Evidence of Functional Connectivity between Auditory Cortical Areas Revealed by Amplitude Modulation Sound Processing

The human auditory cortex includes several interconnected areas. A better understanding of the mechanisms involved in auditory cortical functions requires a detailed knowledge of neuronal connectivity between functional cortical regions. In human, it is difficult to track in vivo neuronal connectivity. We investigated the interarea connection in vivo in the auditory cortex using a method of directed coherence (DCOH) applied to depth auditory evoked potentials (AEPs). This paper presents simultaneous AEPs recordings from insular gyrus (IG), primary and secondary cortices (Heschl’s gyrus and planum temporale), and associative areas (Brodmann area [BA] 22) with multilead intracerebral electrodes in response to sinusoidal modulated white noises in 4 epileptic patients who underwent invasive monitoring with depth electrodes for epilepsy surgery. DCOH allowed estimation of the causality between 2 signals recorded from different cortical sites. The results showed 1) a predominant auditory stream within the primary auditory cortex from the most medial region to the most lateral one whatever the modulation frequency, 2) unidirectional functional connection from the primary to secondary auditory cortex, 3) a major auditory propagation from the posterior areas to the anterior ones, particularly at 8, 16, and 32 Hz, and 4) a particular role of Heschl’s sulcus dispatching information to the different auditory areas. These findings suggest that cortical processing of auditory information is performed in serial and parallel streams. Our data showed that the auditory propagation could not be associated to a unidirectional traveling wave but to a constant interaction between these areas that could reflect the large adaptive and plastic capacities of auditory cortex. The role of the IG is discussed.

Keywords: amplitude-modulated sounds, auditory cortical areas, directed coherence, human, propagation

Introduction

The human auditory cortex includes several interconnected areas. The complexity of these interacting structures presents a challenge to researchers to determine how this system analyzes and uses auditory information. Indeed, auditory perception comprises the discrimination of a vast array of sound features such as pitch, rhythm, timbre, loudness, or amplitude modulations. Neuropsychologically speaking, the discrimination of two successive sounds differing in one parameter reflects the discrimination of two different neural representations evoked in the same or a different group of neurons. Perception of stimulus change is strongly correlated with the amplitude, latency, and other parameters of surface as well as depth-recorded evoked potentials (EPs) (for review, Eggermont and Ponton 2002). Depth EPs, only detected if a sufficient number of neurons are activated synchronously, have allowed physiological distinction of some of the auditory areas defined by cytoarchitectonic criteria (Braak 1980; Galaburda and Sanides 1980; Liégeois-Chauvel and others 1991, 1994; Howard and others 2000). Elloquent auditory cortical areas have been found within the posterior two-thirds of the superior temporal gyrus (STG) including Heschl’s gyrus (HG), planum temporale (PT), the most posterior part of STG (Post T1), insular gyrus (IG), and parietal operculum (Liégeois-Chauvel and others 2004). Little is known about their functional organization and their connectivity, and most current beliefs are derived from work on animals in which physiological and functional data could be interpreted within an anatomical framework (Rauschecker and others 1997; Rauschecker 1998; Kaas and Hackett 1998, 2000). The primate auditory cortex is subdivided into 3 areas: the core, belt, and parabelt. Most work has shown that auditory information is distributed from the core areas to surrounding belts that relay information to parabelt regions (for review, Kaas and others 1999; Kaas and Hackett 2000).

To our knowledge, only a few studies exist on the connectivity between human auditory areas. Most of these have been performed on postmortem human brains by use of tracer injections (Rivier and Clarke 1997; Galuske and others 1999; Tardif and Clarke 2001), which prevented observation of the propagation of evoked activity in vivo or in animals (Ruttgers and others 1990; Morel and Kaas 1992; Kosmal and others 1997; Wallace and others 2002). In a previous study (Liégeois-Chauvel and others 1991), we showed that direct electrical stimulation of HG resulted in unidirectional connection from the medial part of HG (primary auditory cortex [PAC]) to its lateral part (secondary auditory cortex [SAC]) and to PT. In a recent study, Howard and others (2000), using the same method, showed that electrical stimulation of HG resulted in short-latency auditory evoked potentials (AEPs) in an area that overlapped with the posterior lateral STG (associative auditory cortex), indicating that this area received a corticocortical input, either directly or indirectly from HG.

Previous data have shown that 4 auditory areas can be identified from the morphological distribution of AEPs within the STG: 1) the PAC, located in the medial and intermediate part of HG, 2) SAC, located in the lateral part of HG and PT, 3) an area located in the posterior part of STG (Post T1), and 4) an area located in front of HG, in the anterior part of STG (BA 22) (Liégeois-Chauvel and others 1991, 1994). In the present study, we had the opportunity to record depth AEPs simultaneously from some of these auditory cortical areas, in epileptic patients suffering from drug-resistant epilepsy, during the presurgical evaluation of epilepsy surgery (Bancaud and others 1965).

The aim of the present work was to study the connectivity which exists between these areas using the algorithm of directed coherence (DCOH) introduced by Saito and Harashima...
(1981), based on multivariate autoregressive (AR) models and Granger causality, which outputs the directional coherences between 2 electroencephalography (EEG) signals recorded from distinct regions.

Microelectrode studies in the cat have shown that the synchronized firing rate was always strongly affected by modulation frequency (MF) (Schreiner and Urbas 1986, 1988). Indeed, the sensitivity to amplitude modulation (AM) frequency appeared to be distributed in cortical areas and reflected as modulations in firing rate that were synchronous across areas (Eggermont 1994, 1999, 2000). The neural code employed by the auditory system is therefore likely to be determined by the innate areas of the auditory cortex, and the connections of the pathways between these areas and the properties of their neurons produce the coded representation (Ehret 1997). We used amplitude modulation sound of different MFs to identify the different pathways.

Materials and Methods

Patients
Four patients (2 males, 2 females, 25-35 years of age), among the 20 patients who participated in the study reported in Liégeois-Chauvel and others (2004), participated in the present study. They suffered from drug-resistant partial epilepsy and were implanted with chronic stereoelectroencephalography (SEEG) electrodes in the right (2 patients) or in the left auditory cortex (2 patients). Several additional electrodes were implanted in various cortical structures in order to 1) determine which structures were involved in the initiation and propagation of seizures and 2) accurately delineate the limits of future cortical excision (Talairach and Tournoux 1988). The anatomical position of each contact was then identified on the basis of 1) an axial scanner image acquired before the removal of electrodes and 2) an MRI scan performed after the removal of electrodes (Liegeois-Chauvel and others 1991). The 3 remaining patients had only 2 electrodes in the auditory cortex. In Case 12, 3 areas are recorded: the left PAC (H8-H12 T12), the left SAC (T12-T15 C12), and the left posterior part of STG (Post T1 H12). In Case 1, 4 contacts of electrode H1 (H6-H9) were in the right PAC, H10 was in the Transverse HS. Eight contacts were located in right posterior lateral part of the STG (Post T1 H12 and Post T1 H10). Case 20 had 2 electrodes, which explored the left PAC (H10-H15 T10 and T10-T15 T20).

Stimuli
All stimuli were generated using a 16-bit D/A converter at a sampling frequency of 44.1 kHz. The stimuli were white noises modulated sinusoidally in amplitude at frequencies MF = 4, 8, 16, 32, 64, and 128 Hz, with a 100% depth modulation. The starting phase of the modulation was fixed at 270° (thus, each stimulus started at an amplitude minimum in the modulation waveform). All AM stimuli were 1 s in duration and were shaped by rising and falling 25-ms cosine ramps/damps. They were equated in root mean square (r.m.s.) and presented binaurally via Sennheiser headphones at 75 dB sound pressure level (r.m.s). Series of 100 mixed stimuli (+/32 Hz, 8/64 Hz, 16/128 Hz) were delivered to the listener in random order.

Recordings
The recordings of intracerebral AEPs were monopolar, with each contact of a given depth electrode referenced to an extradural lead. All signals were amplified and band-pass filtered between 0.15 and 280 Hz (more precisely, a high-pass filter [cutoff frequency: 0.15 Hz, rolloff: 12 dB/oct] and a low-pass filter [cutoff frequency: 200 Hz, rolloff: 24 dB/oct]) were used to band-pass filter signals. Data acquisition started 164 ms before the presentation of the sound and lasted for 1476 ms. A total of 53 trials were averaged for each sound. During each recording session, the patient lays comfortably in a chair in a sound-attenuated room and listened passively to the sounds. The averaged signals presented a frequency peak at the MF in their power spectral density. The oscillations at the MF were also visible in the temporal shape of the signal in the time window between 200 and 1000 ms poststimulus onset. Figure 1 (top) shows typical synchronized AEPs recorded from third lead of electrode H1 (lead H3 located in the right PAC) in response to a 16-Hz MF stimulus. Periodic activity characterized by phasic responses close to the onset of each modulation cycle is clearly visible in this AEP preceded by initial evoked response (N1/P2). The power spectral density computed in the 200-1000 ms range is shown in Figure 1 (bottom).

Method

Based on a bivariate AR model and the Granger causality, the DCOH has been introduced in Saito and Harashima (1981). Compared with the ordinary coherence defined in Bendat and Piersol (1986), the DCOH provides the direction of propagation between two time series in addition to their degree of linear interaction. The principle of this method, whose complete description is given in Appendix A (cf., Supplementary Material), is to model 2 signals X and Y by a bivariate AR model. From this model, 2 DCOHs DCOHx,Y(f) and DCOHY,X(f), representing the degree of linear interaction from X to Y and from Y to X, respectively, are obtained at any frequency f. In this modeling, different sources are introduced, Wx (respectively Wy) is the source from which signal X (respectively Y) is generated, and Wy (respectively Wx) is a common source to X and Y. Sources Wx, Wy, and Wz are Gaussian white noises with a null mean and a variance of 1. The DCOHs are normalized in the range (0-1) and represent the ratio between the different contributions of sources to one signal.

A simple example is given in equation (1), in which X is AR and Y is computed thanks to X:

\[
\begin{align*}
X(k) &= 0.9 X(k-1) + 10 W_x(k) + W_y(k) \\
Y(k) &= 0.5 X(k-1) + W_x(k) + W_z(k),
\end{align*}
\]

where \(k\) is the current sample.

In this equation, the samples of Y depend on the preceding sample of X, whereas the samples of X do not depend on the samples of Y. Then X is autogenerated and generates Y. The resulting modules of
DCOH\(_y(x)(f)\) and DCOH\(_x(y)(f)\) are given in Figure 2, for the frequency \(f\) in the range (0--500 Hz), with a sampling frequency \(F_s = 1\) kHz.

In Figure 2, we can see that \(\text{DCOH}_{y(x)}(f)\) (left) is close to 1 and \(\text{DCOH}_{x(y)}(f)\) (right) is null, which shows the influence of \(X\) on \(Y\) whatever the frequency. This figure confirms the model given in equation (1).

Our aim is to study the propagation between the auditory areas of the oscillatory part of event-related potentials, which oscillates at the MF of the stimuli. Consequently, signals were examined in their quasi-stationary oscillatory part (from 200 to 1000 ms poststimulus onset), and the DCOH method was applied for each pair of leads at each MF. We particularly computed, for each MF, the modules of DCOH from \(Y\) to \(X\) and from \(X\) to \(Y\) taken at the frequency \(f = \text{MF}\), denoted \(\text{DCOH}_{y(x)}(\text{MF})\) and \(\text{DCOH}_{x(y)}(\text{MF})\), respectively. For the study of DCOH in Case 3, who had the largest sampling of electrodes and auditory regions explored, 4 different stimuli (amplitude-modulated white noise at MF = 4, 8, 16, or 32 Hz) were used, and the corresponding AR model orders were 140, 100, 70, and 50, respectively. For the three other patients, only stimulus at MF = 8 Hz (AR model order = 100) was used because it corresponded to the most representative modulation transfer function across auditory regions as observed in the previous study (Légeois-Chauvel and others 2004).

Threshold Determination for DCOH Significance
To study the connectivity between auditory cortical areas revealed by AM sound processing, we must distinguish the activity induced by AM stimuli from the background EEG activity by determining a threshold for DCOH. To determine this threshold, we compare the values obtained on EEG signals with those obtained on responses to stimuli. This preliminary study is carried out at 8 Hz for the leads of PAC of Case

Figure 1. Above: shape of the AEP recorded on lead H3 of Case 3 in response to a 16-Hz MF stimulus. Below: power spectral density of H3 taken in the range 200--1000 ms posttrigger.

Figure 2. DCOH example.
3. In this purpose, we sent 53 stimuli at 8 Hz, which provided us with 53 responses to stimuli (53 trials) and 53 interstimuli signals (background EEG activity without auditory activity) for each recorded lead. We first applied the DCOH algorithm to the 53 interstimuli signals recorded on each lead of the PAC. A standard deviation is then computed and a confidence interval derived. Second, we applied the DCOH algorithm to the 53 responses to stimuli using a bootstrap technique: we built an AEP by averaging a set of 53 trials randomly chosen with replacement, and we computed the DCOH measure on this AEP. This step is iterated 100 times, and a confidence interval is derived. Results of the propagation expressed by DCOH modules at frequency \( f = 8 \) Hz and the 95% confidence intervals of each DCOH measure are reported in Table 1 for the background EEG activity and in Table 2 for auditory activity. These tables follow the reading convention of source (column) to target (row). The DCOH obtained on background EEG activity is lower than 0.6 with a low variance. We therefore consider that DCOH measures higher than 0.6 are revealing of flow information for auditory activity.

Table 2 shows that 95% confidence intervals of DCOH measures are low and then DCOH measure is accurate.

**Results**

**Anatomical Distribution of AM Responses within the Different Auditory Areas**

The magnitude of the evoked responses (53 trials) was analyzed as a function of the stimulus MF (Liègeois-Chauvel and others 2004). The magnitude values of the spectral components were determined by considering the fast Fourier transforms of the responses over 1200 ms. These values are averaged, and Figure 3 shows the amplitude of the spectral peaks at the MF within main auditory areas (PAC, SAC, BA 22, and Post T1) as a function of AM frequency (4, 8, 16, and 32 Hz) and patients.

As reported in the previous study, the distribution of MF varies from one contact to another, and predominant response of cortical auditory areas to the low AM frequencies (4--8 Hz) is represented.

**Propagation within the PAC**

To study the propagation between the different leads located within the PAC, we distinguished the posterior part from the anterior part of PAC in Cases 3 and 20. The corresponding AEPs are taken in the time window between 200 and 1000 ms poststimulus onset. Results of the propagation expressed by DCOH modules at each frequency \( f = 8 \) Hz are reported in Table 3 for Case 3 and in Table A1 for Case 20 at MF = 8 Hz in Supplementary Material. These tables follow the reading convention of source (column) to target (row). In Tables 3 and A1, the highlighted values correspond to DCOH modules higher than 0.6.

In Table 3, we observe that the auditory flow tends mainly to propagate serially from the medial leads (lead P1 to P2) to the most lateral ones (lead P4 to P5). This direction of propagation is found whatever the AM frequency within the posterior part of PAC (electrode P5). In the anterior part of PAC (electrode H3), this unidirectionality seems less clear because it exists for H3 to H4 whose activity is propagated to H4 and H5, but less for H4 to H3. Moreover, some variations are seen according to the AM sound. Interestingly, the oscillatory activity was propagated from the posterior to the anterior part of PAC (i.e., from electrode P5 to H3) except for 4 Hz.

The values in Tables 3 and A1 for MF = 8 Hz are reported in Figure 4a,b for Cases 3 and 20, respectively. The arrow width codes interaction strength (0 \( \leq \) arrow \( \leq 0.6 \)) < increasing width solid lines in step of 0.2. For reasons of clarity in Figure 4b, only the DCOHs modules superior to 0.8 are represented.

Figure 4a shows that the activity propagates from the posterior part to the anterior part of PAC of Case 3, mainly to H4 and H5. In Figure 4b dealing with Case 20, the location of the electrode H20 is in the same region as H3, and the electrode T420 is more anterior and lateral than H20. There is a strong tendency of mediolateral propagation but which is not strictly serial, for instance, auditory stream mainly goes from H1020 and H1120 to H1420 and H1520 and from T1220 to T1520 skipping T1320 and T1420. In the anterior-lateral part

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**Table 1**

DCOH modules at the frequency MF = 8 Hz and the corresponding 95% confidence intervals between all the leads located in the PAC of Case 3 for the background EEG activity

<table>
<thead>
<tr>
<th>Lead</th>
<th>MF = 8 Hz</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.3713</td>
<td>(0.3713 ± 0.029)</td>
</tr>
<tr>
<td>P2</td>
<td>0.219</td>
<td>(0.219 ± 0.031)</td>
</tr>
<tr>
<td>P3</td>
<td>0.5768</td>
<td>(0.5768 ± 0.027)</td>
</tr>
<tr>
<td>P4</td>
<td>0.2052</td>
<td>(0.2052 ± 0.030)</td>
</tr>
<tr>
<td>H3</td>
<td>0.2243</td>
<td>(0.2243 ± 0.030)</td>
</tr>
<tr>
<td>H4</td>
<td>0.2775</td>
<td>(0.2775 ± 0.032)</td>
</tr>
<tr>
<td>H5</td>
<td>0.2594</td>
<td>(0.2594 ± 0.029)</td>
</tr>
</tbody>
</table>

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**Table 2**

DCOH modules at the frequency MF = 8 Hz and the corresponding 95% confidence intervals determined by bootstrap between all the leads located in the PAC of Case 3 for the auditory activity

<table>
<thead>
<tr>
<th>Lead</th>
<th>MF = 8 Hz</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.43</td>
<td>(0.43 ± 0.011)</td>
</tr>
<tr>
<td>P2</td>
<td>0.88</td>
<td>(0.88 ± 0.009)</td>
</tr>
<tr>
<td>P3</td>
<td>0.48</td>
<td>(0.48 ± 0.015)</td>
</tr>
<tr>
<td>P4</td>
<td>0.74</td>
<td>(0.74 ± 0.008)</td>
</tr>
<tr>
<td>H3</td>
<td>0.89</td>
<td>(0.89 ± 0.006)</td>
</tr>
<tr>
<td>H4</td>
<td>0.7</td>
<td>(0.7 ± 0.013)</td>
</tr>
<tr>
<td>H5</td>
<td>0.51</td>
<td>(0.51 ± 0.019)</td>
</tr>
</tbody>
</table>

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There is a constant interaction inside this area, predominantly from TC20 to HC20. Between Different Anatomical Areas

First, we will describe the results obtained from Case 3 because the exceptional sampling of the recording sites within the auditory cortex (see Materials and Methods) allowed recording of activity in 4 different anatomical areas of the right auditory cortex (PAC, SAC, PT, BA 22) and in the IG. In the same manner that we distinguished the posterior part (PAC P: P1--4) from the anterior part of PAC (PAC H: H3--5), we separate evoked activity recorded from posterior PT P (P5--P9) to anterior PT H (H7--9). We studied the functional connectivity between these 7 subregions.

Figure 3. Values of the amplitude spectrum at 4 modulation frequencies (MF = 4, 8, 16, 32 Hz) for each patient. (a) PAC – Case 1, (b) SAC – Case 1, (c) Post T1 – Case 1, (d) PAC – Case 3, (e) SAC (HG + PT) – Case 3, (f) Area 22 – Case 3, (g) PAC + HG – Case 12, (h) Post T1 – Case 12, (i) PAC – Case 20.

Table 3
DCOH modules at the frequency \( f = MF \) (MF = 4, 8, 16, and 32 Hz) between all the leads located in the PAC of Case 3

<table>
<thead>
<tr>
<th></th>
<th>MF = 4 Hz</th>
<th>MF = 8 Hz</th>
<th>MF = 16 Hz</th>
<th>MF = 32 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>0.38</td>
<td>0.38</td>
<td>0.37</td>
<td>0.72</td>
</tr>
<tr>
<td>P2</td>
<td>0.14</td>
<td>0.14</td>
<td>0.38</td>
<td>0.57</td>
</tr>
<tr>
<td>P3</td>
<td>0.88</td>
<td>0.85</td>
<td>0.37</td>
<td>0.79</td>
</tr>
<tr>
<td>P4</td>
<td>0.80</td>
<td>0.64</td>
<td>0.90</td>
<td>0.54</td>
</tr>
<tr>
<td>H3</td>
<td>0.63</td>
<td>0.64</td>
<td>0.50</td>
<td>0.64</td>
</tr>
<tr>
<td>H4</td>
<td>0.60</td>
<td>0.71</td>
<td>0.33</td>
<td>0.45</td>
</tr>
<tr>
<td>H5</td>
<td>0.27</td>
<td>0.15</td>
<td>0.06</td>
<td>0.53</td>
</tr>
</tbody>
</table>

of PAC\(_{20}\), there is a constant interaction inside this area, predominantly from T\(_{1-20}\) to H\(_{1-20}\).

Between Different Anatomical Areas

First, we will describe the results obtained from Case 3 because the exceptional sampling of the recording sites within the auditory cortex (see Materials and Methods) allowed recording of activity in 4 different anatomical areas of the right auditory cortex (PAC, SAC, PT, BA 22) and in the IG. In the same manner that we distinguished the posterior part (PAC P: P1--4) from the anterior part of PAC (PAC H: H3--5), we separate evoked activity recorded from posterior PT P (P5--P9) to anterior PT H (H7--9). We studied the functional connectivity between these 7 subregions.
The DCOH algorithm was then applied to each couple constituted of AEPs relative to leads located in the different subregions. The corresponding AEPs are taken in the time window between 200 and 1000 ms poststimulus onset. The means of all the DCOH modules over all the frequencies $MF = 4$, 8, 16, and 32 Hz from the different couplings were summarized in Table A2 (see Supplementary Material) and displayed in Figure 5 for Case 3.

This graph shows the major propagations of the oscillations between the 7 auditory subregions of Case 3 independently of the AM frequency. The main source of information is the PAC P, which directs auditory information to the PAC H, confirming the posterior-to-anterior influence within the PAC, and to the SAC T showing primary-to-secondary auditory areas connectivity. In the same way, the PAC H is linked to the PT H (medial to lateral connection) and to the SAC T. This figure presents examples of strong unidirectional influence of primary auditory areas (PAC P and PAC H) on secondary ones (SAC T and A22 T) and on PT (PT P and PT H). The IG (Insula H) also seems to send information to other areas (PT H, SAC T, and A22 T) and receives information only from PAC P.

For Case 3, the modules of DCOH calculated for 8, 16, and 32 Hz are given in Tables A3, A4, and A5, presented as Supplementary Material. We considered the HS (lead H6) as a single area.

Modules of DCOH of Cases 3, 1, and 12 calculated for 8 Hz are summarized on the graphs shown in Figure 6a, b, and c, respectively. Only modules of DCOHs superior to 0.6 are displayed.

In Figure 6a, the main connections are similar to those given in Figure 5, which correspond to the principal directed connections present between the 8 zones whatever the MF. But one can readily see that the HS dispatches information to several zones including PAC P, PT P, Insula H, PT H, SAC T, and A22 T. The other main source of information is the PAC P that propagates information to the PT P, Insula H, PAC H, PT H, SAC T, and A22 T. In general, information flows from posterior to anterior zones and from medial to lateral zones.
In Figure 6b,c, auditory information propagates from primary and secondary auditory areas (PAC and SAC) to the posterior part of STG (Post T1). As previously observed, HS sends information to PAC, but it receives information from Post T1 in Case 12.

Figure 7a shows the information propagation at MF = 16 Hz in Case 3. As in the previous case, PAC P sends information to PT P, PAC H, PT H, SAC T, and A22 T. Mainly, information flows from posterior to anterior zones and from medial to lateral zones. We observe the striking influence of HS, which directs information to the PAC, SAC, and BA 22 and even to the Insula.

Interestingly, we notice that the connectivity is frequency dependent as shown in Figure 7b for 32 Hz. One can readily see that the interaction strengths are very high, particularly from PAC P, Insula H, and PAC H to the other zones. Contrary to the two other MFs, the Sulcus H here almost only receives activity from the other zones, and a strong connectivity is observed between Insula H and Sulcus H, SAC T, and A22 T. More importantly than at other MFs, information flows from posterior to anterior zones and from medial to lateral zones.

Figure 8 summarizes all the results of Case 3 represented in terms of its anatomy. Two main streams emerge, one from the posteromedial part of HG to the anterior part of HG and STG and another from medial to lateral part of HG. The role of HS dispatching auditory stream to the nearby regions is revealed. The connectivity of insula is strongly modulated by the AM frequency and seems maximal for the 32-Hz MF. Data from the three other patients confirm the mediolateral stream in HG and show that Post T1 receives information from PAC and SAC, sending in return to PAC via HS.

Discussion

Overall, the present data indicate 1) a mediolateral propagation within the PAC, 2) a predominant auditory stream from primary to secondary and associative auditory areas, and 3) a hierarchical and parallel processing between the cortical areas. Finally, the data showed 4) the special role played by the HS in the dispatching of auditory stream. These results are discussed below.

The human auditory cortex is currently subdivided into several architectonically defined areas. The number of these areas as well as their extent and exact position vary between authors. Using cytoarchitectonic criteria, Brodmann (1909) distinguished 3 areas, called 41, 42, and 22, and von Economo and Koskinas (1925) 4 areas, as did Braak (1980). Combining cyto- and myeloarchitecture, Galaburda and Sanides (1980) identified in the same region 8 areas.

Primary auditory cortex

As reported by Rademacher and others (2001), the precise location and absolute size of PAC cannot be reliably inferred from the macroanatomic landmarks and could comprise between 16% and 92% of the cortical volume of HG according to subjects. Evidence for identification of PAC came from electrophysiological recordings reported in vivo studies (Celesia 1976; Liégeois-Chauvel and others 1991). Comparison between cytoarchitectonic studies and our data suggests that areas PAC P^T1, PAC H^C20, and PAC T^C20 would correspond to A1 (Rivier and Clarke 1997; Clarke and Rivier 1998) or Te1 (Morosan and others 2001; Rademacher and others 2001). The striking result is the coexistence of simplicity and complexity within PAC connectivity. In one hand, we observed a mediolateral auditory propagation observed along electrodes located in different parts of right and left PAC suggesting a hierarchical processing. On the other hand, the differentiation

Figure 7. (a) Graph of propagation between the 8 auditory subregions of Case 3 at the frequency MF = 16 Hz. The arrow width codes interaction strength (0 < no arrow < 0.6 < increasing width solid lines in step of 0.2). (b) Graph of propagation between the 8 auditory subregions of Case 3 at the frequency MF = 32 Hz. The arrow width codes interaction strength (0 < no arrow < 0.6 < increasing width solid lines in step of 0.2).

Figure 8. Corticocortical connections within the auditory areas of Case 3. Arrows indicate the direction of auditory stream. Localization of intracerebral electrodes in auditory cortex is superimposed on the patient’s MRI slices. Each dashed line (labeled T, H, and P) indicates the anatomical location of a single electrode (each white segment corresponding to a given electrode contact). Each blue, yellow, red, or green line indicates which auditory region is recorded. Note that a single electrode can record cortical activity from different areas.
of physiological regions showed distinct interactions between themselves. Interestingly, these areas were not differentiated by AEPs, but by their connectivities. The first two recorded from H<sup>3</sup> and T<sup>20</sup> showed a unidirectional propagation of auditory stream from right posterior to anterior PAC. This posterior-anterior propagation did not seem to continue to occur in the anterolateral part of PAC, at least in the left hemisphere. We observed that the electrode located in the anterolateral part (T12--15/T20) sent information to H<sup>20</sup>, which is located medially and posteriorly to T<sup>20</sup>. Although we do not have data on cytoarchitectony, we may be able to derive some information on a putative distinction between the 3 primary areas from the connectivity patterns. The first one is located in the tip of HG recorded by P<sup>5</sup>, the second one is located in the medioanterior part (H<sup>3</sup> and H<sup>20</sup>), and the third one in the anterolateral of PAC (T<sup>20</sup>). This physiological distinction could be related to the subdivisions (Te1.1, Te1.0, and Te2) of PAC reported by Morosan and others (2001) and is close to the organization of auditory core of monkey (Kaas and Hackett 2000). Our data showed that the auditory propagation could not be associated to a unidirectional traveling wave but to a constant interaction between these areas. That could reflect the large adaptive and plastic capacities of auditory cortex (Engineer and others 2004; Nelken 2004). Fritz and others (2003) have recently demonstrated rapid plastic changes in ferret auditory cortex within minutes of the beginning of a tone detection task. Such changes were smaller or absent when the animal was listening passively to same sounds. In human, Schneider and others (2002) demonstrated correlation among the amplitude of N19/P30 primary auditory components, the gray matter volume of PAC, and musical aptitude in groups of musicians versus nonmusicians.

**The Role of HS**

The morphology of AEPs in response to tones in HS was quite different from those recorded from the PAC, the PT, or Post T1 that may result in part from differences in thalamic input to these fields. Interestingly, HS dispatches auditory stream to several regions such as Insula, PAC, SAC, PT, and BA 22. It receives information from Post T1. Its place between upstream auditory areas (PAC, SAC) and downstream areas (PT, Post T1) (Rivier and Clarke 1997) leads to speculation regarding its role. Auditory scene analysis needs a continuous processing of sounds that are spectrally and temporally complex. HS would represent an interface between processing in other auditory cortical regions and could play a modulator role because it sends auditory upstream to PAC only for 8 and 16 Hz.

**Role of Insula**

Strong connectivity is seen between the posterior part of the IG (posterior insular cortex [PIC]) and SAC, PT, and BA 22 especially at highest AM frequency (32 Hz). A functional MRI study (Giraud and others 2000) also investigated the cortical representation of AM using a set of white noises modulated sinusoidally in amplitude at frequencies covering a broad range (4--256 Hz). Consistent with animal studies, this study revealed that, in humans, 1) temporal resolution degrades from the brainstem to the auditory cortex and 2) only a few cortical regions were tuned to high AM frequencies, for instance, PIC is known to be an eloquent auditory region and seems to be strongly modulated by high AM frequency rather than low AM. Its functional role remains unclear. First, there were discrepancies in the interpretation of functional and anatomical data. As a matter of fact, PAC and PIC had a cytochrome oxidase profile that was compatible with a primary sensory area (Rivier and Clarke 1997), whereas electrophysiological responses recorded from PIC were clearly different and could not be considered as primary responses (Liégeois-Chauvel and others 2004). Intra-cortical electrical stimulations elicited hypoacusia in the contralateral ear or arrest of speech (Ostrowsky and others 2000), whereas electrical stimulation of PAC elicited auditory hallucinations (De Graaf and others 2000; Howard and others 2000).

### Hierarchical and Parallel Processing within Human Auditory Areas?

Given that, similarly to the visual system (for review, Felleman and Van Essen 1991), auditory areas might be organized in a hierarchical system (Rauschecker and others 1997), we may be able to derive some information on a putative hierarchical order from the DCOH values. An auditory stream from the PAC to the secondary cortex (lateral part of HG and PT) and to BA 22 is observed. The hierarchical organization within the human auditory cortex proposed by previous studies (Mesulam and Geula 1994; Hutslers and Gazzamiga 1996) seemed to be confirmed here. However, our results suggest an organization with a certain degree of parallel processing as observed in a recent study using magnetoencephalography (Inui and others 2006). These authors found 6 different cortical areas as a function of latency onset of cortical activity and inferred the existence of a serial model of auditory processing along the mediolateral axis as well as several parallel streams running from the PAC to the belt region and then the posterior STG and PT and anteriorly from PAC to BA 22. We also observed a direct propagation from the PAC to BA 22 and to Post T1. The projections from PAC to BA 22 have been shown in neurophysiological studies of the temporal auditory fields in the chimpanzee (Bailey and others 1943) and rhesus monkey (Ward and others 1946; Sugar and others 1948). Later, electrophysiological (Bignall 1969) and anatomical (Hackett and others 1998; Kaas and Hackett 1998, 2000) results have confirmed these auditory corticocortical connections in the nonhuman primate. The existence of a projection of HG upon Post T1 has been observed with direct cortical stimulation (Howard and others 2000; Brugge and others 2003). While applying electrical stimulation to sites in HG, Howard and others (2000) recorded short-latency evoked responses in posterior lateral superior temporal (PLST) area, which corresponds to the area that we called Post T1. Moreover, Brugge and others (2003) showed widespread convergence and divergence of input from HG to posterior STG with evidence for a reciprocal functional projection, from postero lateral STG to HG. By our study, we specified that this reciprocal projection was done via HS.

We were unable, however, to ascertain whether these were direct connections between 2 areas or an indirect one, the latter being consistent with the hierarchical connectivity model of Kaas and Hackett (1998) based on extensive electrophysiological mapping and neuroanatomic tracer studies in the monkey.

### Is DCOH an Accurate Tool?

The objective of using DCOH is to find the propagation direction between 2 given leads located in auditory cortical areas. The problem may be viewed in terms of delay. Various methods based on linear systems have been proposed. Among
nonparametric methods, the most classical corresponds to the maximum of the cross-correlation function. Some variants introducing a weighting window in the frequency domain were derived, such as the maximum likelihood. In the field of parametric methods, besides methods based on the fact that an observation is the sum of one signal derived from another observation and an additive noise, a vectorial AR model was proposed in Hannan and Thomson (1981) from which a delay estimation is derived using the cross-power spectral density matrix (Hamon and Hannan 1974). The first nonlinear method, the average amount of mutual information based on mutual entropy, was proposed in Mars and Van Arragon (1982). In Moddemeyer (1989), the estimation of the probability law is carried out using the histogram method leading to the information-theoretical delay estimator. Methods based on higher order moments (Nikias and Raghveer 1987) containing phase information are increasingly studied (Emile and Comon 1995). Parametric approaches have also been proposed in the nonlinear field such as the method based on the nonlinear regression coefficient (Pijn 1989).

Contrary to these methods that we have briefly summarized, and other methods of DCOH such as directed transfer function (Kaminski and Blinowska 1991) or partial directed coherence (PDC) (Baccala and Sameshima 2001), DCOH uses a different approach. It takes into account the influence of the rest of the brain on the two investigated signals, in modeling the rest of the brain by a common source influencing these 2 signals, and thus seems more appropriate to study neuronal connections. This characteristic of the DCOH method, although it does not give the delay, provides the propagation information directly from the relations between samples. The DCOH has already been applied to EEG signals recorded by scalp electrodes in healthy subjects (Jing and Takigawa 2000) and in epileptic subjects (Takigawa and others 1996), or by intracranial electrodes in rats (Wang and others 2002). Auditory event-related potentials have also been investigated by DCOH (Jing, Takigawa, Hamada, and others 2001; Jing, Takigawa, Okamura, and others 2001), but to our knowledge this paper is the first to study intracranial auditory event-related potentials.

Conclusion
The aim of the present work was to study the connectivity which exists between human auditory areas using the method of DCOH, applied to depth AEPs. DCOH allowed the estimation of causality between 2 signals recorded from different cortical sites. The results showed 1) a predominant auditory stream within the PAC from the most medial region to the most lateral one whatever the MF, 2) unidirectional functional connection from the primary to secondary auditory cortex, 3) a major auditory propagation from the posterior areas to the anterior ones, particularly at 8, 16, and 32 Hz, and 4) a particular role of HS, dispatching information to the different auditory areas. These findings suggest that cortical processing of auditory information is performed in serial and parallel streams.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes
Conflict of Interest: None declared.

References