Lateralisation of sound in temporal-lobe epilepsy: Comparison between pre- and postoperative performances and ERPs

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HIGHLIGHTS

- Sound-lateralisation performance of temporal-lobe epilepsy (TLE) patients and the amplitudes of their N1 and P2 responses to auditory directional stimuli proved to be lower than those of the normal population.
- Only insignificant effects of anterior temporal lobectomy on TLE patients' sound-lateralisation performance and on their auditory directional ERPs were noted.
- Standard audiometry should be supplemented with detailed directional hearing tests in TLE patients.

ABSTRACT

Objective: Our aim was to investigate if spatial hearing is impaired in mesial temporal lobe epilepsy and temporal lobectomy has an effect on this function.

Methods: Thirteen patients with mesial temporal lobe epilepsy (TLE) due to sclerosis in their left ($n = 6$) or right ($n = 7$) hippocampus were studied. Their sound lateralisation performance indexed by d0 was tested against that of a group of normal subjects ($n = 13$). Patients' ERPs to lateralisation shifts induced by interaural disparities of intensity (IID) and time (ITD) were also recorded. Eight of the patients were re-tested after they underwent anterior temporal lobectomy, which involved the resection/removal of medial structures including amygdala, hippocampus and parahippocampal gyrus.

Results: The sound-lateralisation performance of the TLE patients was significantly lower than normal subjects, and this disadvantage of the patients was specific to IID-based lateralisation. Amplitudes of their N1 and P2 responses to laterally shifting sounds were much lower than those reported previously for normal subjects. Lobectomy did not have a statistically significant effect on patients' sound-lateralisation performance nor on the amplitude of their auditory directional ERPs.

Conclusions: The results show that especially the IID-based sound-lateralisation performance is impaired in TLE patients and that lobectomy should not cause any further deterioration.

Significance: This study suggests that a test for assessing the ability of sound lateralisation based on each of the IID and ITD cues should be included in the evaluation of TLE patients.

1. Introduction

Anterior temporal lobectomy is one of the most commonly used surgical procedures in patients with temporal-lobe epilepsy (TLE) (Vives et al., 2007). Memory impairment is generally seen as a complication of temporal lobectomy (Pauli et al., 1999). However, studies reporting acquired hearing problems are relatively scarce, despite the fact that the primary auditory area resides near the border of the resected lateral temporal lobe. We suspect that some auditory dysfunction resulting from temporal lobectomy might go unnoticed by the patients themselves and in standard audiometric and neuropsychological tests. The ability to localise sound sources is a crucial aspect of auditory perception, creating in turn a general sense of space, and providing information about the spatial locations of environmental objects, which can have critical value for survival. Hence, dysfunctions of sound localisation can affect activities in patients' daily life, such as walking or driving in a crowded street. They are also known to cause educational problems such as learning difficulties, especially in children (Lieu, 2004). It is therefore important to know if sound-localisation function is impaired by lobectomy.

Binaural sound localisation is known to be a function based largely on the comparison of signals arriving at the two ears (Blauert, 1982), and the main cues to this function are the interaural intensity and interaural time differences (IID and ITD, respectively). There is evidence that the primary auditory cortex itself is capable of sufficiently handling contralateral localisation (Jenkins and Merzenich, 1984). A variety of sound-lateralisation deficits that have been observed after unilateral lesions in humans may give information about the associated brain regions and mechanisms. In this context, Efron and Crandall (1983) described deficits occurring only in the contralateral hemifield after damage to either temporal lobe. Moreover, Pinek et al. (1989) reported that sound lateralisation deficits occur in both hemifields, especially after left hemisphere damage; in contrast, (Ruff et al., 1981) stated that deficits occur primarily after right hemisphere damage. These and similar diverse findings in the literature may be attributed to localisation of the individual lesions in different cortical regions such as temporal (Clarke et al., 2000) or parietal lobes (Griffiths et al., 1998), and to differences in experimental paradigms that may involve auditory short-term memory (Lancelot et al., 2003) or psychophysical explorations (Griffiths et al., 1997), as well as to differences in imaging techniques employed, such as magnetic resonance imaging (Zatorre and Penhune, 2001) and positron emission tomography (Weeks et al., 1999).

Impaired temporal processing in mesial temporal lobe epilepsy (MTLE) was reported by Ehrle et al. (2001), who tested the role that temporal lobes play in this function by assessing the temporal processing of sequential auditory information. They found that in MTLE the anisochrony discrimination threshold deteriorated for relatively short inter-onset intervals. Furthermore, in a recent study, where frequency pattern, duration pattern, and dichotic tests were performed in 28 TLE patients with normal hearing on pure tone audiometry, Han et al., (2011) reported that a significant fraction of these patients displayed impairment of central auditory processing and that the risk was higher in patients with hippocampal sclerosis. Involvement of the mesial temporal lobe or hippocampus in auditory localisation does not seem likely because these structures are in fact not in physical proximity to the auditory cortex. However, there is evidence indicating that resection of the temporal neocortex, even in regions anterior to A1, can cause an adverse effect also on auditory localisation (Efron et al., 1983; Zatorre and Penhune, 2001). In TLE with HS because there may also be abnormalities or structural lesions that can manifest as directional hearing deficit, we compared TLE patients with normal subjects to see if there was a significant difference between the two groups in their sound lateralisation abilities. We also investigated possible changes in this ability that would be caused by temporal lobectomy.

There are only a few studies on auditory dysfunction in patients with TLE in which auditory evoked potentials are used as electrophysiological markers for evaluating the level of auditory dysfunction (Bougeard and Fischer, 2002; Baez-Martin and Cabrera-Abreu, 2005). Electrophysiological data related to IID- and/or ITD-based directional hearing with accompanying psychophysical test result in patients having similar temporal-lobe lesions could supply us with more informative data. In line with this expectation, we studied patients with TLE due to HS (TLE-HS) who had been scheduled to undergo standardised anterior temporal lobectomy in our epilepsy center, all by the same neurosurgeon. In this relatively homogeneous group, the function of sound lateralisation in pre- and postoperative periods was studied by means of psychophysical and electrophysiological tests. Since evidence from human studies indicates that resection of the temporal neocortex, even in regions anterior to A1, can disrupt auditory localisation (Efron et al 1983; Zatorre and Penhune 2001) and that

sound lateralization performance is correlated positively with the amplitude of the magnetoencephalographic N1 (Palomaki et al., 2005), we decided to study further the effect of anterior temporal lobectomy on sound lateralization performance together with its possible effects on the ERP components elicited by the lateralization shifts of an auditory image.

2. Materials and methods

2.1. Patients and controls

Thirteen patients with MTLE due to sclerosis in their left or right hippocampus, who had been scheduled to undergo anterior temporal lobectomy between March 2008 and March 2010, were included in the study. Mean age of the patients was 29 ± 9 years (range: 19–44 years). Seven of them were male and all of them were right-handed. Seven of the patients underwent right and six of them left-temporal lobectomy. Of the eight patients we were able to test postoperatively, the recordings of one with left temporal lobectomy were excluded from the analysis because of excessive artefacts in his EEG. Mean age of the remaining seven patients who were included in the postoperative statistics was 28 ± 9 years. None of the patients was mentally retarded, and there was no evidence of objective hearing loss or impairment as assessed by standard audiometric analysis before surgery. Each patient was monitored for 3–10 days by means of a 32-channel video-EEG system (Grass Telefactor). A montage including T1 and T2 scalp electrodes placed according to the standard 10–20 system was used. MRI scans of each patient were obtained using either 1.5T (Symphony) or 3.0T (Allegra) scanners (Siemens, Erlangen, Germany). The standard MRI protocol for patients with epilepsy in our institution consisted of coronal 3D T1-weighted gradient-echo imaging (MPRAGE) slices obtained parallel to the brainstem, fluid-attenuated inversion recovery (FLAIR) with T2-weighted turbo spin-echo and T1-weighted inversion recovery images obtained perpendicular to the hippocampi, in addition to routine brain imaging. Findings from presurgical evaluations of each patient were discussed in a multidisciplinary case conference, where decisions were made concerning the possibility and type of surgery. For patients having HS seen on MRI, a surgical operation was the chosen approach in cases of interictal and ictal EEG findings concordant with MRI. The patients were excluded from the study if they had EEG abnormality contralateral to the HS as seen on MRI or if they had other lesion(s) in addition to HS (i.e., dual pathology). The standard procedure for treating TLE-HS was anterior temporal lobectomy, which involved the resection/removal of medial structures, including the amygdala, hippocampus and parahippocampal gyrus. The lateral temporal-lobe resection was 3.5 and 5 cm from the anterior temporal tips for the dominant and non-dominant hemispheres, respectively. Thirteen healthy adults (seven males) without hearing loss and ear pathology were also recruited to serve as the control group. They were all right-handed and their mean age was 32 ± 7 years (within the range of 22–49 years). The study was approved by the Ethical Committee of the Hacettepe University Faculty of Medicine, and written informed consent was obtained from all patients and controls before the experiments.

2.2. Experimental protocol

The experimental protocol, consisting of ERP recording and psychophysical test sections, was applied 1 week before and after the patients' anterior temporal-lobectomy operation. Preoperatively, the psychophysical and ERP tests were conducted in 13 patients. We were able to repeat postoperatively the psychophysical test in only eight of them and the ERP test in only seven of them, because in some members of the patient group some non-specific medical problems such as headache or skin infections were observed. None of the patients had seizures in the 7 days before the preoperative recordings. During the postoperative period, they were seizure-free since surgery. All of the patients were on two or three antiepileptic drugs. These drugs were not changed during the preoperative or postoperative recordings. Only psychophysical tests were administered to the control group. All multichannel EEG/ERP recordings as well as a variety of psychophysical tests were conducted at the Brain Research Laboratory of the Department of Biophysics, Hacettepe University Faculty of Medicine, using the 'Octopus' system being actively developed since 2005 in this laboratory (Ilhan, 2008, 2009). All EEG recordings were screened by an epileptologist during the tests. There were no electrophysiological or clinical seizures but lateralised epileptiform discharges of almost equal severity were present in all patients.

2.3. Stimulation and recording of ERPs

The sounds for binaural stimulation were trains of 0.5-ms clicks presented at a rate of 100 clicks/s. The auditory pattern used in the IID-ITD stimulus paradigm consisted of 50-ms periods of interaural disparities alternately occurring in favor of either ear at intervals of 1 s, in otherwise diotic click trains with randomly timed squarewave amplitude alterations between nHL of 50 and 70 dB (Ungan and Özmen, 1996; Ungan et al., 2001). The details related to the generation of these sounds delivered to the left and right ears to produce the lateralisation shift stimuli based on IID and ITD cues are illustrated in Fig. 1A. Directional stimuli were in the form of 50 ms sound image shifts to either side produced by introducing dichotically either an IID of 20 dB or an ITD of 1 ms. Design details of these IID and ITD stimuli, which were presented at a rate of 1 shift/s and following a regular sequence of 'IID-Left, ITD-Left, IID-Right, ITD-Right, . . .', can be found in an earlier article (Ungan et al., 2001). An audiological insert-earphone set (ER-3A, Etymotic Research, Elk Grove Village, IL, USA) was used for the dichotic presentation of stimuli.

Fig. 1. Stimuli used in ERP and psychophysical tests. (A) Dichotically presented IID and ITD stimuli used in ERP recordings (adopted from Ungan and Özmen, 1996 and Ungan et al., 2001). IID stimuli are produced by impairing the interaural synchronization of random intensity alterations for 50 ms so that the click intensity at one ear is 10 dB below and that at the other ear is 10 dB above an average level of 60 dB, thus introducing an IID of 20 dB for 50 ms. ITD stimuli, on the other hand, are produced by delaying for 50 ms the clicks at one ear by 0.5 ms and by advancing those at the other ear also by 0.5 ms, thus introducing an ITD of 1 ms for a duration of 50 ms. (B) Six difficulty levels in the IID and ITD paradigms used in the psychophysical tests. The binaural sounds that are the most and the least difficult to lateralize in the IID paradigm had interaural intensity differences of 1 dB and 20 dB; and those in the ITD paradigm had interaural time differences of 10 μs and 600 μs, respectively.

During ERP recording, the patients were sitting in a moderately illuminated soundproof room, and they were instructed to read a book of their own choice, ignoring the stimuli to prevent attention-related higher-level/late ERP components. Continuous EEG recordings were made using 19 scalp electrodes (Electro-Cap International Inc., Eaton, OH, USA) in standard 10-20 system attached at sites Fz, Cz, Pz, F3, F4, P3, P4, FP1, FP2, O1, O2, C3, C4, F7, F8, T3, T4, T5 and T6 and two additional earlobe electrodes. Electrode impedances were kept smaller than 5 kΩ. The gain of individual EEG channels was 50,000 and the sample rate was 500 sps. A notch-filter was not used,

and the high-pass and low-pass filter cut-off values of the EEG amplifier were 0.3 and 70 Hz, respectively.

2.4. Psychophysical test

Sound-lateralisation performances of the patients were assessed by using a forced-choice psychophysical test in which the patients were asked to judge the laterality of the brief sounds that were dichotically presented to them with different interaural intensity or time disparities. The design and presentation of the IID- and ITD-lateralised stimuli and the recording of the subjects' button-press responses were also performed using the Octopus system (Ilhan, 2009). In the psychophysical test protocol, the patients were presented with brief auditory stimuli that were laterally shifted by either an IID or an ITD and they were instructed to press one of the two buttons on the keypad they were holding to indicate as accurately and quickly as possible the lateralisation of the sound they perceived at that time.

A psychophysical test session consisted of 10 repetitions of stimulus sets each with 25 randomly ordered bilateral auditory positions (six left positions and six right positions produced by IID; six left positions and six right positions produced by ITD). Lateralised stimuli were 100-Hz click trains of 1-s duration presented with silent intervals of 2 s between them. Details of the auditory stimuli lateralised by IID and ITD are given in Fig. 1B. Before the main test session started, instructions about the experiment were given to the subject and a trial session was run using an extra set of 25 stimuli to verify that he/she had understood the task and his/her responses had been reasonably correlated with the side of the stimuli at least for the extreme lateral positions.

2.5. Analysis

2.5.1. Analysis of EEG and ERPs

Recorded EEG data were digitally filtered with a moving average filter for 50-Hz interference and its harmonics, and then a 0.5–30-Hz pass-band Butterworth filter was applied to them. EEG traces were then epoched between prestimulus 100 ms and poststimulus 500 ms, and the epochs were averaged. Averaged ERP data were classified as ipsilesional or contralesional according to the direction of the stimulating sound shifts with respect to the side of the diagnosed HS.

N1 and P2 peak latencies were determined according to the maxima of the mean global field power (GFP, Lehmann, 1987) in the time ranges of 80–170 and 180–250 ms, respectively. Amplitudes of these ERP components were measured from the 'Cz-linked ear' derivation as the mean amplitude within the 20-ms time period around these peak latencies.

2.5.2. Analysis of psychophysical data

Results of the psychophysical tests that were carried out in 13 patients before lobectomy and eight patients after lobectomy were compared with the results of the control group. The sound lateralisation performances in the pre- and postoperation periods were compared, however, using the data from the eight patients who could be tested after lobectomy. All of the responses to the stimuli with six different stages of lateralisation in each side were pooled for statistical analysis.

To compare between the sound-lateralisation performances of patient and control groups as well as those of the patients with HS in their left and right hemispheres, an index called d' was used. This index, based on signal detection theory, was chosen because it takes into account not only the rate of hits but also the rate of false alarms, eliminating the risk of evaluating a bias in favor of one side as successful lateralisation on that side. Such a risk would have occurred if only the rate of hits (correct lateralisation) had been considered. Since a forced choice task with no missed trials was used, the d' values corresponding to the stimuli dichotically shifted to the two sides were identical to each other. Consequently, the lateralisation performance of a group or in a certain case was represented by a single index, rather than separate indices for the two sides. The index d_0 was calculated from the proportions of hits and false alarms. In this context, to calculate d_0 for ipsilesionally presented stimuli, for instance, ipsilesionally presented stimuli were assumed as signal and contralesionally presented

ones as noise. d' values were calculated as the difference between the z-scores of two ratios as follows:

$$d' = z(A) - z(B)$$

where A is the proportion of the sounds correctly lateralised at one side in all sounds dichotically shifted to that side, and B is the proportion of the sounds falsely lateralised at that side (i.e., false alarms) in the number of all sounds dichotically shifted to the opposite side.

The statistical significance of differences between controls and different groups of pre- and postoperation patients as well as those between the patients with HS in their left and right hemispheres was assessed by the Mann–Whitney U-test. Preoperation versus postoperation comparisons were made using the data of the eight patients who agreed to participate in the tests after the operation, and the statistical significance of the effect of the operation was assessed by means of the Wilcoxon signed-rank test.

3. Results

3.1. Psychophysical tests

3.1.1. Comparison between preoperative patients and controls

Bar graphs illustrating the medians and quartiles of the d' values computed from the hit and false alarm rates of different subject groups as well as those of the patients before and after the operation are given in Fig. 2. The p values associated with intergroup differences are also provided. Mann–Whitney-U tests ($N: 13 + 13$) revealed that the IID-based sound-lateralisation performance was lower for the patient group (median = 2.36) than for the control group (median = 3.43) [$U = 34$, $p = 0.01$] and this deficit in patients did not appear to be as significant for ITD-shifted sounds (medians: 1.7 vs. 1.87), [$U = 59.5$, $p = 0.21$]. When the two groups of patients having HS in their left or right hemispheres were separately compared with the controls ($N: 6 + 13$ and $7 + 13$, respectively), this lack of performance was observed to be present in both groups of patients ($U = 13$, $p = 0.02$; and $U = 21$, $p = 0.05$, respectively). There was no notable difference between the left- and right-lesioned patients in their IID- or ITD-based lateralisation performances before the operation ($N: 7+6$; $p = 0.48$ and $p = 0.56$, respectively).

Fig. 2. Medians of the d' values of the control group and different groups of patients. Vertical bars show the interquartile range of distribution. p Values of the differences between controls and different groups of pre- and postoperation patients as well as those between the patients with HS in their left and right hemispheres (analyzed by means of Mann–Whitney U test), and the p values between pre-operation and postoperation data (analyzed by means of the Wilcoxon signed-rank test) are also given above the bars.

3.1.2. Comparison between pre- and postoperative patients

When the preoperation test results of eight patients were compared with their postoperation test results, a drop was observed in the IID- and ITD-based lateralisation performance of patients after lobectomy (indicated by a decrease in median d' from 2.50 to 2.21 for IID and from 1.56 to 1.11 for ITD). However, these changes were not significant in either the left-lesioned [$z = 0$; $p = 0.5$] or the right-lesioned [$z = -0.42$; $p = 0.67$] patient groups. Nevertheless, this relatively small drop in d_0 was sufficient to push down the already (but not significantly) below normal ITD-based lateralisation performance of the patients to a level significantly lower than that of the control group [$U = 20$; $p = 0.02$].

3.2. ERP results

Grand average ($N = 7$) waveforms of the ERPs recorded are presented in Fig. 3. Mean amplitudes of the N1 and P2 responses to the stimuli shifted by IID and by ITD towards the ipsilateral and contralateral sides of the HS in the pre- and postoperation periods are given in Table 1. In preoperative recordings, the amplitude of the N1 evoked by contralesionally ITD-shifted stimuli was larger than the amplitude of the N1 to ipsilesional shifts ($z = -2.37$; $p = 0.018$). In the amplitude of preoperative P2, however, no significant ipsilesional versus contralesional difference was noted either with IID-shifted or with ITD-shifted stimuli. A comparison of prewith postoperative ERP results (see Fig. 3) showed that N1 amplitudes were notably smaller in postoperative recordings. However, this effect of the operation on N1 amplitude did not prove to be statistically significant and only reached near significance ($z = -1.859$; $p = 0.064$) for ITD-induced contralesional shifts. Nonetheless, the above-mentioned N1 amplitude difference observed in preoperative recordings in favor of the contralesionally ITD-shifted stimuli was lost after lobectomy. Comparison of N1 latencies was not attempted since the differences among them were only on the order of the sampling interval used for recording EEG.

Fig. 3. Grand average ($N = 7$) waveforms of the ERPs to the IID- and ITD-shifts towards the ipsilateral and contralateral sides of the HS in patients during their pre- and postoperation periods. Zero on the time axis indicates the onset of the lateral shifts of the sound image.

Table 1. Mean values of the N1 and P2 amplitudes under different stimulus and patient conditions. Note that the effect of operation on wave amplitudes is statistically significant only for the N1 to the stimuli shifted by ITD towards the side contralateral to the lesion (amplitude values compared are shown in bold).

Cue	N1 amplitude (μV)				P2 amplitude (μV)			
	Ipsilesionally		Contralesionally		Ipsilesionally		Contralesionally	
	Preop	Postop	Preop	Postop	Preop	Postop	Preop	Postop
IID	-0.8	-0.5	-1.6	-0.7	2.6	1.4	2.4	2.6
ITD	-0.9	-0.9	-2.1	-0.5	3.3	4.0	4.0	3.5

4. Discussion

The main result of the psychophysical sound-lateralisation tests we performed is that the sound lateralisation performance of the patients with MTLE was lower than that of the normal population and that this disadvantage of MTLE patients was observed especially for IID-based sound lateralisation. When the two groups of patients having HS in their left or right hemispheres were separately compared with the control group, this lack of performance was observed to be present in both groups of patients. Moreover, the right- and left-lesioned patients did not significantly differ from each other in terms of performance either before or after the operation.

Parallel to the deficiency observed in their sound-lateralisation abilities, we found that the mean amplitudes of the N1 and P2 recorded from the MTLE patients to laterally shifting sounds are much lower than those we reported previously (Ungan et al., 2001) for normal subjects (1.4 vs. 4.5 μ V for N1 and 2.8 vs. 5.5 μ V for P2, respectively). However, because of the dependence of these responses on stimulus characteristics, the validity of such a comparison relies on the equivalence of the magnitudes and spectral characteristics of the stimuli used in both experiments, which is a condition that cannot be taken for granted. Nonetheless, in both experiments the stimuli were trains of 1-ms clicks shifted laterally by interaural intensity disparities of 20 dB introduced for 50 ms. It should therefore be possible to assume the equivalence of the auditory directional stimuli used in both studies. The parallelism between reduced sound lateralization performance and reduced N1 amplitude in MTLE patients is, in fact, in line with the findings of Palomaki et al., (2005) who reported that sound lateralization performance is correlated positively with the amplitude of the N1m, magnetic counterpart of the N1.

Our observation that the operation did not have a significant effect on performance or on auditory directional ERP amplitudes might be interpreted as indicating non-involvement of the resected cortical areas in sound lateralisation. After all, cortical areas that are suspected to be involved in auditory spatial analysis include the temporal lobe, the posterior parietal and prefrontal regions (Bushara et al., 1999), parietal lobes (Griffiths et al., 1998), the posterior auditory areas, the insula and the parietal convexity (Clarke et al., 2000). Such an interpretation, however, would not be consistent with the finding that TLE patients with HS display lower sound-lateralisation performance and auditory directional ERP amplitudes than normal controls. Apart from the work by Bougeard and Fischer (2002), which suggests that the structures such as the amygdala, the hippocampus and the temporal pole might have a major impact on activity in the auditory cortex, there is no information about the involvement of the mesial temporal lobe or hippocampus that would explain the loss of sound lateralisation function preoperatively with mesial temporal lobe lesions such as HS. However, the deterioration in sound-lateralisation ability that we observed in our preoperative MTLE patients certainly implies the involvement of these lesioned cortical areas in sound lateralisation, although these areas are not included in the main cortical structures suspected to be involved in this function. A possible explanation would be that this function is not significantly altered by the operation because the major structures responsible for sound lateralisation are preserved during surgery. However, the apparent ineffectiveness of the operation does not mean that the areas surgically removed are totally unrelated to sound lateralisation in the normal brain. They are probably involved in this function but not crucially, and some other cortical structures have taken over their function due to the brain's plasticity. The fact that TLE patients with HS display lower sound lateralisation performance and ERP amplitudes than normal subjects may be because the transfer of their auxiliary function has not been perfectly and completely accomplished.

As pointed out above, impairment of sound-lateralisation performance in MTLE patients was accompanied by decreased N1 amplitude to laterally shifting sounds, suggesting an overlap between the cortical sources of the N1 and the cortical areas lesioned in MTLE. On the other hand, behavioral and electrophysiological effects were not similarly affected by lobectomy. The amplitude of the N1 to ITD-induced contralesional shifts was notably smaller in postoperative than in preoperative recordings ($p = 0.064$). Another electrophysiological effect of the operation we observed was that the significant N1-amplitude advantage in preoperative recordings in favor of the contralesionally ITD-shifted stimuli was lost after lobectomy. Behavioral sound-lateralisation-test results, however, indicated no significant effect of lobectomy at all. This discrepancy between our behavioural and electrophysiological results can be explained by the fact that the stimuli used in psychophysical and ERP experiments were not identical, although both were auditory directional. Although the sounds used in both experiments were click trains lateralised by introducing interaural time and intensity disparities, they were of somewhat different complexity levels. Therefore, it is quite possible that different mechanisms and thus different

regions of the cortex were activated by these two different directional stimuli. In fact, there is evidence in the literature suggesting that the supra-temporal plain in primates contains a rostrally directed, hierarchically organised, auditory processing stream, with gradually increasing stimulus selectivity extending from the primary auditory area to the temporal pole (Kikuchi et al., 2010). It might be possible to explain from this viewpoint the discrepancy between our psychophysical and electrophysiological test results, considering the fact that the sound pips with static lateralisation used in the psychophysical test can be evaluated as less complex than the dynamic stimuli in the form of lateralisation shifts of a sound used in ERP recording. Because only the anterior temporal areas of the cortex was removed or severed and more posterior areas remained intact during the lobectomy performed, one may expect the auditory functions based on processing lateralisation shifts to be negatively affected due to the operation and those for processing simple sound pips to be spared.

The amplitude of the N1 evoked by contralesionally ITD-shifted stimuli was found to be notably larger than the amplitude of the ipsilaterally evoked N1 in patients before the operation. No such difference was noted, however, for the P2 regarding the lateralisation of the stimulus with respect to the side of HS. Moreover, despite the total inertness of P2 to the operation, nearly significant amplitude differences were noted between the N1 components recorded before and after lobectomy. These findings, which indicated that the dipolar sources underlying these two ERP components were differentially affected by the operation, can be evaluated as another piece of evidence (Hari et al 1987; Pantev et al 1988; Ugan and Özmen 1996; Maeder et al. 2001), suggesting different cortical sources for these two auditory responses.

In a sound-lateralisation-performance test, because not only the rate of correct lateralisation in one auditory hemifield but also the rate of false lateralisation in the same hemifield (false alarms) must be evaluated, we used d0 for assessing performance in this study rather than using merely the rate of hits for the same purpose. For the reasons explained in the Methods section, the lateralisation performance belonging to a group or a certain case was represented by this single index, rather than separate indices for the two sides. Therefore, a comparison between the patients' performances for sounds in the left and right or ipsilesional and contralesional hemifields was not possible. However, we were able to compare between the performances of the right- and left-lesioned patients and, neither before nor after operation was there any significant difference between these patient groups. This finding is in agreement with the study by Han et al. (2011), who were not able to find significant differences in dichotic test results with the laterality of TLE. However, besides studies in which no evidence was found for lateralisation in auditory spatial processing (Bushara et al., 1999; Woldorff et al., 1999), there are others in which left- (Lancelot et al., 2003) or right- (Sanchez-Longo and Forster, 1958; Altman et al., 1979; Ruff et al., 1981; Bisiach et al., 1984; Pinek and Brouchon, 1992; Griffiths et al., 1998; Weeks et al., 1999; Palomaki et al., 2000) hemisphere specialisation has been proposed for the same function. Spierer et al. (2009) reported more specifically that, during IID-based spatial processing, deficits were less severe in the right hemispheric brain damage- than in the left hemispheric brain-damage group. They also argued that the binaural sound-localisation system was predominantly based on interaural time-difference cues and primarily supported by the right hemisphere. Within the frames of the lesioned and/or resected cortical areas in our patients, the results of the present study do not seem to imply a functional hemispheric dominance of this sort.

Our results, which indicate that the impaired sound lateralisation performance of MLTE patients is much more apparent for sounds lateralised with IID than ITD, are in contradiction with the observations reported by Spierer et al. (2009); in their study, deficits were more frequent and much more severe for the processing of interaural time- than intensity-difference cues. However, different effects of hemispheric lesions on IID- and ITD-based lateralisation performances observed in both studies support the previous reports suggesting different cortical areas for processing IID and ITD (Schroger, 1996; Yamada et al., 1996; Palomaki et al., 2005; Tardif et al., 2006). Our finding that a lesion in either of the hemispheres does not have a significant effect on ITD-based lateralisation performance also supports earlier results reported by our group suggesting equal involvement of both hemispheres in ITD processing (Ugan et al., 2001).

Evaluation of sound-lateralisation performance appears to be an important supplement to the standard audiometric tests for TLE patients, since our patients who passed the standard tests could nonetheless display lower performance than the control group in lateralising sounds. The disadvantage of the patients in sound lateralisation was specific, however, to sounds lateralised by a disparity in interaural intensity; their performance for the sounds lateralised by ITD proved not to be

different from that of normal subjects. This fact may cause a reduction in the differentiation power of an auditory directional test conducted with real sound sources (e.g., speakers in a room) or by their simulations where both IID and ITD cues are used. This is because their performance will be raised with the help of their normal (at least close-to-normal) ITD-based lateralisation ability, and some patients would pass unnoticed. This may explain why in some studies similar performances can be observed between patients with TLE and control groups in their sound source-direction discrimination despite confirmed deficiencies in some other auditory functions of the patients (Ehrlé et al., 2001; Meneguello et al., 2006). We suggest, therefore, that such auditory directional tests should be carried out under dichotic conditions (with earphones) where the sounds presented can be lateralised by either ITD or IID in two separate test sessions. It should also be noted that the two most medially positioned IID-shifted sounds and the one most medially positioned ITD-shifted sound employed in our study proved to be inappropriate for such a psychophysical test because even the hit rates of the normal controls were not above chance with these sounds.

When assessing auditory functions in epileptic patients who have undergone surgery, one should be careful when interpreting the results. First, a deficiency in a function in patients compared to normal controls should not be taken as evidence for an adverse effect of the surgical intervention. As shown by the results of the present study, such defects may well already be present in the patients before the operation. Second, when pre- and postoperation performances are compared, absence of any change should not be taken as evidence for non-involvement of the resected part of the cortex in the function studied. This is because impaired functions of the sclerotic tissue or of the cortical areas affected by epileptic discharges may have been taken over, at least partially, by other pathways in the course of some functional reorganisation. Moreover, surgical removal of the lesioned regions, which may in fact be involved in auditory processing in the normal brain, may not cause any further or notable impairment in that function.

In conclusion, the present findings indicate that MTLE-HS and HS could be a leading cause of dysfunction in sound lateralisation. This dysfunction appears especially for sound lateralisation based on IID. We suggest, therefore, inclusion of special audiometric tests for assessing the patient's ability of sound lateralisation using the IID cue, and evaluation of these test results together with those of the conventional pre- and postoperative examinations. A deficit in sound-lateralisation ability may affect the patient's daily life and academic performance, but other factors such as epilepsy duration, frequency of seizures and antiepileptic drugs can also affect the cognitive functions and daily life. In this study, we were unable to investigate these, because all of our patients had similar lower performances on preoperative recordings. Furthermore, we had no objective tests to compare pre- and postoperative performances. In large number of patients, the possible factors such as epilepsy duration and frequency of seizures that may affect Daily life and academic performance can be compared in different degrees of psychophysical performances. The effect of antiepileptic drugs on performance, however, could not be easily studied in this group of patients with intractable seizures and receiving polytherapy. Further studies using functional MRI and diffusion-tensor imaging in patients with TLE are worth pursuing. These clinical, neuroradiological and neuropsychological findings should provide us with neuroanatomical information about the exact cortical areas and neural connections involved in sound lateralisation. The resection borders of anterior temporal lobectomy may accordingly be redefined to avoid worsening the auditory dysfunction that seems to be already present, or even to minimise it.

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REFERENCES

- Altman J, Balanov L, Delgin V. Effects of unilateral disorder of the brain hemispheric functions in man on directional hearing. *Neuropsychologia* 1979;17:295–301.
- Baez-Martin MM, Cabrera-Abreu I. Effects of lobectomy on the auditory mid-latency response in temporal lobe epileptic patients. *Rev Neurol* 2005;41:81–5.

- Bisiach E, Cornacchia L, Sterzi R, Vallar G. Disorders of perceived auditory lateralization after lesions of the right hemisphere. *Brain* 1984;107:37–52.
- Blauert J. Binaural localization. *Scand Audiol Suppl* 1982;15:7–26.
- Bougéard R, Fischer C. The role of the temporal pole in auditory processing. *Epileptic Disord* 2002(Suppl. 1):S29–32.
- Bushara KO, Weeks RA, Ishii K, Catalan MJ, Tian B, Rauschecker JP, et al. Modality specific frontal and parietal areas for auditory and visual spatial localization in humans. *Nat Neurosci* 1999;2:759–66.
- Clarke S, Bellmann A, Meuli RA, Assal G, Steck AJ. Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. *Neuropsychologia* 2000;38:797–807.
- Efron R, Crandall PH. Central auditory processing. II. Effects of anterior temporal lobectomy. *Brain Lang* 1983;19:237–53.
- Efron R, Crandall PH, Koss B, Diveni PL, Yund EW. Central auditory processing. III. Effects of anterior temporal lobectomy. The “cocktail party” effect and anterior temporal lobectomy. *Brain Lang* 1983;19:254–63.
- Ehrlé N, Samson S, Baulac M. Processing of rapid auditory information in epileptic patients with left temporal lobe damage. *Neuropsychologia* 2001;39:525–31.
- Griffiths TD, Rees A, Witton C, Cross PM, Shakir RA, Green GG. Spatial and temporal auditory processing deficits following right hemisphere infarction. A psychophysical study. *Brain* 1997;120:785–94.
- Griffiths TD, Rees G, Rees A, Green GG, Witton C, Rowe D, et al. Right parietal cortex is involved in the perception of sound movement in humans. *Nat Neurosci* 1998;1:74–9.
- Han MW, Ahn JH, Kang JK, Lee EM, Lee JH, Bae JH, et al. Central auditory processing impairment in patients with temporal lobe epilepsy. *Epilepsy Behav* 2011;20:370–4.
- Hari R, Pelizzone M, Mäkelä JP, Hällström J, Leinonen L, Lounasmaa OV. Neuromagnetic responses of the human auditory cortex to on- and offsets of noise bursts. *Audiology* 1987;26:31–43.
- Ilhan, B. Electrical source imaging: improvements in EEG applications. Doctoral Dissertation. Hacettepe University Medical Faculty, Ankara, 2009.
- Ilhan B, Yagcioglu S, Ungan P. “Octopus”: EEG/ERP bioelectromagnetic source imaging network #1 – online applications. Adana, Turkey: 7th National Neuroscience Congress; 2008.
- Jenkins WM, Merzenich MM. Role of cat primary auditory cortex for sound localization behavior. *J Neurophysiol* 1984;52:819–47.
- Kikuchi Y, Horwitz B, Mishkin M. Hierarchical auditory processing directed rostrally along the monkey's supratemporal plane. *J Neurosci* 2010;30:13021–30.
- Lancelot C, Samson S, Ahad P, Baulac M. Effect of unilateral temporal lobe resection on short-term memory for auditory object and sound location. *Ann N Y Acad Sci* 2003;999:377–80.
- Lehmann D. Principles of spatial analysis. In: Gevins AS, Rémond A, editors. *Methods of analysis of brain electrical and magnetic signals, Handbook of Electroencephalography and Clinical Neurophysiology* 1987; vol.1. Amsterdam: Elsevier; 1987. p. 309–54.

- Lieu JE. Speech-language and educational consequences of unilateral hearing loss in children. *Arch Otolaryngol Head Neck Surg* 2004;130:524–30.
- Maeder PP, Meuli RA, Adriani M, Bellmann A, Fornari E, Thiran JP, et al. Distinct pathways involved in sound recognition and localization: a human fMRI study. *Neuroimage* 2001;14:802–16.
- Meneguello J, Leonhardt FD, Pereira LD. Auditory processing in patients with temporal lobe epilepsy. *Rev Bras Otorrinolaringol* 2006;72:496–504.
- Palomaki K, Alku P, Makinen V, May P, Tiitinen H. Sound localization in the human brain: neuromagnetic observations. *Neuroreport* 2000;11:1535–8.
- Palomaki KJ, Tiitinen H, Makinen V, May PJ, Alku P. Spatial processing in human auditory cortex: the effects of 3D, ITD, and ILD stimulation techniques. *Brain Res Cogn Brain Res* 2005;24:364–79.
- Pantev C, Hoke M, Lehnertz K, Lütkenhöner B, Anaogianakis G, Wittowski W. Tonotopic organization of the human auditory cortex revealed by transient auditory evoked magnetic fields. *Electroencephalogr Clin Neurophysiol* 1988;69:160–70.
- Pauli E, Pickel S, Schulemann H, Buchfelder M, Stefan H. Neuropsychologic findings depending on the type of the resection in temporal lobe epilepsy. *Adv Neurol* 1999;81:371–7.
- Pinek B, Brouchon M. Head turning vs manual pointing to auditory target in normal subjects and in subjects with right parietal damage. *Brain Cogn* 1992;18:1–11.
- Pinek B, Duhamel JR, Cave C, Brouchon M. Audio-spatial deficits in humans: differential effects associated with left versus right hemisphere parietal damage. *Cortex* 1989;25:175–86.
- Ruff RM, Hersh NA, Pribram KH. Auditory spatial deficits in the personal and extrapersonal frames of reference due to cortical lesions. *Neuropsychologia* 1981;19:435–43.
- Sanchez-Longo LP, Forster FM. Clinical significance of impairment of sound localization. *Neurology* 1958;8:119–25.
- Schroger E. Interaural time and level differences: integrated or separated processing? *Hear Res* 1996;96:191–8.
- Spierer L, Bellmann-Thiran A, Maeder P, Murray MM, Clarke S. Hemispheric competence for auditory spatial representation. *Brain* 2009;132:1953–66.
- Tardif E, Murray MM, Meylan R, Spierer L, Clarke S. The spatio-temporal brain dynamics of processing and integrating sound localization cues in humans. *Brain Res* 2006;1092:161–76.
- Ungan P, Özmen B. Human long-latency responses to brief interaural disparities of intensity. *Electroencephalogr Clin Neurophysiol* 1996;99:476–90.
- Ungan P, Yagcioglu S, Goksoy C. Differences between the N1 waves of the responses to interaural time and intensity disparities: scalp topography and dipole sources. *Clin Neurophysiol* 2001;112:485–98.
- Vives K, Lee G, Doyle W, Spencer DD. Anterior temporal resection. In: Engel J, Pedley TA, editors. *Epilepsy: a comprehensive textbook*. Philadelphia: Lippincott Williams & Wilkins; 2007. p. 1859–67.
- Weeks RA, Aziz-Sultan A, Bushara KO, Tian B, Wessinger CM, Dang N, et al. A PET study of human auditory spatial processing. *Neurosci Lett* 1999;262:155–8.
- Woldorff MG, Tempelmann C, Fell J, Tegeler C, Gaschler-Markefski B, Hinrichs H, et al. Lateralized auditory spatial perception and the contralaterality of cortical processing as studied with functional magnetic resonance imaging and magnetoencephalography. *Hum Brain Mapp* 1999;7:49–66.

Yamada K, Kaga K, Uno A, Shindo M. Sound lateralization in patients with lesions including the auditory cortex: comparison of interaural time difference (ITD) discrimination and interaural intensity difference (IID) discrimination. *Hear Res* 1996;101:173–80.

Zatorre RJ, Penhune VB. Spatial localization after excision of human auditory cortex. *J Neurosci* 2001;21:6321–8.