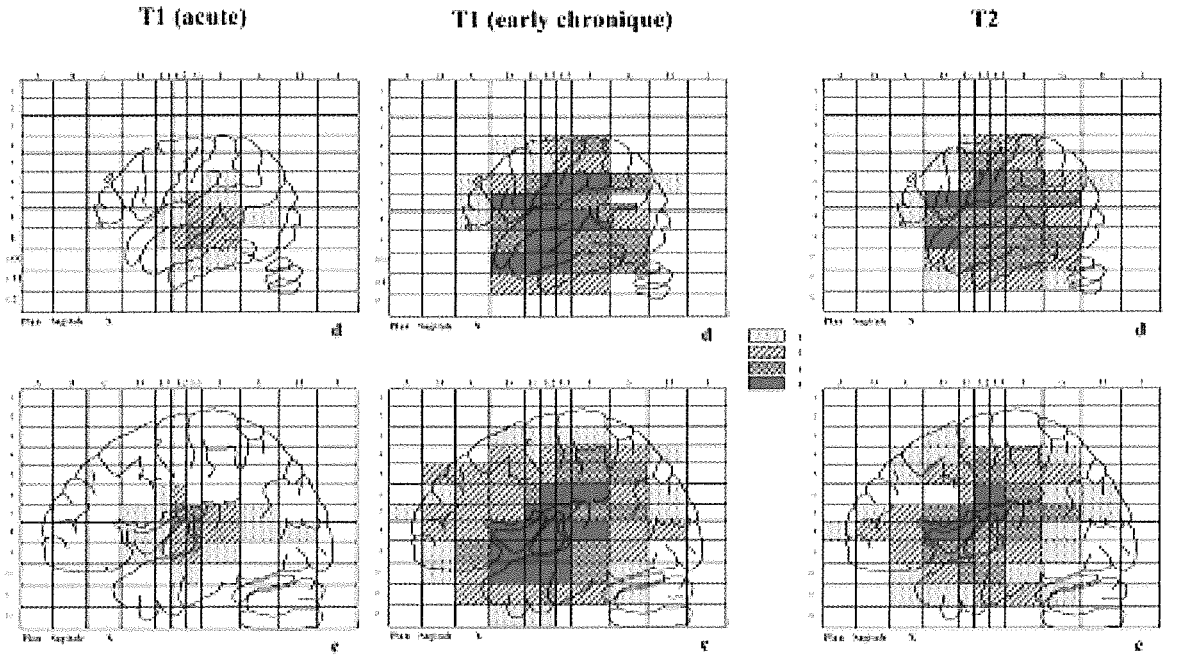

Fig. 3. Superposition of lesion sites associated with the occurrence of auditory spatial deficits (sound localization and/or sound motion perception deficit) in the acute stage (5 patients with right hemispheric lesion; left column), early chronic stage (4 patients with right hemispheric lesions; middle column), or at the second testing in the chronic stage (4 patients with right hemispheric lesions; right column). The lesions are represented in Talairach space, sections c and d. Hatching indicates the number of patients in whom a given Talairach cube was completely or partially (at least one third) damaged.

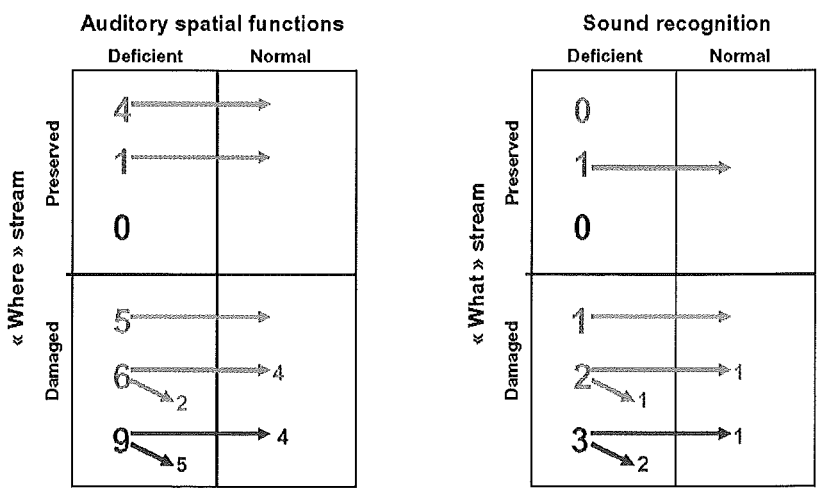

Fig. 4. Recovery of auditory spatial (i.e., sound localization and/or sound motion perception deficits; left panel) or sound recognition deficits (right panel) associated or not with damage to the specific auditory streams. Numbers denote the number of cases in each subgroup. Colours code the time of the first testing: green acute; orange subacute; and red early chronic stage. Arrows indicate changes at the time of the second testing.

part of the patients who were included in the subacute and early chronic stages. A similar relationship was observed for sound recognition and the damage to the auditory "What" stream. On the whole, a deficit was more likely to become permanent when damage to the specialized stream was accompanied by the persistence

of deficits beyond the acute stage.

3.4. Recovery and size of lesion

The experimental requirements of our paradigm introduced a bias into the selection of patients. In the acute stage, only patients with relatively small lesions could be included, since those with larger lesions were not well enough to allow for an intensive testing of several hours, which was necessary for our auditory battery plus a general neuropsychological assessment. A similar bias was still present in the subacute stage. In the early chronic stage we tested initially a wide range of patients (i.e., all patients joining our rehabilitation program) and retained those, who were deficient (see selection criteria in Methods). Thus, we cannot rely on between group comparisons for establishing a relationship between lesion size and probability of recovery.

Within a given subgroup, recovery did not correlate with the size of lesion (Fig. 1). The relatively small numbers of patients par group did not allow a statistical analysis, but it is striking that from patients who were included in the subacute stage, two with relatively small lesions did not recover, while others, with larger lesions, recovered. The discrepancy between lesion size and recovery is even more striking for patients who were included in the early chronic stage. Several patients with rather small lesions did not recover, while those with much larger lesions did.

4. Discussion

4.1. The relationship between deficits and damage to specific networks changes between the acute and chronic stages

The cognitive functions investigated here have been shown previously to depend on specific auditory processing networks, the "What" (involving the anterior part of the middle temporal gyrus, the ventral part of the precuneus on the both sides and the left prefrontal cortex) and "Where" (involving the infero-parietal lobule, parts of the prefrontal and the premotor cortex and the dorsal part of the precuneus) streams. These streams have been demonstrated in human activation studies (Alain et al., 2001; Maeder et al., 2001) and large lesions centred on one of the network were shown to cause in the chronic stage the corresponding deficit (Clarke et al., 2000; Clarke et al., 2002).

The occurrence of non-specific deficits, i.e. deficit in one of these auditory cognitive domains without a lesion to the corresponding auditory network was described in the acute stage in a previous study (Adriani et al., 2003), we demonstrated here that these deficits are entirely transient. Their occurrence is unlikely to be linked to the penumbra, since the testing here and in the previous study was performed at a time when the penumbra is resolved (Hossmann, 1994). Furthermore, we show here that non-specific deficit can be found up to the end of the first month postlesion, also with a subsequent recovery. The non-specific deficits are, however, no longer present in the early chronic stage.

The non-specific transient effects that we observed in the acute and partially in the subacute stage may be due to changes in the efficacy of existing excitatory synapses, that had been unmasked by the lesion (Jacobs & Donoghue, 1991), resulting in enhanced excitability in the neighbourhood of the damage area and in functional disturbance (Schiene et al., 1996). Recovery that we have observed from the early chronic stage on is likely to involve other mechanisms, such as potentiation (Hagemann, Redecker, Neumann-Haefelin, Freund & Witte, 1998), axonal regeneration (David & Aguayo, 1981), sprouting of new connections (Adams, Lee, Fahnestock & Racine, 1997; Florence, Taub & Kaas, 1998) or utilisation of redundant brain circuiting with parallel pathways (Fries, Danek, Scheidtmann & Hamburger, 1993).

Changes in cortical organization between the acute and chronic stages have been well documented for the recovery of motor deficits following hemispheric lesions. Recovered movements were often described to activate networks comprising the ipsi-and contralesional motor and non-motor areas. A good recovery is believed to be particularly associated with the involvement of ipsilesional motor networks (e.g. Calautti & Baron, 2003) and to rely on the recruitment of parallel pathways within the motor system (for review see e.g. Chen, Cohen & Hallett, 2002). Several studies demonstrated the dynamics of these changes between the acute and chronic stages. During the acute stage of corticospinal tract lesions, finger movements with the paretic hand were shown to activate the ipsilesional motor network and additional ipsi-and contralesional areas; with recovery the ratio of ipsi-vs contralesional activation increased (Marshall et al., 2000). Similar changes were observed when comparing patterns of activation obtained in the first and in the second month after a hemispheric lesion (Nelles et al., 1999). In the chronic stage, successful rehabilitation was also found to be

associated with increased involvement of ipsilesional motor regions (Johansen-Berg et al., 2002) or enhanced representation of the affected hand in the ipsilesional motor area (Liepert, Terborg & Weiller, 1999).

4.2. *The size of lesion plays a secondary role in auditory recovery*

Several studies examined the pattern of recovery after brain injury (Goldman & Plum, 1997) (Luders, Comair, Bleasel & Holthausen, 1997) and focus their interest on the factors that determine the severity of deficits and the extent of recovery. Whereas the age of the patient and the location of the lesion are recognized like essential in the recovery process, the influence of lesion size is on the other hand controversial. In the patient with middle cerebral infarcts, some authors (Mohr et al., 1993) found correlation between infarct size and the severity of motor weakness. However, several other studies found little (Binkofski et al., 1996; Binkofski et al., 2001) or no (Pantano et al., 1996) correspondence between degree of damage and infarct size. Our results suggest absence of simple relation between patterns of recovery and size of lesions for auditory cognitive functions.

4.3. *Persistence of deficits beyond the acute stage decreases the probability of recovery*

We can confirm our initial hypotheses. Lasting deficits in a given domain do not occur without damage to the corresponding network and they are more likely to be permanent if still present in the weeks beyond the acute stage. Furthermore, our results suggest that different mechanisms underlie deficits and recovery at different time points. In the acute and subacute stages (but beyond the penumbra) a widespread and non-specific dysfunction occurs in the auditory network, causing transient deficits even in domains, whose specialised networks are anatomically preserved. From the early chronic stage on, the presence of deficits is associated with damage to the specialized network and the likelihood of recovery is variable.

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