Serial and Parallel Processing in the Human Auditory Cortex: A Magnetoencephalographic Study

Koji Inui, Hidehiko Okamoto, Kensaku Miki, Atsuko Gunji and Ryusuke Kakigi
Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki 444-8585, Japan

Although anatomical, histochemical and electrophysiological findings in both animals and humans have suggested a parallel and serial mode of auditory processing, precise activation timings of each cortical area are not well known, especially in humans. We investigated the timing of arrival of signals to multiple cortical areas using magnetoencephalography in humans. Following click stimuli applied to the left ear, activations were found in six cortical areas in the right hemisphere: the postero medial part of Heschl’s gyrus (HG), corresponding to the primary auditory cortex (PAC), the anterolateral part of the HG region on or posterior to the transverse sulcus, the posterior parietal cortex (PPC), posterior and anterior parts of the superior temporal gyrus (STG), and the planum temporale (PT). The mean onset latencies of each cortical activity were 17.1, 21.2, 25.3, 26.2, 30.9 and 47.6 ms respectively. These results suggested a serial model of auditory processing along the medio-lateral axis of the supratemporal plane and, in addition, implied the existence of several parallel streams running postero-superiorly (from the PAC to the belt region and then to the posterior STG, PPC or PT) and anteriorly (PAC-belt-anterior STG).

Keywords: auditory cortex, auditory evoked response, magnetoencephalography

Introduction

In primates, auditory cortical areas are usually divided into three regions — the core, belt and parabelt — based on their cochleatopic organization, anatomical connections and architectonic features (for review, see Kaas et al., 1999). The core field has histological features of the primary sensory cortex (Galaburda and Pandya, 1983; Morel et al., 1993; Jones et al., 1995; Hackett et al., 1998), and receives dense projections from the ventral subdivision of the medial geniculate nucleus complex (MGv) (Burton and Jones, 1976; Morel et al., 1993). The belt region, which surrounds the core, does not exhibit the histological features of the primary sensory cortex, and receives main inputs from the core region with a minor contribution from MGv (Galaburda and Pandya, 1983; Jones et al., 1995; Hackett et al., 1998). The parabelt region, which surrounds the belt, has strong connections with the belt region and minimal connections with the core (Hackett et al., 1998). These findings suggest that auditory information is processed serially through the core, belt and parabelt. In addition, there are several subdivisions in each of the three regions and a subregion tends to receive main inputs from its adjacent area, for example, the caudal parabelt receives main inputs from the caudal belt areas, while the rostral parabelt receives inputs selectively from the rostral belt fields (Hackett et al., 1998). These patterns of connection indicate that there are several parallel streams of auditory processing. In addition to these anatomical and histochemical studies, there are some electrophysiological studies that support such modes of auditory processing (Rauschecker et al., 1997) or functional segregations of neurons in each cortical zone (Kosaki et al., 1997). However, only a few studies have compared the response latency of neurons in different cortical fields of monkeys (Benson and Hienz, 1978; Pfingst and O’Connor, 1981; Vaadia et al., 1982; Kajikawa et al., 2005) and other mammals (Kowalski et al., 1995; Eggermont, 1998).

In humans, less is known about the processing mode of auditory information because of limitations of experimental methods. However, in general, data from humans suggest a hierarchical and parallel auditory processing similar to that found in monkeys. Cytoarchitectonic studies have distinguished several human auditory areas (Galaburda and Sanides, 1980) and, furthermore, have proposed a hierarchical and parallel organization within them based on the systematic change of histochemical features of each area (Mesulam and Geula, 1994; Hutslar and Gazzaniga, 1996; Rivier and Clarke, 1997). The distributions of response latencies in auditory evoked potential (AEP) and magnetic field (AEF) studies are roughly consistent with serial processing along the medio-lateral axis of the supratemporal plane (Celesia, 1976; Liégeois-Chauvel et al., 1994; Gutschalk et al., 1999; Howard et al., 2000; Yvert et al., 2001). However, precise temporal relationships among activities in multiple cortical areas are not well understood.

In a previous study using magnetoencephalography (MEG), we showed that tactile signals are mainly processed in two parallel pathways, each of which processes information in a serial fashion: one through areas 3b, 1 and 5 (posterior parietal cortex, PPC) and another through area 3b and/or area 1 and the secondary somatosensory cortex (Inui et al., 2004), which is consistent with anatomical and electrophysiological findings in monkeys showing serial somatosensory processing along the postcentral gyrus and through primary (SI) and secondary (SII) somatosensory cortices (for review, see Iwamura, 1998). In the present study, we sought to clarify the precise activation timing of auditory cortical areas using similar methods and to find some streams of auditory processing.

Materials and Methods

The experiment was performed on ten (two female and eight male) healthy right-handed volunteers, aged 25–51 years (mean 33.5 ± 7.4). Their hearing thresholds were below 15 nHL in the frequency range from 250 to 8000 Hz as tested by means of pure tone audiometry. The study was approved in advance by the Ethical Committee of the National Institute for Physiological Sciences and written consent was obtained from all the subjects.

The experiments were carried out in a quiet, magnetically shielded room. The subjects lay in a right lateral position, and their heads were

© The Author 2005. Published by Oxford University Press. All rights reserved.
For permissions, please e-mail: journals.permissions@oupjournals.org
fixed to the device with adhesive tape to minimize head movements. Clicks with a duration of 0.3 ms were created by a speaker placed outside the room and presented to the subjects’ left ear through a plastic tube 5 m in length and ear-pieces (E-A-Rtone 3A, Aero Company, Indianapolis, IN). The intensity of the clicks was adjusted to 60 dB above the threshold for each subject before the session. Clicks were delivered at a random rate of between 2.7 and 3.3 Hz. While the subjects watched silent movies, evoked magnetic fields were recorded with a 37-channel biomagnetometer (Magnes, Biomagnetic Technologies, San Diego, CA) as described previously (Inui et al., 2004). The magnetic fields were recorded with a filter of 0.1–200 Hz at a sampling rate of 2083 Hz, and then digitally filtered with a high-cut filter of 150 Hz. The window of analysis was from 40 ms before to 120 ms after the stimulus onset, and the pre-stimulus period was used as the DC baseline. In one trial, 1500 responses were collected and averaged. Two trials were obtained with intervals of a few minutes. After the reproducibility had been confirmed, the two trials were averaged and used for the analysis.

Source locations and time courses of source activities were determined by a multiple source analysis, brain electric source analysis (Neuroscan, McLean, VA), as described previously (Inui et al., 2004).

Model adequacy was assessed by examining: (i) percent variance (Hari et al., 1988); (ii) F-ratio (ratio of reduced chi-square values before and after adding a new source) (Supek and Aine, 1993); and (iii) residual waveforms (i.e., the difference between the recorded data and the model). Percent variance measures the goodness-of-fit (GOF) of the model comparing the recorded data and the model. The integral probability of obtaining a F-ratio value equal to or greater than the obtained value is calculated to evaluate whether a model with a larger number of dipoles represents a statistically significant improvement of the fit over a model with a smaller number of dipoles. When a P-value was <0.05, we considered the new dipole as significant. We continued to add a source to the model until the addition of a dipole did not significantly improve the fit. The procedure used to assess the model’s accuracy was basically the same as described elsewhere (Inui et al., 2004).

Magnetic resonance imaging (MRI) scans (Shimadzu, Kyoto, Japan, 150XT 1.5 T) were obtained from all subjects. T1-weighted coronal, axial and sagittal image slices obtained every 1.5 mm were used for superimposition of the MEG source locations. The same anatomical landmarks used to create the MEG head-based three-dimensional (3D) coordinate system (the bilateral pre-auricular points and nasion) were visualized in the MR images by affixing to these points high-contrast cod liver oil capsules (3 mm in diameter). The common MEG and MRI anatomical landmarks allowed easy transformation of the head-based 3D coordinate system used for MEG source analyses into the MRI coordinate system. The origin of the head-based coordinate system was the mid-point between the pre-auricular points. The x-axis indicated the coronal plane with a positive value toward the anterior direction, the y-axis indicated the mid-sagittal plane with a positive value toward the left pre-auricular point, and the z-axis indicated the transverse plane pre-auricular to the x-y plane with a positive value toward the upper side.

To reduce the interindividual variability of the location and extension of the auditory cortical area, we employed a common internal landmark. The landmark was the crown of the posteriormost part of Heschl’s gyrus (HG) for identification of point A (upper panels). The most lateral slice showed a dipolar pattern of field distributions consistent with sources pointing antero-superiorly (Fig. 2). In six out of ten subjects, the topography at ~40 ms showed a dipolar pattern that was clearly different from that of 1M or 2M (see waveform and topography at 39 ms in subject 2, Fig. 2). That is, the isocontour map at this latency indicated a source in the parietal region pointing posteriorly. After the 2M component, a topography consistent with a source pointing superiorly with a more superficial location than that for 1M or 2M was identified in seven subjects at 55–85 ms. Similar topographies were sometimes identified at a latency of 40–50 ms. In five subjects, a topography at 70–100 ms showed a dipolar pattern pointing postero-inferiorly (see topography at 90 ms in subject 1, Fig. 2). This topography indicated a source with a slightly posterior location than that for 1M.

Results

Waveforms and Topographies

In all subjects, two clear components around 30 and 50 ms after the stimulation were identified (Fig. 2) by the time course of the root mean square (RMS) and were termed 1M and 2M respectively. To examine the reproducibility of the response between two sessions, the peak latency, peak amplitude (peak RMS) and field distribution patterns for 1M and 2M were compared between the first and second session. The field distribution was compared using a correlation coefficient, r. A two-way analysis of variance (session × component) showed no significant effect of the session on either peak latency (F = 0.48, P = 0.50) or peak amplitude (F = 0.022, P = 0.88). The mean correlation coefficient r was 0.98 (0.95–0.99) and 0.97 (0.93–0.99) for 1M and 2M respectively. These results indicated that the first and second 1500 click stimuli evoked magnetic responses with a similar latency, amplitude and topography. Therefore, trials of both sessions were averaged and the averaged waveform was used for the analyses.

The peak latency (peak RMS) of 1M was 32.6 ms on average, ranging from 29.3 to 35.0 ms. The peak latency of 2M was 53.0 ms on average, ranging from 49.4 to 57.1 ms. Both components showed a dipolar pattern of field distributions consistent with sources pointing antero-superiorly (Fig. 2). In six out of ten subjects, the topography at ~40 ms showed a dipolar pattern that was clearly different from that of 1M or 2M (see waveform and topography at 39 ms in subject 2, Fig. 2). That is, the isocontour map at this latency indicated a source in the parietal region pointing posteriorly. After the 2M component, a topography consistent with a source pointing superiorly with a more superficial location than that for 1M or 2M was identified in seven subjects at 55–85 ms. Similar topographies were sometimes identified at a latency of 40–50 ms. In five subjects, a topography at 70–100 ms showed a dipolar pattern pointing postero-inferiorly (see topography at 90 ms in subject 1, Fig. 2). This topography indicated a source with a slightly posterior location than that for 1M.

Point A

Point B

Figure 1. Landmarks A and B. The most medial sagittal MRI slice with a clear Heschl’s gyrus (HG) for identification of point A (upper panels). The most lateral slice with a clear HG for identification of point B. HS, Heschl sulcus; STG, superior temporal gyrus; STS, superior temporal sulcus.
Two Sources during 1M
These topographies indicated that at least several distinct sources were active during the period of analysis. Therefore, we analyzed the data using a multiple source method to differentiate each cortical activity. We started the analysis with 1M. As shown in Figure 3A, the maximum influx and outflux activities differed in latency, indicating that two or more sources contributed to shape the 1M component. Figure 3B shows that the waveforms recorded from 37 sensors did not show a simple dipolar pattern, but showed peaks at different latencies. For example, the outflux of the sensors 1, 7, 17 and 18 peaked slightly later than the peak of 1M, while that of sensors 20, 21 and 22 peaked slightly earlier than the 1M peak. When a single dipole analysis was applied to 1M, the best GOF value was obtained at 27 ms, 2 ms earlier than the peak of 1M in this case (Fig. 3C). This finding was constant across subjects (Fig. 3D) and the best GOF value was obtained 3 ms earlier than the peak of 1M on average. This finding indicated that one or more sources were active at least at the peak of 1M in addition to the first source. Therefore, we tried to separate these sources during the period of 1M. The procedures and results of the analysis in a representative case are shown in Figure 4. When a single dipole analysis was applied to the peak of 1M (29 ms), the dipole was estimated to be located in the deep area of the Sylvian fissure (dipole A in Fig. 4Ca). Waveforms in Figure 4Ab show the residual magnetic fields obtained by subtraction of the theoretical magnetic fields due to this dipole from the original data (Fig. 4Ac). The residual waveform shows weak but clear activities in both the early and late parts of 1M (shown by arrowheads in Fig. 4Ab). When the best dipole was calculated at a latency point slightly earlier than the peak of 1M, the dipole (dipole B) was located slightly more posterior, medial and superior than dipole A. The residual waveform obtained by the subtraction of magnetic fields due to dipole B from the original record (Fig. 4Ac) shows that this dipole could explain the early part of the 1M component well, while leaving substantial activities during the late part of 1M unexplained. On the other hand, when the best dipole was obtained at a latency point slightly later than the peak of 1M, this dipole failed to explain the early part of 1M (Fig. 4Ad). This dipole (dipole C) was estimated to be located slightly more anterior and inferior than dipole A. Therefore, the dipole location became more anterior, lateral and inferior with an increase of the latency. These results suggested that no single dipole could successfully explain the overall 1M activities as expected. Therefore, at first, we tested how a two-dipole model improved the fit during the latency

Figure 2. Evoked magnetic fields and topographies. Data from two subjects. Upper trace, superimposed waveform recorded from 37 channels. Lower trace, isocontour maps at several latency points.
period of 1M. To obtain the best model, we started the analysis with a tentative source (source 1) estimated at the latency point where the highest GOF value was obtained (3 ms earlier than the 1M peak on average). Then, a second source (source 2) was calculated at the latency point where the residual activities were largest in the presence of source 1. After the location and orientation of the two dipoles were slightly adjusted to provide the best fit during this period, we obtained the best two-dipole model. Figure 4A shows the residual magnetic fields that could not be explained by the two-dipole model (Fig. 4B). As compared with each single dipole model (dipole A, B and C), this two-dipole model significantly improved the fit. For example, as compared with the dipole A model, the two-dipole model increased the GOF value from 96.7 to 99.4% ($F$ ratio = 4.63, $P < 0.0001$) at 25 ms, and from 97.5 to 99.1% ($F$ ratio = 2.45, $P = 0.01$) at 32 ms. Figure 4B shows the time course of the two source activities. Their time courses are very similar with a 5 ms time delay for the second source. The activity of source 1 peaked at 27.4 ms and that of source 2 at 33.1 ms, supporting the view that at least two source activities overlap at the peak latency of 1M (29.3 ms). In this case, the activity of the second source is relatively weak at the peak latency of the first source (27.4 ms), which well explains why the largest GOF value was obtained by a single-dipole model at 27.4 ms (Fig. 3C) not at the peak latency of 1M. Since source 1 was located in the postero-medial part of Heschl’s gyrus (HG) and source 2 in the antero-lateral part of the HG region (Fig. 6), we refer to these sources by the anatomical name, HG-M and HG-L, respectively in the text.

Sources that Are Active Later than 1M

The location and orientation of the dipoles were fixed, and we continued the analysis to include the best third source in the model. Figure 5A shows residual magnetic fields obtained by subtraction of theoretical waveforms due to dipole A (b), dipole B (c) and dipole C (d) from the original data. Dipoles A, B and C were obtained by a single dipole analysis at the peak of 1M, and 3 ms earlier and 3 ms later than the 1M peak respectively (shown by vertical bars). The waveform in Ab shows the residual magnetic fields that could not be explained by dipole A. There are weak but clear magnetic fields in both early and late parts of 1M shown by arrowheads, indicating that dipole A could not explain overall 1M activities. Likewise, both dipole B and dipole C left some magnetic fields unexplained (Ac and Ad). (Ba) Residual magnetic fields after subtraction of the theoretical magnetic fields due to the best two-dipole model (source 1 and source 2). (Bb) Time course of source strength of source 1 and source 2. (Ca) Schematic presentation of locations of each dipole. (Ca) Dipole A, B and C. (Cb) Source 1 and 2.
a subtraction of the magnetic fields due to the two-dipole model from the original data. There are clear residual magnetic fields around 40 ms. To explain the residual magnetic fields, the best source was estimated to be located posterior to the postcentral gyrus in the posterior parietal cortex (PPC). With the addition of this source, the GOF value at 39.8 ms increased markedly from 86.6 to 98.4% (F ratio = 8.46, P < 0.0001). Finally, the fifth source to explain the residual magnetic fields (Fig. 5Ad) was estimated to be located around the anterior part of the STG (STG-A). The GOF value at 62.9 ms increased from 90.9 to 98.7% (F ratio = 3.78, P = 0.0064) with the addition of this source. After the fitting of these five sources, the mean GOF value for all the data (0–120 ms) was 98.7% and no additional source significantly improved the fit. Figure 5B shows time courses of each source strength and they were used for the analysis of the latency of each activity. Figure 5C shows the location and orientation of each source. Figure 6 shows the location of each source superimposed on MR images.

Location of Each Source

Similar procedures were applied to data obtained for the remaining nine subjects. By applying our criteria, two distinct sources responsible for the 1M component were identified in nine of the ten subjects. The mean x,y,z coordinates relative to point A of each source are shown in Table 1. The mean location of the HG-M source was 2.9 mm anterior, 6.4 mm lateral and 3.7 mm inferior to point A, which fell in the postero-medial part of the HG. In the present study, five subjects had one HG (single HG) and four subjects showed two HGs of a common stem type (duplicated HG, Leonard et al., 1998). Among the five subjects who had a single HG, the source location of the HG-M was coextensive with the HG in four and was on the first Heschl sulcus (HS1) in one. The HG-M source was located in the first HG (H1) in all four subjects who had a duplicated HG. The second source, HG-L, was located more anterior (3.9 mm), lateral (8.9 mm) and inferior (5.2 mm) than the HG-M source. Among the five subjects with a single HG, the HG-L source was located in the HG in one, on the HS1 in two and posterior to the HS1 in two. Among the four subjects with a duplicated HG, the HG-L source was in the second HG (H2) in three and posterior to the second Heschl sulcus (HS2) in one. Figure 7 shows the location of the HG-M and HG-L sources of a representative case with a duplicated HG.

The third source, PPC, was identified in seven subjects, and was located on or slightly posterior to the postcentral sulcus. The next two sources were located in the lateral aspect of the STG, but were clearly separated by their anterior–posterior and superior–inferior coordinates. That is, one (STG-P, six subjects) was located in the postero-superior part of the STG, the other (STG-A, six subjects) in the antero-inferior part of the STG. As shown in Figure 8, the STG-P source was located around the superior crown of the STG or, in some subjects, around the inferior crown of the supramarginal gyrus. The STG-A source tended to be located in the upper bank of the superior temporal sulcus (STS). The latest source activity was identified in seven subjects, which originated from an area slightly posterior to point A (2.7 mm on average), corresponding to the planum temporale (PT). Figure 9B shows schematic drawings of the mean location and orientation of each source. Figure 9C shows the locations of each source relative to points A and B of all subjects.
Time Course of Each Cortical Activity

Figure 9A shows the time course of each source strength of all subjects (blue lines) and their group-average (black lines). In general, the activity in the HG-M, HG-L and PPC reversed its polarity twice with an interval of ~10 ms, which resulted in a triphasic waveform. On the other hand, the STG-A and PT sources showed long-lasting (usually >50 ms) activities. STG-P source activities were identified in six subjects. Three subjects showed the triphasic waveform (Fig. 10), although the early two components did not significantly increase the fit according to our criteria in two subjects. The onset and peak latencies of each source activity are shown in Table 1. The onset latency of the HG-M source was the shortest (17.1 ms) followed by that of the HG-L (21.2 ms), PPC (25.3 ms), STG-A (30.9 ms), STG-P (39.8 ms) and PT (47.6 ms). Similarly, the peak latency became longer in this order (28.0, 33.5, 38.2, 48.3, 55.3 and 76.2 ms). If we accept the early component of the STG-P activity in three subjects (Fig. 10), its mean onset latency was 26.2 ms, which was 4.0 ms longer than that for the HG-L activity, and its peak latency was 34.9 ms, which was longer by 2.9 ms than that for the HG-L source in these subjects. The peak latency of 1M (32.6 ms) was between the peak latencies of the first
component of the HG-M (28.0 ms) and HG-L (33.5 ms) activities. The peak latency of 2M (53.0 ms) was between the peak latencies of the third component of the HG-M (49.6 ms) and HG-L (55.1 ms) activities.

**Discussion**

The present MEG study revealed the precise timing of arrival of signals to multiple auditory cortical areas and the time course of each cortical activity. The shift of the response latency along the medio-lateral axis of the supratemporal plane is consistent with the hierarchical auditory processing in monkeys through the core, belt and parabelt regions on the supratemporal plane (for review, see Kaas et al., 1999). There are several possible pathways other than cortico-cortical connections for activating each cortical source such as thalamo-cortical, cortico-thalamo-cortical and interhemispheric connections. Therefore, the latency shift among cortical sources might be due to the different conduction time of the pathway between the thalamus and each cortical area or due to different kinds of pathways (for discussions, see Brugge et al., 2003). However in animals, it has been shown that the latency from the thalamus to a cortical cell is remarkably constant across multiple cortical areas, irrespective of the variability of traveling distance (Salami et al., 2003). In addition, the present results that early cortical responses exhibited a similar triphasic time course suggest that they reflect a similar intra-laminar processing, probably ‘feedforward’ pattern processing, which supports that the early cortical responses were driven mainly by successive cortico-cortical feedforward projections.

Successive activities found in this study are summarized as follows:

- 28 ms (peak latency of the first component, source HG-M): activity originating from the postero-medial part of the HG.
- 33 ms (HG-L): activity in a region antero-lateral to the HG-M source, just posterior to the first transverse sulcus of Heschl (H1) or intermediate sulcus.
- 38 ms (PPC): activity in the posterior parietal cortex.
- 35–50 ms (STG-P): activity in the posterior part of the STG around its superior crown.
- 48 ms (STG-A): activity in the anterior part of the STG, around the upper bank of the STS.
- 76 ms (PT): activity in a region posterior and slightly superior to the HG-M source, in the planum temporale.

### Table 1

<table>
<thead>
<tr>
<th>Source</th>
<th>Latency (ms)</th>
<th>Location (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG-M</td>
<td>17.1</td>
<td>28.0/38.7/49.6</td>
</tr>
<tr>
<td>HG-L</td>
<td>21.2</td>
<td>32.5/44.2/55.1</td>
</tr>
<tr>
<td>PPC</td>
<td>25.3</td>
<td>38.2/50.6/63.3</td>
</tr>
<tr>
<td>STG-P</td>
<td>26.2</td>
<td>34.9/42.4/59.8</td>
</tr>
<tr>
<td>STG-A</td>
<td>30.9</td>
<td>48.3</td>
</tr>
<tr>
<td>PT</td>
<td>47.6</td>
<td>76.2</td>
</tr>
</tbody>
</table>

Coordinates relative to point A (posteriormost point of Heschl’s gyrus). x, antero-posterior; y, medio-lateral; z, superior-inferior. Latencies for the STG-P source activity were the mean value among three subjects with the first component. In the remaining three subjects, the triphasic structure was not clear and the mean onset latency of the activity was 36.3 ms.

**Figure 7.** Locations of the two sources in and around Heschl’s gyrus (HG) in a subject with a duplicated HG. The HG is divided into the first (H1) and second (H2) HG by an intermediate sulcus (SI). The HG-M source is located in H1, while the HG-L source is located more laterally in H2.

**Activation In and Around the HG**

We found two separate early activations in and near the HG, HG-M and HG-L. The HG-M source was located in the dorso-postero-medial part of the HG, which approximately corresponds to the location of the primary auditory cortex (PAC) identified by several techniques. First, this location appears to correspond to cytoarchitectonically defined koniocortical areas, KAm (Galaburda and Sanides, 1980), AI (Rivier and Clarke, 1997) and Te1.0 (Morosan et al., 2001) in humans, and KA (Galaburda and Pandya, 1983) and AI (Morel et al., 1993) in monkeys. In addition, the scatter plots of the location of the HG-M source in Figure 9C are approximately coextensive to a high probability area of the probabilistic map of the PAC drawn by Rademacher et al. (2001). The present results that the HG-M source was located within the H1 in most of the cases are also consistent with findings in cytoarchitectonic studies that the core region was usually identified in the most anterior HG (Rademacher et al., 1993; Hackett et al., 2001). Second, this region receives dense thalamic inputs in primates, as expected for primary cortical fields (for reference, see Kaas and Hackett, 1998). Third, this location is consistent with the location of the electrophysiologically defined primary area of the auditory cortex. In intracerebral recording studies in humans, early auditory evoked potentials were recorded in the posterior part of the HG (Celesia, 1976; Liégeois-Cauvel et al., 1991, 1994). In a unitary recording study in monkeys (Kosaki et al., 1997), neurons in the core (AI) were sharply tuned, while neurons in the surrounding fields (L) showed a broader frequency tuning. In addition, clear tonotopic organizations have been found in this region in both humans (Romani et al., 1982; Pantev et al., 1989, 1995) and monkeys (Merzenich and
Brugge, 1973; Pfingst and O'Connor, 1981; Morel et al., 1993). Based on these observations, the earliest MEG activity of cortical origin in this study is considered to arise from the PAC. However, there remains a possibility that the present study missed the earliest activity originating from the PAC. Previous intracranial recordings (Celesia, 1976; Liegeois-Chauvel et al., 1991) identified cortical activities originating from the deep H1 area with a latency earlier than that of the first activity in the present study. The present MEG study might not have detected this early activity due to its deep origin. Previous studies showed that it is difficult for MEG to detect PAC activities earlier than 1 ms (Yoshiura et al., 1995; Yvert et al., 2001).

The second source, HG-L, was located more anterior (4 mm) and lateral (9 mm) than the HG-M source. This location is on the HS1 or just posterior to it, and probably corresponds to a parakoniocortical area, PaAI (Galaburda and Sanides, 1980) or LA (Rivier and Clarke, 1997), rather than koniocortical areas. The view that the HG-L source is located outside the PAC is further supported by a histochemical study of the human auditory cortex using acetylcholinesterase (AChE) staining (Hutsler and Gazzaniga, 1996), in which the transition between AChE-cell-sparse (PAC) and AChE-cell-dense (planum temporale) regions is at the HG, and therefore does not coincide with the transverse sulcus. In an MEG study with deconvolution of 40 Hz steady-state magnetic fields, Gutschalk et al. (1999) concluded that two adjacent sources are responsible for the middle latency components, one in the medial part of the HG and the other in a region 1 cm lateral to the former, which is very similar to the locations of our HG-M and HG-L sources. In addition, the time course of each activity is also similar to ours. Their components P30 (28.8 ms) and N41 (40.6 ms) from the first source and P36 (35.2 ms) and N46 (46.2 ms) from the second source seem to correspond to our two successive peaks of the HG-M (28.0 and 39.7 ms) and HG-L (33.5 and 44.2 ms) sources respectively. Therefore, the present results confirmed that these two sources are not specific for the steady state but also are activated following a transient stimulation. The delay of both the onset (4.1 ms) and peak (5.5 ms) latencies of the HG-L activity relative to those of the HG-M activity suggests serial activations through these areas. In support of this view, Liegeois-Chauvel et al. (1991) recorded activities in the lateral part of the HG in response to electrical stimulation of the medial

Figure 8. Locations of the STG-P and STG-A sources superimposed on six subjects' coronal MR images.
part of the HG with a latency of 6–8 ms. In unitary recording studies in monkeys, the response latency of neurons in the lateral belt region was longer than that of neurons in the core region (Benson and Hienz, 1978; Vaadia et al., 1982). Serial activations through these areas are also consistent with anatomical findings in monkeys that the belt regions are strongly connected with adjacent core regions (Merzenich and Brugge, 1973; Galaburda and Pandya, 1983; Morel et al., 1993; Jones et al., 1995).

Activity in the PPC

The third source was located in the posterior parietal cortex. In functional MRI (fMRI) and positron emission tomography (PET) studies, activation in this region is related to auditory localization tasks (Griffiths et al., 1998; Bushara et al., 1999; Alain et al., 2001; Zatorre et al., 2002). The involvement of this region in the localization of sounds has been also demonstrated by a transcranial magnetic stimulation study (Lewald et al., 2002). Therefore, the PPC activity in this study may reflect an early stage of localization processing of sounds. To localize a sensory source and execute spatially accurate behaviors, transformation of the spatial coordinates from head-centered to body-centered or world-centered coordinates is required. The role of the posterior parietal cortex in such a transformation is well established (Andersen, 1995).

The onset latency of this source (25 ms) was clearly longer than that of the HG-M (17 ms) or HG-L (21 ms) source, but shorter than those of the STG and PT sources. Therefore, the PPC source appears to depend on the HG-M or HG-L source for activation. In monkeys, the PPC (area 7) receives projections from a subdivision of the belt region, CL (Romanski et al., 1999b). This may suggest that the PPC source is driven by the HG-L source, forming a stream from the HG-M, HG-L and then PPC, which may be involved in 'where' processing in the auditory system.

Activity in the STG

We found two lateral activities in the STG, one in the anterior and another in the posterior part. As for the STG-P source, its location was similar to that reported in an intracerebral AEP study (Howard et al., 2000). The reason why these source activities could be identified in only six subjects in spite of their more superficial location than the earlier sources in the HG could be explained by their radial orientation. Since these dipoles were located around the crown of the STG, they should create mainly radially oriented components, which are difficult to detect by MEG. Previous scalp EEG studies (Scherg and Von Cramon, 1986; Cacace et al., 1990) have suggested a radial component peaking at ~40 ms originating from the STG. Another reason for the difficulty in detecting STG activities in
the current study might be their sensitivity to the stimulation rate. Howard et al. (2000) examined the effects of the interstimulus interval on AEP activities originating from both the HG and posterior STG (termed the PLST). The recovery rate of the HG and STG activities at an interstimulus interval of 0.25 s relative to that at 2 s was ~60% and ~25% respectively. The response latency of the STG-P activity was consistent with values reported in previous AEP (Scherg and Von Cramon, 1986: 39 ms; Cacace et al., 1990: 41 ms), AEF (Yvert et al., 2001, 40–60 ms) and intracranial recording (Celesia, 1976: 40 ms; Howard et al., 2000: 45 ms) studies in humans, and an intracerebral AEP study in monkeys (Areszio et al., 1975: 27 ms). In the present study, clear early activity from this area could be identified in three subjects in whom the onset latency of the STG-P activity (26.2 ms) was longer than that of the HG-M and HG-L by 8.9 and 4.0 ms respectively. An electrophysiological study in humans (Howard et al., 2000) provided evidence for the existence of cortico-cortical projections from the HG to the posterior part of the STG by showing that electrical stimulation of the HG elicits responses in the STG with an onset latency of 3 ms and a peak latency of 10–20 ms, which approximately corresponds to the time delay between the HG-M and STG-P activities in this study. Therefore, it seems possible that the STG-P was directly driven by the HG-M or HG-L. Findings in a recent study using electrical stimulation and intracranial recording methods in humans (Brugge et al., 2003) favored a possibility that the STG-P source is directly driven by the HG-M activity. They showed that electrical stimulation of the medial HG elicited responses consisting of several components in the posterior STG region while stimulation of the lateral HG was ineffective in evoking some of the components. Although the present results could not determine the actual sequence of activations, successive activations through the HG-M, HG-L, and STG-P with a 4–5 ms time delay implied a serial processing through them. The sequential activation through the HG and STG-P is also consistent with a histochemical study in humans using cytochrome oxidase staining. Rivier and Clarke (1997) demonstrated that the primary auditory area had a cytochrome oxidase profile compatible with a primary sensory area, while STA, which probably corresponds to our STG-P, had a very different profile compatible with a high-order association area. The view that the STG-P is located at a higher level in the auditory processing stream than the HG is supported by recent PET and fMRI studies, in which this region was usually more strongly activated by complex acoustic (Thivard et al., 2000; Hall et al., 2002), word (Petersen et al., 1988; Price et al., 1992) and speech (Zatorre et al., 1992; Scott et al., 2000) stimuli than simple sounds.

Another source in the lateral aspect of the STG was located around the superior bank of the STS. The mean onset latency of this activity (30.9 ms) was clearly longer than that for the HG-M (17.1 ms) or HG-L (21.2 ms) source. Therefore, the STS source appears to depend for its activity on earlier activations in adjacent auditory regions. However, the latency difference of 10 ms between HG-L and STS sources left a possibility that the STS source was driven by a feedback or lateral projection. Activation in this area in neuroimaging studies was related to frequency-modulated tone (Hall et al., 2002), speech (Binder et al., 2000), intelligible speech (Scott et al., 2000) and voice (Belin et al., 2000) stimuli, suggesting a role for this region in higher-level acoustic processing. In monkeys, regions lateral to the core contain neurons that are sensitive to complex sounds or species-specific vocalizations (Rauschecker et al., 1995). Therefore, the STS activity in the present study may represent a beginning of the processing of sound patterns.

In monkeys, belt regions surrounding the core area receive inputs from the core area, and the belt fields in turn project to the surrounding parabelt fields and auditory-related fields on the STG, caudal STG and rostral STG (Kaas and Hackett, 1999). The anterior region of the belt projects to the anterior parabelt and STG, while the posterior region of the belt projects to the posterior parabelt and STGc (Seltzer and Pandya, 1978; Hackett et al., 1998). Then the subdivisions of the lateral belt and parabelt/STG fields project to distinct regions of the prefrontal cortex (Hackett et al., 1999; Romanski et al., 1999a, b). Anterior auditory fields tend to project to non-spatial domains and posterior fields tend to project to spatial domains, forming separate auditory streams corresponding to ‘what’ and ‘where’ pathways. Therefore, the two separable source activities in the STG region in this study may be the third stage of temporal lobe processing of each stream, i.e. from the core or HG-M to the belt or HG-L, the parabelt or STG and finally the prefrontal cortex.

**Activation in the Planum Temporale**

The last source was located in an area posterior to the HG in the planum temporale and exhibited a long-duration activity peaking at ~80 ms. Since both the orientation and timing of this source activity were similar to those of a well-known auditory evoked component around 100 ms, N1, we considered that the activity from the PT source in this study contributes to the formation of N1. The reduced strength of the activity in the present study compared to other studies is due to our short interstimulus interval, since it is reported that a short interstimulus interval reduces the N1 amplitude (Schwent et al., 1976; Hari et al., 1982). The view that the PT is one of the source regions responsible for N1 is consistent with the result of intracranial recording (Liegeois-Chuvel et al., 1994; Godey et al., 2001), AEP (Pantev et al., 1995) and AEF (Pelizzone et al., 1987; Pantev et al., 1995; Lütkenhöner and Steinsträter, 1998) studies. The slightly shorter latency of the PT source activity
than that of N1 (90–110 ms) in other reports may suggest that this source is responsible for the early part of N1.

**Comparison between Somatosensory and Auditory Processing**

In a previous MEG study, we showed the precise activation timing of several somatosensory cortical areas following tactile stimuli (Inui et al., 2004). Since we found some common features between somatosensory and auditory processing, we want to discuss this matter here briefly.

**Serial Activation in a Stream in One Direction**

As one might expect, signals in a cortical area are basically conveyed to an adjacent area at least in the early stages of processing and serial activations through several areas make a stream in one direction. Following tactile stimulation, areas 3b, 1 (and 2) and 5 are serially activated, forming a stream running posteriorly in the postcentral gyrus. In the present study, click stimuli activated the HG-M, HG-L and STG sources sequentially, forming a stream(s) running laterally in the supratemporal plane. Such processing is quite natural in terms of speed.

**Timing of Serial Activation**

In somatosensory processing, the time delay between two sequential activations is ~4 ms, 3.6 ms between areas 3b and 1, ~4.4 ms between areas 1 and 5, and ~3.7 ms between area 1 and SII. In the present study, the time delay was 4.1 ms between HG-M and HG-L, 4.1 ms between HG-L and PPC, and 4.0 ms between HG-L and STG-P (three subjects). Although the physiological meaning of the 4 ms time delay is not clear, these results suggest that somatosensory and auditory information is processed in steps with similar timing.

**Biphasic (Triphasic) Nature of Early Response**

Early activities following tactile stimulation in area 3b, area 1, the PPC and the SII region exhibit reversals of polarity after 10 ms once or in some cases twice, resulting in a biphasic or triphasic time course. Similarly, the time course of activities of the HG-M, HG-L, PPC and STG-P sources showed a triphasic waveform. Such a structure was also found in the earliest cortical activity in SI following noxious stimuli (Inui et al., 2003). This phenomenon might correspond to the surface positive-negative sequence of potentials, the so-called primary evoked response, recorded from the brain surface of experimental animals (for review, see Schlag, 1973). Although the precise mechanisms responsible for the polarity reversals are unclear in humans, these findings suggest that there is a similar intra-laminar processing among these somatosensory and auditory cortical areas. For dipoles with opposite orientations to be produced in the same cortical field, different combinations of a current sink and source in different layers must exist. In monkeys, such an intra-laminar processing pattern has been studied using a current source density (CSD) analysis. According to a series of studies by Schroeder’s group (Schroeder et al., 1995, 1998, 2001; Schroeder and Foxe, 2002), CSD analysis can clearly differentiate feedforward from feedback and lateral input patterns. The laminar profiles of feedforward responses triggered by ascending synaptic inputs show a characteristic activation sequence composed of an initial depolarization of input terminals in and near lamina 4 and a later excitation of supra- and infragranular pyramidal cells, which is consistent with the biphasic structure of the early responses in the present study. In addition, their data indicated that such laminar profiles of feedforward responses are common between auditory and somatosensory processing. Based on our MEG and previous CSD results, it seems natural to consider that the similar time course of the response sequence of the early cortical activities in the present (auditory) and previous (somatosensory) studies mainly reflect the cortico-cortical feedforward pattern response.

In the present study, the second component of the triphasic structure often did not exceed the baseline, especially the HG-L source. This is probably due to the similar time course of the HG-M and HG-L activities with a 4–5 ms time delay for the latter and due to the similar orientation of these source activities. Around the peak of the second component of the HG-M activity oriented postero-inferiorly (Fig. 5B), the HG-L activity is still directed antero-superiorly. Because of the proximal positions and opposite orientations of the two sources, activities from the two sources around this latency might cancel each other out to some extent. This phenomenon may explain why auditory evoked magnetic fields do not shape a clear component at a latency corresponding to the second peak of these source activities (~40 ms) like the well-known second component at 30 ms following tactile stimulation to the hand area and a second component at 50 ms following visual stimulation (K. Inui et al., unpublished data).

Interestingly, the late activity from the SII region and late activity from the PT do not have such clear polarity reversals and are long-lasting. Therefore, these activities should differ in function from early activities with the triphasic structure. We postulate that a basic role of early cortical areas is to receive inputs from the thalamus or convergent inputs from the thalamus and/or adjacent multiple cortical areas and to send their signals to the next point, while the later long-lasting activities are related to recognition of the stimuli. Early activities some 10 ms in duration or successive activations with a 4 ms time delay seem not appropriate for activities relating to recognition. Both the late SII activity (Hari et al., 1990) and the N1 activity (Hillyard et al., 1973) are substantially influenced by the subject’s attentional state.

**Notes**

Address correspondence to Koji Inui, Department of Integrative Physiology, National Institute for Physiological Sciences, Okazaki 444-8585, Japan. Email: inui@nips.ac.jp.

**References**


Rademacher J, Caviness VS Jr, Steinmetz H, Galaburda AM (1993) Topographical variation of the human primary cortices: implications...