# Chapter 3
# Invasive Research Methods

**Matthew A. Howard III, Kirill V. Nourski, and John F. Brugge**

## Abbreviations

| | |
|---|---|
| AEP | averaged evoked potential |
| CT | computed tomography |
| ECoG | electrocorticography |
| EEG | electroencephalography |
| ERBP | event-related band power |
| fMRI | functional magnetic resonance imaging |
| HDE | hybrid depth electrode |
| HG | Heschl's gyrus |
| IFG | inferior frontal gyrus |
| LFP | local field potential |
| MEG | magnetoencephalography |
| MRI | magnetic resonance imaging |
| PET | positron emission tomography |
| STG | superior temporal gyrus |
| vPFC | ventral prefrontal cortex |

M.A. Howard III
Department of Neurosurgery, University of Iowa, 200 Hawkins Drive, 1823 JPP, Iowa City, IA 52242, USA
e-mail: matthew-howard@uiowa.edu

K.V. Nourski (✉)
Department of Neurosurgery, University of Iowa, 200 Hawkins Drive, 1815 JCP, Iowa City, IA 52242, USA
e-mail: kirill-nourski@uiowa.edu

J.F. Brugge
Department of Neurosurgery, University of Iowa, 200 Hawkins Dr. 1624 JCP, Iowa City, IA 52242, USA
e-mail: john-brugge@uiowa.edu

D. Poeppel et al. (eds.), *The Human Auditory Cortex*, Springer Handbook of Auditory Research 43, DOI 10.1007/978-1-4614-2314-0_3,

## 3.1 Introduction

Auditory cortex, in the classic sense of the term, is taken to be the cluster of anatomically and physiologically distinct areas of temporal neocortex that are uniquely and reciprocally connected with one another and with the medial geniculate body and related thalamic nuclear groups. In humans, as many as seven or eight anatomically distinct auditory cortical fields have been identified on the supratemporal plane and posterolateral superior temporal gyrus (STG) (see Clarke and Morosan, Chapter 2). Lying outside of the classical auditory cortical fields of humans are areas of the middle and inferior temporal gyri and of the anterior polar region of the STG, all of which are considered involved in speech and language processing (see Giraud and Poeppel, Chapter 9). Reciprocal connections between temporal auditory cortical fields and auditory-related areas of frontal and parietal lobes are pathways underlying higher-level auditory and auditory–visual processing including speech perception, goal-directed motor action, and feedback critical for the modulation of voicing (Romanski, 2004; Cohen et al., 2009).

Most research on auditory cortex has been, and continues to be, performed in experimental animals, including nonhuman primates, using invasive physiological and anatomical methods. These invasive techniques are best suited, and in many instances uniquely suited, to address fundamental questions about the functional organization of auditory and auditory-related cortex. The results of systematic physiological and anatomical studies using these approaches in monkeys have given rise to a working model of hierarchical and serial-parallel processing of acoustic information within the auditory forebrain (Kaas & Hackett, 2005). Because certain features of the auditory forebrain are shared between humans and nonhuman primates, this model has become an attractive starting point for studying its functional organization in human (Hackett, 2003, 2007, 2008; Rauschecker & Scott, 2009). Applying this model to humans, however, should be exercised with some constraint as there are more than 200 living species of primates, including humans, each having evolved distinct auditory–vocal specializations within its respective ecological niche (Preuss, 1995). Indeed, there may not even be an appropriate single "primate model" of auditory cortical organization to apply to humans, especially where speech, language, and other higher-level cognitive processes are concerned. Understanding the mechanisms that underlie these processes requires research performed on human subjects.

In recent years a wide range of experimental methods has become available to advance the understanding of the structure and function of human auditory cortex. Among the noninvasive approaches are electroencephalography (EEG) and magnetoencephalography (MEG), which record cortical activity at a distance using electrodes glued to the scalp or from sensors distributed around the head (see Alain & Winkler, Chapter 4, and Nagarajan, Chapter 5), and brain-imaging methods based on changes in cerebral blood flow, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (see Talavage and Johnsrude, Chapter 6). Invasive approaches involve electrophysiological recording from and electrically stimulating or locally cooling cortex directly, usually in neurosurgical patients undergoing diagnosis and treatment of medically intractable epilepsy.

This research is performed either in the operating room (acute experiments) or in a specially equipped neurosurgical ward that allows for long-term clinical electrocorticography (ECoG) and video monitoring of patients with chronically implanted electrodes (chronic experiments). Each of these noninvasive and invasive approaches has its limitations, but when used in complementary ways can yield new information not obtainable by any single approach used alone.

ECoG refers to recording of electrical activity directly from the brain surface or from deep brain structures. When an acoustic stimulus is presented, a local field potential (LFP) may arise in an auditory or auditory-related area reflecting activity evoked by that stimulus in an ensemble of neurons in the vicinity of the recording electrode. A variant of this approach allows for recording from single neurons or neuronal clusters (Engel et al., 2005). Focal electrical stimulation, often performed in the same subject and applied to the same electrodes through which the ECoG is obtained, aims to map cortical sites critical for hearing, speech, and language by creating a reversible "functional lesion" and thereby temporarily disrupting cortical processing around the site of stimulation (Boatman, 2004; Sinai et al., 2005). Focal cooling also creates a functional lesion but by reversibly blocking synaptic transmission in a small cortical area beneath a cooling probe (Bakken et al., 2003). Focal electrical stimulation and electrophysiological recording may be used together to trace functional connections within and between cortical fields (Liegeois-Chauvel et al., 1991; Brugge et al., 2003, 2005; Greenlee et al., 2004, 2007; Matsumoto et al., 2004, 2007). Invasive brain research is opportunistic in nature in that it takes advantage of patients' willingness to participate during surgical procedures usually performed for accurate localization of a seizure focus.

This chapter presents a brief historic overview of intracranial studies of auditory cortex in humans followed by a description of intracranial methods currently employed in recording from, stimulating, and deactivating auditory cortex of human subjects. These experimental approaches are designed to address questions of the locations, boundaries, and interconnections of the multiple auditory fields that make up human cortex, and how each of these fields contributes to processing of auditory information.

## 3.2 Brief Historic Overview

Progress in invasive human brain research has paralleled advances in the field of functional neurosurgery, electronic engineering, computer technology, and signal processing. Although technical aspects of invasive human brain research have changed markedly over the years, the importance of a multidisciplinary research team, pioneered by neurosurgeon Wilder Penfield, has remained. Today, research of this kind draws heavily on the disciplines of anatomy, physiology, psychophysics, neuropsychology, radiology, theoretical modeling, statistics, acoustics, signal processing, electronic engineering, and computer programming.

In 1934, Penfield founded the Montreal Neurologic Institute, where neurosurgical care and human brain research were first seamlessly integrated and where many landmark scientific studies were performed (Penfield & Rasmussen, 1950; Penfield

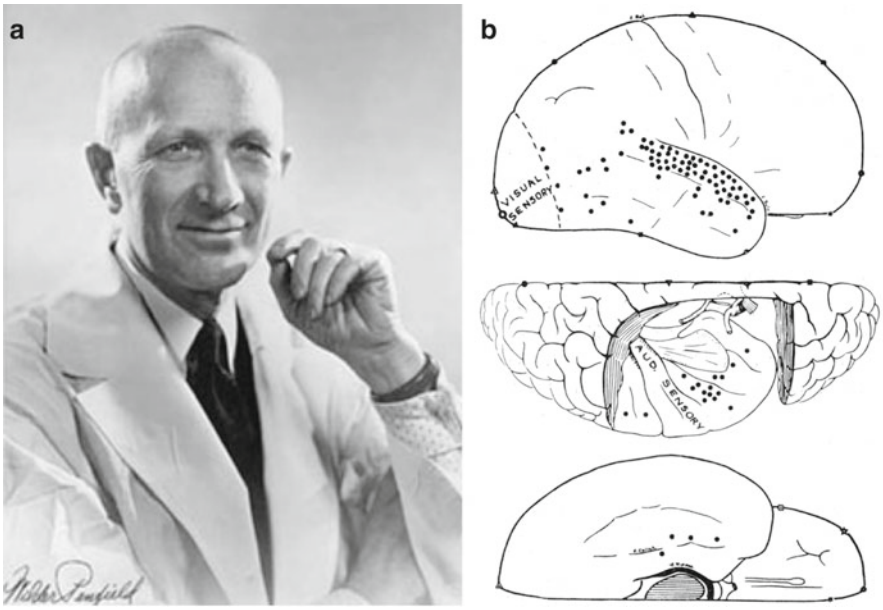


**Fig. 3.1** (**a**) Wilder Penfield, pioneer neurosurgeon and founder of the Montreal Neurological Institute. (**b**) Sites on human temporal lobe from which electrical stimulation elicited experiential responses. Top: Lateral surface. Middle: Supratemporal plane; HG labeled AUD. SENSORY. Bottom: Inferior surface. (Adapted from Penfield & Perot, 1963.)

& Perot, 1963). With the awake patient's brain exposed, Penfield and his team carefully recorded bodily movements and verbal reports of sensations evoked by an electrical stimulus delivered to a cortical site through a hand-held stimulator. The anatomical location of each stimulated cortical locus was documented on a high-resolution intraoperative photograph of the brain surface. The results provided the first direct, systematic evidence of how human cerebral cortex is functionally organized. Auditory sensations aroused by cortical electrical stimulation were confined to sites on the lateral STG, or on the exposed supratemporal plane (Fig. 3.1). Crude auditory sensations (e.g., buzzing) were evoked by stimuli applied to sites deep within the Sylvian fissure, in what would now likely be considered the auditory core or belt fields. Complex auditory experiential hallucinations, on the other hand, were typically evoked by stimuli applied along the exposed lateral surface of the STG, though it is now thought that many of these latter sensations were the result of activating distant brain sites, including the limbic system (Gloor et al., 1982; cf. Moriarity et al., 2001).

Shortly after electronic recording instrumentation became available it was established that the brain itself was the source of the EEG and, further, that an acoustic stimulus could arouse an electrical event visible in the raw EEG trace (Davis, 1939). Another breakthrough came some 20 years later with the development of the laboratory computer and its use in extracting small acoustically evoked neural activity from background noise by signal averaging (Geisler et al., 1958). This opened the door for systematic study of the averaged auditory evoked potential

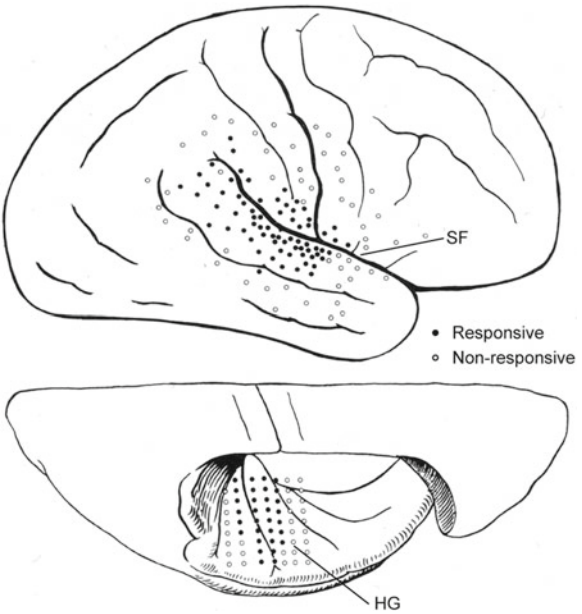


**Fig. 3.2** Composite diagram showing cortical regions on the lateral brain surface (upper panel) and supratemporal plane (lower panel) explored with recording electrodes in acute experiments on 19 epilepsy surgery patients. Filled circles, sites excited by acoustic stimulation; open circles, no response to acoustic stimulation. HG, anterior transverse (Heschl's) gyrus; SF, Sylvian fissure. (Modified from Celesia, 1976.)

(AEP), and it was not long before this technology was introduced into the operating room where recordings were made through electrodes placed on different regions of the STG and supratemporal plane while sounds were presented to the patient during wakefulness and sleep and under general anesthesia (Fig. 3.2) (Celesia & Puletti, 1969; Celesia, 1976).

Much of what is now known about the functional organization of auditory cortex is derived from data obtained from single-unit studies performed in experimental animals using rigid metal or glass microelectrodes. Adapting this method for use in human subjects is particularly challenging because the potential for tissue damage represents an unacceptable human research risk under most circumstances. This risk is eliminated, however, by confining recording sites to regions of the temporal lobe that will be subsequently resected for clinical reasons. Experiments using this approach have generated important and unique data on the functional properties of auditory neurons within the cortex of the anterior STG and middle temporal gyrus (Creutzfeldt & Ojemann, 1989; Creutzfeldt et al., 1989a, b).

Technical advances in electrode fabrication have led to the development of hybrid depth electrodes (HDEs), which allow recording in human cortex of both LFPs from neuronal assemblies and action potentials from single neurons or neuronal clusters at multiple sites in auditory cortex deep within the supratemporal plane in awake patients over sustained periods of time (Howard et al., 1996b; Fried et al., 1999). HDEs are modified clinical depth electrodes and hence pose no additional surgical risk to the patient. With advances in electrode design and fabrication have come advances in computerized data acquisition, storage, and management systems capable of handling data obtained simultaneously from hundreds of recording sites. This in turn has been accompanied by innovative signal processing strategies.

## 3.3 Contemporary Research

### *3.3.1 Research Subjects*

Invasive studies of auditory cortex in humans are carried out in neurosurgical patients, the vast majority of whom are being treated for medically intractable epilepsy. Epilepsy is a common neurological disorder that affects approximately 50 million people worldwide (World Health Organization, 2005). These individuals are at risk of losing consciousness suddenly and without warning and thus often are unable to operate a motor vehicle or hold a job that requires sustained vigilance and attention. There is also evidence that persistent seizure activity may lead to structural brain damage (Bonilha et al., 2006; Bernhardt et al., 2009). It is estimated that in the United States alone, more than 400,000 individuals with epilepsy continue to have seizures despite receiving appropriate medical treatment (Engel, 2001). A subset of this medically refractory patient population can be treated effectively with surgery that removes brain tissue that is the source of the seizure activity.

Candidates for resection surgery must fulfill three criteria. First, they must have failed to respond to medical management. Second, their quality of life would be markedly enhanced by achieving a seizure-free surgical outcome. The ideal surgical candidate is a young person whose educational and vocational opportunities promise to be enhanced substantially by eliminating seizures. These patients also are ideal subjects for invasive brain research. Third, their seizure focus must be localized to a circumscribed portion of the brain that can be safely removed surgically. Making this latter determination is the most challenging aspect of the presurgical evaluation process, which includes EEG recording, anatomical magnetic resonance imaging (MRI), and formal neuropsychological testing. The patient's history and test data are discussed at a multidisciplinary epilepsy surgery conference where a consensus is sought regarding whether the patient is a candidate for surgery, and, if so, the type of operation that should be performed. Surgical patients then wishing to participate in research are given a detailed explanation of the planned research protocols and provide informed consent before becoming a "research subject" and undergoing additional "research only" preoperative testing.

Once a patient has agreed to participate as a subject in research, structural (and in some instances functional) MRI scans are obtained. These images provide the subject's preoperative anatomical template. The locations of experimental recording sites are subsequently superimposed on the preoperative image set. Subjects involved in auditory research may also undergo a preoperative hearing evaluation to objectively measure possible hearing deficits. Acoustic stimuli used during experiments are typically generated digitally and may be delivered in the open field or through earphones. The acoustical properties of a stimulus are difficult to control in the open field, especially in a clinical environment that may have many reflecting surfaces and high levels of ambient background sound. Over-the-ear headphones are impractical to use because the head bandage does not allow for a good acoustical seal. Insert earphones, on the other hand, may be integrated into custom fitted ear molds of the

kind commonly worn by hearing aid users. Ear molds created for each subject conform to the anatomy of a subject's external ears, thereby providing an acoustic seal that assures accurate sound delivery while attenuating unwanted ambient noise; their snug fit also resists dislodgement by head movement. Importantly for chronic experiments, these earphones can be removed repeatedly and reliably reinserted.

### *3.3.2 Acute Experiments*

In a typical epilepsy center, approximately half of the patients who are deemed to be candidates for resection surgery will undergo the procedure without additional preoperative diagnostic testing. In these cases experiments are performed in the operating room, when the subject is awake and alert and able to communicate with the research team and follow instructions. To gather additional information about the location of the seizure focus, two 30-minute ECoG recordings are obtained directly from the brain using multicontact grid and strip electrodes placed over the lateral surface of the exposed lateral and inferior surfaces of the temporal lobe. Experimentation is permitted during these intraoperative ECoG recording sessions. In acute experiments, recording and stimulating devices of various configurations are permitted for research purposes (Fig. 3.3). These include densely spaced multicontact recording and stimulating arrays, penetrating microelectrodes, stimulating probes, and local cooling devices (Fig. 3.4). With a typically wide exposure of the brain, it is safe to place and reposition these devices directly on the brain surface without injuring underlying tissue. The primary limitations of intraoperative experimentation relate to the time available for conducting experiments and the types of research tasks that subjects are capable of performing. The 30-minute time windows of opportunity are sufficiently long to perform experiments successfully if they are performed efficiently. If technical problems arise (e.g., electric power line noise), there is little time available to solve them. This places a premium on careful preoperative research planning and equipment testing. Subjects are typically in a supine position with a cushion under one shoulder. Surgical drapes are arranged to form a sterile barrier while at the same time allowing the patient to have a clear view of the anesthesiologist. Because most of the patient's body is covered in surgical drapes, and only minimal movement is allowed, the manual operations the patient can perform are usually limited to such simple tasks as verbalizing or button pushing. Finally, there is a high level of ambient noise in the operating room, which makes this a challenging environment for auditory experimentation, insert earphones notwithstanding.

### *3.3.3 Chronic Experiments*

In some cases the results of the preoperative evaluation strongly suggest that although the patient is a candidate for resection surgery, there is some residual uncertainty about the location of the seizure focus. For these cases additional diagnostic

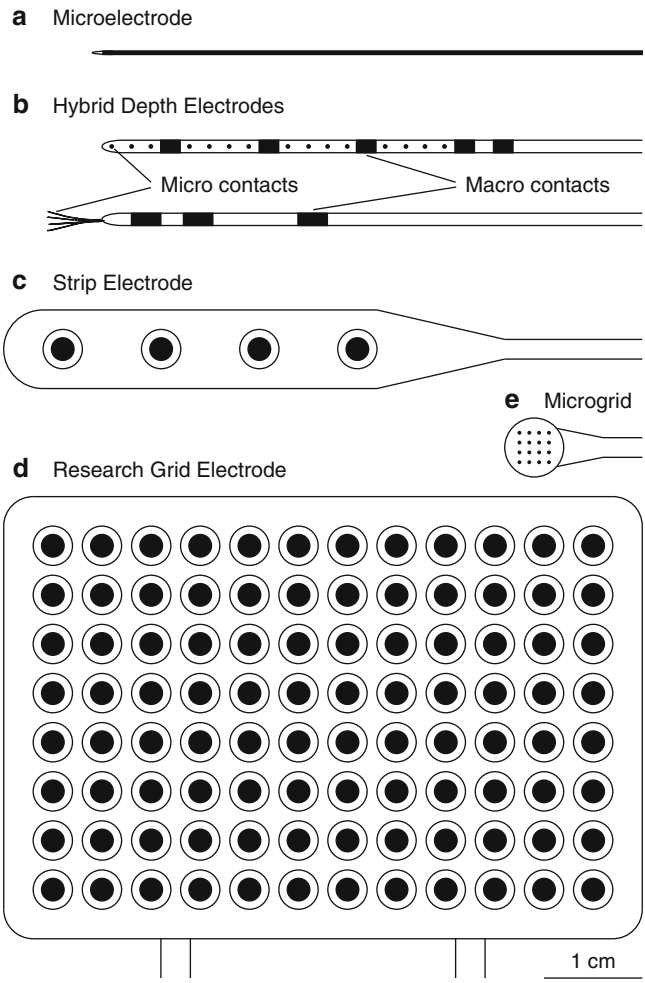


**Fig. 3.3** Schematic diagram of types of electrodes used in invasive studies of human auditory cortex. (**a**) Microelectrode. Metal (usually tungsten) microelectrode, insulated except for the tip, capable of recording single neurons or neuronal clusters (multiunit activity) and used in acute studies of human auditory cortex. (**b**) Hybrid depth electrodes. Modified clinical electrodes having large (macro) contacts capable of recording field potentials, and small (micro) contacts capable of recording both field potentials and action potentials. Two types of HDEs are shown. Top: Micro contacts are cut ends of microwires conforming to the shaft of the electrode. Bottom: Micro contacts are micro wires that are extruded from the end of the electrode after implantation. (**c**) Strip electrode. Clinical electrode with macro contacts used both in acute and chronic studies. (**d**) Research grid electrode. Clinical grid electrode modified such that macro contacts in the array are separated by 4–5 mm (rather than 10 mm) and used primarily in chronic studies. (**e**) Microgrid. Surface grid electrodes with microwire contacts having 1 mm separation

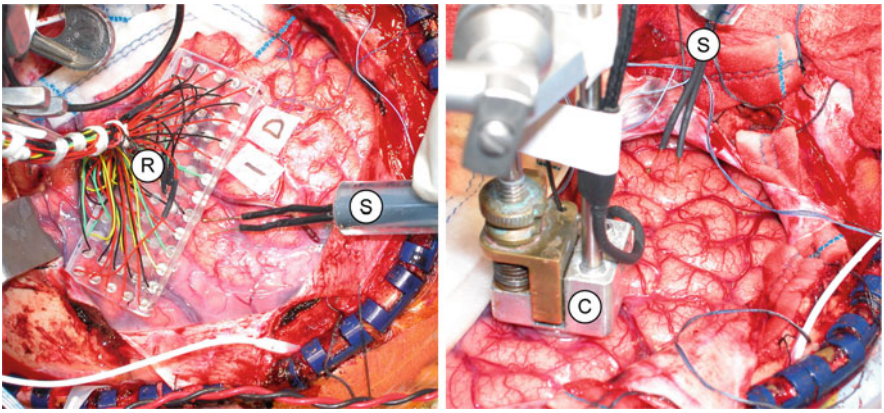


**Fig. 3.4** Acute experiments. Photographs taken in the operating room showing a recording grid (R), hand-held bipolar electrical stimulator (S), and cooling probe (C) in direct contact with brain surface

testing is needed, which may include ECoG recording from electrode arrays chronically implanted directly on the pial surface or within cortical tissue, or both. Experiments are subsequently carried out in a specially equipped hospital suite while the patient is recovering from implant surgery and undergoing longer-term clinical video and ECoG monitoring. The proportion of patients undergoing invasive ECoG monitoring before resection surgery varies from one clinical research center to another, and the devices and techniques used to perform this monitoring vary as well. The electrodes, electronic instrumentation, and experimental protocols associated with chronic recording may also differ substantially from those of acute experimentation. When used in complementary ways, however, acute and chronic recording together provide important information about auditory cortical organization not gained by relying on one approach alone.

All chronic invasive research on auditory cortex of humans is performed using standard, or custom modified, clinical ECoG electrodes (see Fig. 3.3). These devices fall into two broad categories: depth electrodes and surface arrays. Patients undergo implantation of recording electrodes directly in and on the brain in the vicinity of the suspected seizure focus (Fig. 3.5). Implantation is performed under general anesthesia, and usually no experiments are conducted during this stage.

#### 3.3.3.1 Depth Electrodes

Depth electrodes are designed for clinical ECoG recordings from brain sites deep beneath the cortical surface. They are thin, flexible, silicon-based cylinders, typically 1–2 mm in cross-sectional diameter with low impedance, circumferential platinum contacts positioned along the electrode shaft. For experimental purposes a clinical depth electrode may be modified to create a "hybrid," with additional contacts added for higher spatial resolution and capable of recording both LFPs and single

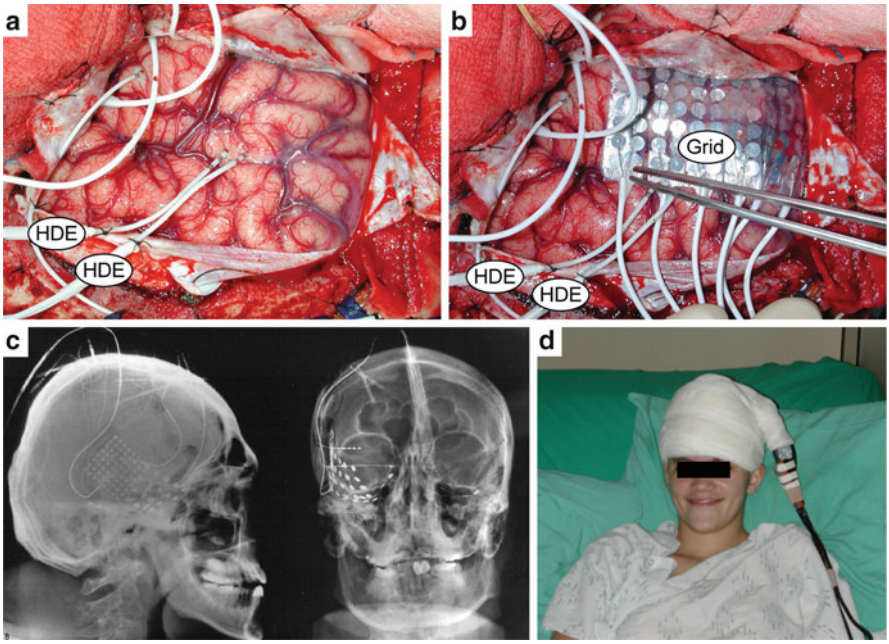


**Fig. 3.5** Chronic invasive ECoG monitoring. Top: Photographs taken during electrode implantation showing the sites of entry of two HDEs (**a**) and the placement of a research grid array (**b**). (**c**) Lateral and frontal postimplantation head X-ray images showing a 64-channel grid array over perisylvian cortex, a frontal grid, and two HDEs, one in HG and the other in the amygdala. (**d**) Postimplantation photograph of a research subject

neurons or neuronal clusters (see Fig. 3.3b). One type of HDE has insulated platinum–iridium microwires (25–50 μm diameter) inserted into the lumen of the clinical electrode with cut ends brought to the surface of the shaft at regular (~2 mm) intervals between the clinical ECoG contacts (Howard et al., 1996b). This linear array of 14–16 microcontacts is particularly well suited to mapping response properties of auditory fields on Heschl's gyrus (HG), as described later in this chapter. A different type of HDE also employs insulated microwires that, once the electrode is in place, can be extruded beyond the distal tip of the shaft (Fried et al., 1999). This approach may be more suitable for isolating single neurons or neuronal clusters because recordings can be made some distance from the electrode shaft, but it has the disadvantage that the locations of recording sites are difficult to specify and later to identify. The requirement for microwires, however small in diameter, is one of the limiting factors in using HDEs as currently designed, as only a relatively small number can be fitted into the electrode shaft. In addition to carrying microwires, the HDE may also be equipped with a microdialysis probe within its lumen capable of sampling in situ neuroactive substances in the extracellular milieu (Fried et al., 1999).

A slotted cannula, temporarily inserted stereotactically into the brain parenchyma using standard or minimally modified neurosurgical techniques, serves as a

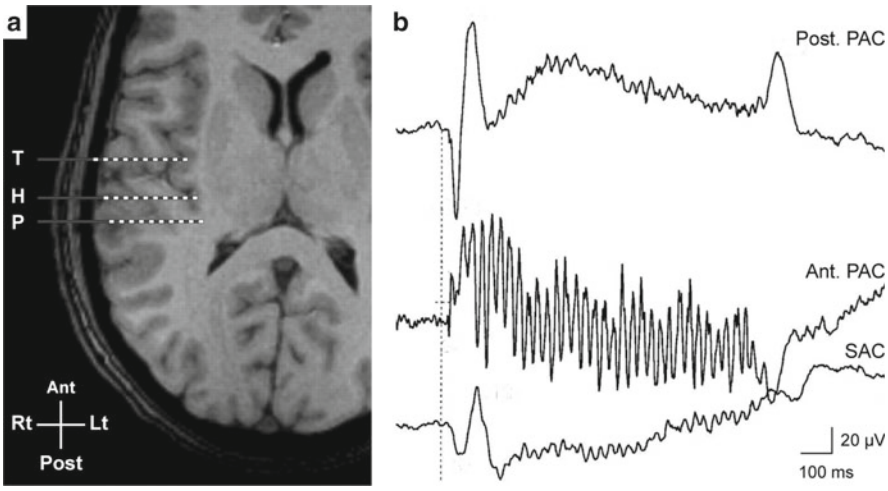


**Fig. 3.6** Multiple depth electrodes implanted in the supratemporal plane. (**a**) Horizontal MR image through supratemporal plane of a human epilepsy surgery patient showing the trajectory (dashed lines) of three chronically implanted electrodes. (**b**) AEPs recorded from posterior (Post. PAC) and anterior (Ant. PAC) core cortex on Heschl's gyrus and from secondary auditory cortex (SAC). (Modified from Liégeois-Chauvel et al., 2004.)

guide to the implantation of the flexible HDE. Two broad categories of stereotactic systems are available for use: rigid frame and frameless systems. Because of the highly complex contour of the supratemporal plane in humans, including the orientation of the transverse gyri, along with the considerable intersubject variability in the overall structure of the STG, the choice of the frame system used impacts the way in which auditory cortex on the supratemporal plane is approached anatomically and, hence, how the research is carried out.

Rigid frame devices are firmly attached to the patient's skull with multiple fixation points before surgery. The frame serves as a fixed three-dimensional spatial reference system for target selection and as a platform to which an electrode insertion device is attached. In contemporary practice, the patient typically undergoes a brain imaging study (usually MRI or computerized tomography [CT]) with the frame in place. Cerebral angiography, which provides images of cerebral blood vessels, may also be performed. Using imaging data, the three-dimensional coordinates for each brain target are calculated within the frame-based spatial reference system. This method may be used to implant electrodes in auditory cortex by neurosurgeons trained in the Talairach school of stereotactic surgery. The Talairach coordinate system is one devised to describe, in three-dimensional space, the location of brain structures across individuals independent of their brain shape or size. With this approach, a patient's brain images are used to select targets and choose electrode trajectories. Multiple depth electrodes may be inserted through burr holes in the skull along straight, lateral-to-medial trajectories that are parallel to one another and perpendicular to the sagittal plane (Fig. 3.6). Liégeois-Chauvel and colleagues (Liégeois-Chauvel et al., 1991, 1994, 1999, 2004) have taken full advantage of this arrangement to

record auditory evoked activity over a wide area of the supratemporal plane. Although this approach allows functional study of several areas of auditory cortex including those on the planum temporale, it is not the optimal approach to the auditory core and belt area(s) located on HG. In this approach, HG is oriented obliquely with respect to the trajectory of the electrodes. Each depth electrode, therefore, crosses cortical laminae obliquely as it traverses a restricted segment of the gyrus, and as a consequence the sampling of auditory cortex on HG is necessarily limited.

Frameless stereotactic methods were developed to allow surgeons access to brain sites with stereotactic precision without being encumbered by the mechanical constraints associated with rigid head frames. A variety of frameless systems have been developed over the years, but the systems used most often in contemporary neurosurgical practice are based on infrared spatial-localization technology. Before surgery, fiducial markers are placed at multiple locations around the patient's scalp. An anatomical MRI is obtained, which includes the fiducial markers, and from this image a three-dimensional brain space is created. In the operating room, the patient's head is secured in a stationary position while the three-dimensional image is used to guide the depth electrode to its intended target(s). Because there are no mechanical constraints associated with the frameless system, there are no physical restrictions on the selection of electrode trajectories. At the University of Iowa, for example, the flexibility of the frameless system has been exploited to develop an electrode implantation technique that results in placement of the entire shaft of a depth electrode within HG (Reddy et al., 2010). The electrode is introduced into the cortex at the anterolateral boundary of HG, and then gently inserted along the crest of the gyrus in a direction oblique to the cortical surface. Because the electrode is somewhat flexible, even with the insertion stylette in place, it usually stays within the gray matter of the gyrus without penetrating the pial surface and entering the overlying Sylvian fissure. When properly performed, this method results in the placement of a linear array of 18 or more recording contacts along the full length of HG (Fig. 3.7). This approach has made it possible to obtain a spatial pattern of recordings that reveal the transition from presumed core auditory cortex, to more anterolaterally positioned belt, or parabelt fields, all located within HG (Brugge et al., 2008, 2009; Nourski et al., 2009). The entry point of this electrode is anterior enough on the STG to allow a grid array to be implanted on auditory cortex posterior to it, thereby providing an opportunity to record simultaneously from auditory cortical fields of HG and posterolateral STG.

Whereas stable LFPs are routinely obtained from chronically implanted penetrating microelectrodes, recording from single neurons or neuronal clusters is a greater challenge. The problem of obtaining high-quality recording arises in large part from the reactive response of cortical tissue to the chronic implant. After implantation, a glial barrier forms around the electrode shaft, which over time effectively reduces the signal-to-noise ratio of the recordings (Pierce et al., 2009). Various approaches are being used in an attempt to rejuvenate microelectrode sites, aimed at increasing biocompatibility, reducing electrode impedance, and improving electrode interface properties (Johnson et al., 2004; Lempka et al., 2006).

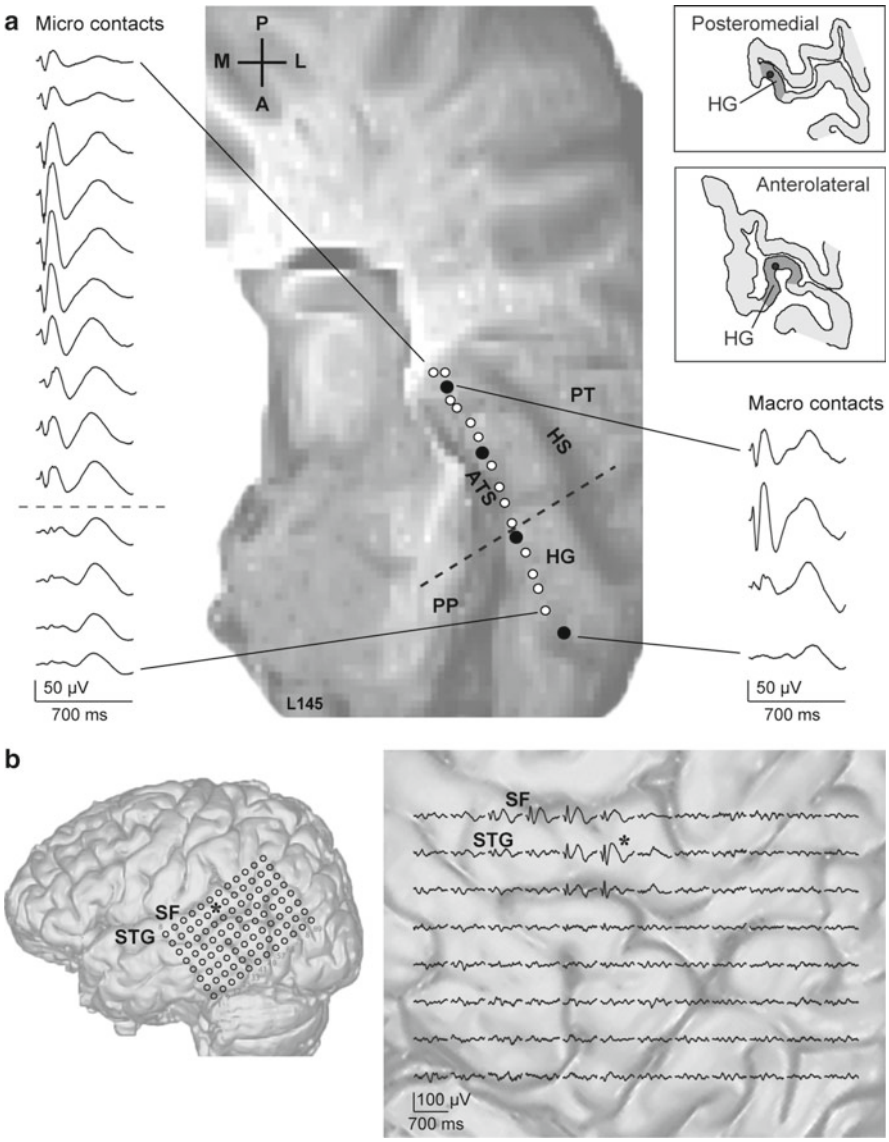


**Fig. 3.7** Responses to click-train stimulation, recorded simultaneously from a HDE and a research grid electrode. (**a**) MR image of supratemporal plane showing the locations of micro and macro contacts on an HDE chronically implanted in Heschl's gyrus and click-evoked AEPs recorded at these locations. Insets: Line drawings of MRI cross sections showing the position of the electrode within posteromedial (core) and anterolateral (belt) cortex. Approximate boundary between core and belt indicated by dashed line. (**b**) Location of a 96-contact research grid on an MRI of the lateral brain surface (left), with AEPs superimposed (right). (Modified from Brugge et al., 2008.)

#### 3.3.3.2 Surface Grid Electrodes

Research grid arrays, which are commonly rectangular in shape and consist of flat low impedance platinum–iridium discs within a flexible silastic membrane (see Fig. 3.3d), are placed on the pial surface of the brain under direct visual control. Strip electrodes, which are fabricated from the same materials but usually consist of only a single row of contacts, typically have a narrow configuration (see Fig. 3.3c). This makes them well suited for insertion into subdural spaces beyond the boundaries of the craniotomy. It is common practice, for example, to insert strip electrodes into the subdural space at the inferior boundary of a temporal craniotomy and gently slide the array under the temporal lobe to obtain coverage of the ventral surface of the temporal lobe, an area that cannot be visualized directly during surgery. Standard clinical grid and strip electrode are manufactured with 1 cm spacing between contacts. This spacing is adequate for purposes of obtaining clinical ECoG recordings, and many investigators have used these same electrode arrays to perform electrical stimulation (Boatman, 2004) and electrophysiological recording (Crone et al., 2001) experiments. When higher spatial resolution is called for in research studies, modified surface arrays with as little as 4 or 5 mm spacing between contacts are employed (Howard et al., 2000; Brugge et al., 2008; Flinker et al., 2011). Surface grid electrodes with an even finer grain (1 mm separation) designed for studies of human brain computer interface have been introduced to studies of the cortical representation of speech (Kellis et al., 2010; see Fig. 3.3e). With modern cable and connector technology it is feasible to implant a patient with more than 200 depth and surface recording contacts without increasing the surgical risks. As with any wire conductors, however, electrical noise is easily coupled to them, and reducing this kind of interference is a particular challenge in a clinical environment. Further, wires may break, especially when a subject experiences an epileptic seizure. Wireless systems for cochlear stimulation have long been used to help restore hearing in deaf individuals, and such wireless multichannel systems are under development for electrical brain stimulation through chronically implanted microarrays (Ghovanloo et al., 2004).

#### 3.3.3.3 Anatomical Reconstruction

Studies of functional organization of auditory cortex, whether in humans or nonhuman experimental animals, require accurate anatomical reconstruction of each recording and stimulation site. In human studies each experimental subject commonly undergoes whole-brain MRI scanning before and after implant surgery. Pre- and postimplantation MRIs are then co-registered and coordinates for each electrode contact obtained from postimplantation MRI volumes are transferred to preimplantation MRIs. This approach may include reliance on stereotaxic coordinates as well as CT and angiographic imaging. The position of depth electrodes and location of each recording site is then reported in Talairach coordinates. A related approach utilizes lateral and anterior–posterior X-ray imaging along with skull landmarks for co-registration

with the standardized Talairach coordinate system (Miller et al., 2007). There are several confounding factors faced in anatomical reconstruction of recording sites. The first is that the presence of metallic electrodes in the brain creates substantial artifact in the postimplant MR image. To circumvent this, a companion CT image may be used along with MRI. Second, the head of the subject is not in exactly the same position for pre- and postoperative MR imaging. Yet another factor, which applies mainly to the HDE reconstruction, is that implantation surgery with the introduction of grid arrays and HDEs displaces the cerebral hemisphere medially, with superficial brain tissue being distorted more than deeper structures. Accurate assignment of recording loci on preimplantation MR images may require adjustments based on careful comparison of surrounding brain structures between the pre- and postimplantation MRI volumes. Nonlinear compression causes the depiction of electrode trajectory and the spacing of contacts, when transferred to the preoperative images, to appear irregular, as seen for example in Figure 3.7, where the location of each contact is projected on to the surface of HG.

While the trajectory of a depth electrode may be depicted by transferring the recording loci to a rendering of the cortical surface (see Fig. 3.7), it is equally important to know for each contact where in the depth of the cortex recordings were made. This is accomplished by obtaining serial MR cross-sectional images containing each of the depth recording contacts. The optimal orientation of the MR volumes should show the cortical grey matter in cross section, which for HG would be oblique with respect to the standard coronal plane of the brain. With the HDE inserted along the long axis of HG, for example (Howard et al., 1996b), these cross sectional images are obtained roughly orthogonal to the trajectory of the electrode. Either MR images or outline drawings derived from them along with reconstruction of the electrode trajectory depict the position of each recording contact in detail (see Figs. 3.6 and 3.7).

#### 3.3.3.4 Stimulation and Recording

After electrode implantation and surgical recovery, patients are transferred to a monitoring facility. Here the epileptologist uses information from video and ECoG recordings to formulate a hypothesis as to the site(s) of origin of the patient's seizures. Meanwhile the patient is awake and alert during many of the daytime hours while clinical monitoring is progressing, and, though tethered by a cable bundle to the EEG monitoring equipment, is usually capable of participating in a wide range of research protocols.

Initially the patient is maintained on antiepileptic medications, but is then slowly weaned from these drugs during the monitoring period. In most instances, patients are able to participate fully in research protocols 2–3 days after the implantation surgery is performed. A typical experimental session is scheduled to last approximately 2 hours, including the time needed to arrange specialized equipment for specific protocols. With the exception of a head dressing and a thick bundle of cables exiting the bandage (see Fig. 3.5d), there are no mechanical or environmental constraints on a

patient's ability to participate in experimental protocols. Thus, along with verbal responses and button presses, patients usually have no difficulty operating a computer mouse or other mechanoelectric devices. Patients are able to move from the hospital bed to a chair and back without assistance, and usually have no difficulty sitting upright for a 2-hour research session without becoming fatigued. Many are capable of participating in two, and some in as many as three, experimental sessions per day.

There are several advantages of chronic over acute cortical recording and stimulation. First, the time constraints associated with acute experimentation are not associated with chronic work, hence substantially more physiological data can be gathered, and experiments can be replicated in the same subject over days. The latter consideration becomes important as the stationarity of neuronal response properties could be affected by a number of factors changing over time, including slight postoperative movement of the recording array, recovery from trauma associated with electrode placement, or insertion and withdrawal of antiepileptic medication. Second, by using both electrode grid arrays for surface recording and HDEs for depth recording in the same subject it is possible to obtain data simultaneously from auditory cortical areas within HG and from other auditory fields represented on the supratemporal plane and lateral surface of the brain. By doing so, functional differences observed across recording sites can be attributed to differences in auditory field representations rather than to differences between experimental subjects or experimental conditions, or both. Third, patients are able to perform relevant tasks during recording and stimulation sessions, which allows for studies of relationships between brain activity and the level of task performance (Jenison et al., 2011).

Finally, at the end of the clinical monitoring period and when research recording and stimulation are coming to a close, an opportunity often exists to perform one last, and very limited, experiment to test the effects of general anesthesia on a particular aspect of auditory cortical physiology. This session is carried out in the operating room just before removal of the electrodes and surgical resection. Recording begins just before induction of anesthesia and is continued through loss of consciousness.

Although the chronic experimental setting has enormous advantages, there are also some important limitations to this approach as well, which have to be taken into account in designing experiments and interpreting results. Perhaps the most important relates to the fact that electrode arrays can be placed only in cortical areas dictated by clinical criteria. With considerable intersubject variation in the structure of the STG and the locations and boundaries of auditory cortical fields in it (Rademacher et al., 1993; Leonard et al., 1998), even in cases where extensive arrays are implanted, there are many auditory areas simply not sampled. This is particularly true for cortex within sulci even though penetrating electrodes may be placed into the cortex of the supratemporal plane. One approach that promises to address this limitation is to combine, in the same subject and under the same stimulus conditions, chronic intracortical recording with fMRI, taking advantage of the former for obtaining highly localized physiological measures and the latter for obtaining a global view of cortical activity (Mukamel et al., 2005). Success with this approach will require a better understanding of the relationship between the fMRI signal and neural activity recorded with implanted electrodes (see Cariani and Micheyl, Chapter 13).

## 3.4 Experimental Paradigms

The use of invasive methods to study the auditory and auditory-related cortical areas in humans with modern technology has provided opportunities to ask questions related both to the fundamental organization of these parts of the brain and to cortical mechanisms of speech and language processing that may be beyond the realm of study in nonhuman animals.

The organizational framework that forms the foundation for the understanding of auditory cortex is constructed around the concept of multiple interconnected fields, differentiated from each other anatomically and physiologically and each contributing to processing acoustic information in its own way. Extensive studies in experimental animals have shown the existence of multiple auditory fields in temporal cortex. As many as a dozen or more have been demonstrated anatomically in monkeys (Hackett, 2003, 2007, 2008). These fields have been shown to differ in their anatomical locations, neuronal response properties and connectivity patterns. While it has been shown in postmortem tissue that humans may exhibit 7 or 8 such fields on the STG (see Clarke and Morosan, Chapter 2), it has not been possible to use many of the anatomical and physiological approaches that have made experimental work in animals so fruitful. The successes in functionally identifying auditory fields in humans by means of invasive approaches have come through the use of three methodologies: electrophysiological recording, electrical stimulation tract tracing, and creation of functional lesions through focal electrical stimulation.

### *3.4.1 Functional Mapping by Electrophysiological Recording*

Based mainly on mapping studies in human subjects with chronically implanted electrodes, a small area on posteromedial HG has been demonstrated to exhibit response properties that are consistent with it being the primary and primary-like (core) auditory cortex (Liégeois-Chauvel et al., 1991; Howard et al., 1996a; 2000; Brugge et al., 2008, 2009). It differs in fundamental ways from the area around it on the supratemporal plane and the lateral surface of the STG (see Figs. 3.6 and 3.7). The responses recorded from posteromedial HG differ from those recorded from the posterolateral STG in the overall morphology of the polyphasic AEPs and in specific physiological response properties (Howard et al., 2000). Compared to the posteromedial HG, cortex on the posterolateral STG is characterized by a slower recovery from previous stimulation, a lower phase-locking capacity, and a greater sensitivity to general anesthesia (Howard et al., 2000; Brugge et al., 2008).

To date, little is known of the functional properties of the auditory core and even less about multiple fields that surround it. Advances in this research area will require the use of complex auditory stimuli, and subjects will need to be engaged in tasks related to attention and higher cognitive processes including those related to speech and language. Because human communication engages the other sensory systems as well, vision and touch need to be introduced into stimulus paradigms. These issues and related computational challenges are addressed extensively in later chapters.

#### 3.4.1.1 Signal Processing

As described in the historical overview, the development of computers capable of averaging evoked field potential activity was one of the technical breakthroughs that allowed systematic and quantitative study of evoked field potentials recorded from human auditory cortex. At the time there was no other practical means of detecting the low-amplitude evoked voltage deflections that were obscured by ongoing background activity. Computerized averaging methods became an indispensible element in the armamentarium of researchers investigating the physiological properties of auditory cortex of humans and nonhuman mammals. As long as the evoked response is precisely time locked to the onset of an auditory stimulus, and if a sufficient number of stimulus presentations are given, the random background activity is reduced (and the signal-to-noise ratio is enhanced) through the averaging process. As with any method, simple signal averaging in the time domain has limitations. Perhaps the most significant of these is that the relatively low-frequency AEP does not capture non–phase-locked field potential activity, particularly oscillatory responses at relatively high frequencies (>70 Hz) (termed "high gamma" range).

The biological importance of non–phase-locked cortical activity was first established in experimental animal studies (Freeman, 1978; Gray et al., 1989; Engel et al., 1991). More recent experiments performed in nonhuman primates have provided additional information regarding the cellular mechanisms mediating these high-frequency responses within auditory cortex (e.g., Steinschneider et al., 2008). Crone and his colleagues at Johns Hopkins University have studied successfully this so-called "induced" activity in human auditory cortex by combining ECoG recording with signal processing methods that measured the spectral content of the stimulus-related brain activity (Crone et al., 2001, 2006). There is now convincing evidence from several laboratories indicating that non–phase-locked high-frequency activity recorded from human auditory cortex contains information about the acoustic stimulus not found in the AEP (Ray et al., 2008; Brugge et al., 2009; Edwards et al., 2009; Nourski et al., 2009).

Spectral analytic methods (e.g., fast Fourier transform, wavelet transform) can now be efficiently performed on field potential data using standard computers. Using these techniques, it is feasible to objectively measure stimulus-induced power changes—the so-called event-related band power (ERBP)—throughout the spectral range of the evoked response. Although the *absolute* ECoG power in the high-frequency range is very low compared to that in the low-frequency range, ERBP, which represents *proportional* changes in power after sensory stimulus presentation compared to a prestimulus baseline, can be much greater in the high-frequency range than in the low-frequency range.

The application of time–frequency ERBP analysis in studies of human auditory cortex is illustrated in Figure 3.8. Here, responses of core auditory cortex to a variety of acoustic stimuli are displayed as AEP waveforms and time–frequency ERBP plots. Trains of acoustic transients evoke frequency-following responses, evident at relatively low repetition rates, as well as increases in high-frequency ERBP (Fig. 3.8a; Brugge et al., 2009). Regular-interval noise, generated by introducing temporal

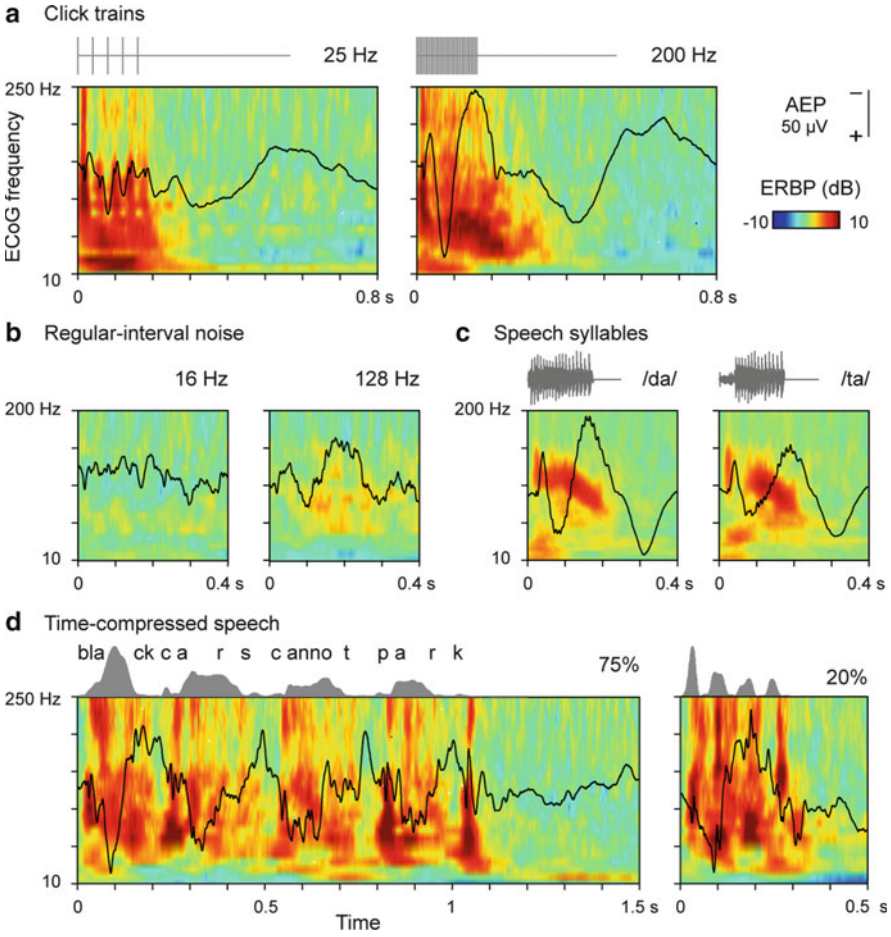


**Fig. 3.8** ERBP analysis of intracranial recordings recorded from human core auditory cortex in response to different acoustic stimuli. (**a**) Click trains presented at 25 (left) and 200 (right) Hz (replotted from Brugge et al., 2009). (**b**) Transition from random to regular-interval noise, generated using delays corresponding to 16 (left) and 128 Hz (right) periodicity (replotted from Griffiths et al., 2010). (**c**) Speech syllables /da/ (left) and /ta/ (right). (**d**) Speech sentence "black cars cannot park," time-compressed to 75% (left) and 20% (right) of its original duration (replotted from Nourski et al., 2009). AEP waveforms are superimposed on the ERBP time–frequency plots. Stimulus schematics are shown in gray

regularity to a broadband noise stimulus, elicits an increase in ERBP when this temporal regularity is associated with a pitch percept, but not when the repetition rate is below pitch frequency range (Fig. 3.8b; Griffiths et al., 2010). When presented with speech utterances, patterns of ERBP within core auditory cortex represent voice onset time, that is, the time interval between consonant release and the onset of voicing (Fig. 5.8c; see also Steinschneider et al., 2005). Temporal envelope of a

speech sentence can be tracked by cortical high gamma activity when the stimulus is moderately compressed in time (accelerated), as well as at greater degrees of compression that make the sentence unintelligible (Fig. 3.8d; Nourski et al., 2009). Spectral-based signal processing such as shown in these examples has evolved to become a standard analytical approach in modern invasive human auditory cortex research.

#### 3.4.1.2 Coding of Stimulus Acoustic Features

Traditionally, studies of auditory cortex in humans and nonhumans have involved presenting a stimulus and recording the electrophysiological response of single neurons or ensembles of neurons. Implicit in this approach is that buried in the responses recorded is the information being transmitted to and through the cortex—the code for that particular stimulus or stimulus attribute. A number of coding mechanisms (e.g., rate, time, place) are generally agreed upon. Evidence for their presence is provided by analysis of physiological data and its relationship to behavior.

The frequency content of a sound is a strong identifier of the sound source, and becomes particularly important in human speech communication. Many auditory cortical neurons are responsive to a restricted range of stimulus frequencies, referred to as their frequency response areas. Such neurons are typically most sensitive to a narrow range of frequency, the center of which is referred to as the "best" or "characteristic" frequency. Frequency tuning has been considered one mechanism by which frequency is discriminated, and auditory cortex has been considered a place where requisite neurons are located. Single neurons in HG of human subjects recorded with implanted HDEs have been found that are extraordinarily narrowly tuned ("ultra sharp"), and their frequency selectivity may account for a listeners threshold of frequency discrimination as measured psychophysically (Bitterman et al., 2008). Tuning curves similar to those recorded in auditory cortex of laboratory animals have also been recorded in human HG, and their distribution has confirmed the presence of at least one tonotopic field in the human auditory core (Howard et al., 1996a).

The amplitude and frequency of natural sounds, including speech, vary over time, and the auditory system has evolved mechanisms for detecting amplitude and frequency modulations. For slowly varying amplitude-modulated stimuli, below about 50 Hz, auditory cortical neurons in monkey phase-lock strongly to the modulation envelope, and hence encode the modulation frequency "explicitly" in the temporal cadence of their discharge (Steinschneider et al., 1998; Lu et al., 2001). Modulation envelopes in running speech in this frequency range are associated with individual words, syllables, and phonemes (Rosen, 1992). Local field potentials recorded in the human auditory core by means of HDEs implanted in HG show locking to repeated transients over a frequency range similar to that of monkeys (Liégeois-Chauvel et al. 2004; Brugge et al. 2009; see Figs. 3.7 and 3.8).

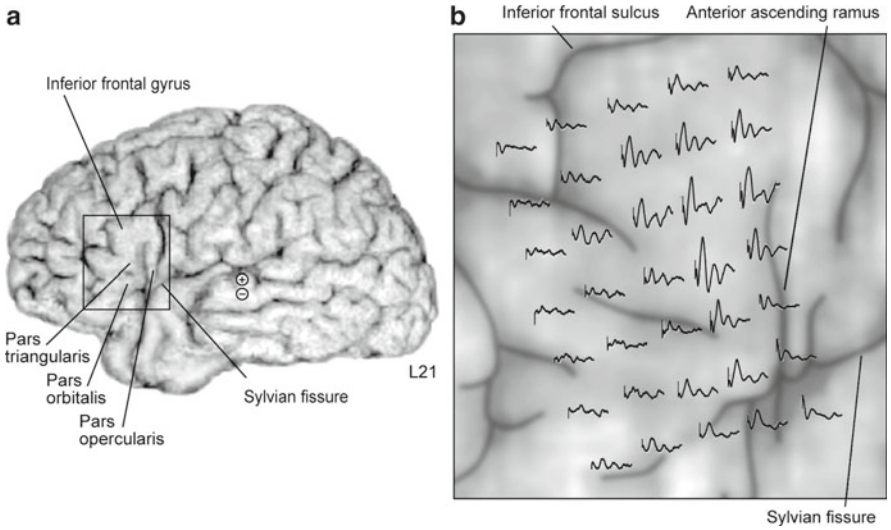


**Fig. 3.9** Cortical responses to electrical stimulation of posterolateral STG. (**a**) Lateral view of the left cerebral hemisphere showing stimulation and recording areas (circles and rectangle, respectively). (**b**) Enlarged view of the recording area on prefrontal cortex showing polyphasic electrically-evoked potentials

### *3.4.2 Functional Connectivity*

In nonhuman primates, auditory cortical fields of the temporal lobe and the auditory-related fields of the parietal and frontal lobes are highly interconnected to allow for both serial and parallel processing of acoustic information (Kaas & Hackett, 2005; Rauschecker & Scott, 2009). Anatomical tract tracing methods that have been used so effectively in mapping auditory cortical connectivity in the living monkey brain cannot, however, be used in humans. The use of diffusion tensor imaging has been effective in tracing major white matter tracts in the living human brain (see Talavage, Johnsrude, and Gonzalez Castillo, Chapter 6). One such tract is the arcuate fasciculus that connects temporal cortex with parietal and frontal fields and that, from the time of Wernicke, has been associated with language function and dysfunction. Another includes a pathway coursing through the external capsule and a third reaches orbitofrontal cortex by way of the uncinate fasciculus (Catani et al., 2003, 2005; Glasser & Rilling, 2008). An alternative method of tracing auditory cortical pathways used effectively in the past in animal experiments and more recently in human subjects involves focal electrical stimulation (single charge-balanced 0.1–0.2 ms current pulse) of one cortical site while recording from distant sites (Liegeois-Chauvel et al., 1991; Howard et al., 2000; Brugge et al., 2003; Greenlee et al., 2004; Matsumoto et al., 2004). This method may be applied in acute and chronic situations. In the example illustrated in Figure 3.9, an electrical stimulus applied to auditory cortex on posterolateral STG evoked complex, polyphasic, AEPs

that aggregated on ventral prefrontal cortex (vPFC), an area that may be the homolog of vPFC in the macaque monkey that receives a direct anatomical projection from auditory belt and parabelt areas (Hackett et al., 1999; Romanski et al. 1999; Romanski & Goldman-Rakic, 2002). This method is particularly well suited for use in the operating room, as specially designed and fabricated recording and stimulating electrodes may be quickly placed on cortical sites under visual control (see Fig. 3.4), and there is no required action on the part of the subject. Although this approach provides no direct information on the cellular origin or anatomical trajectories of neural pathways, it does give direct information in the living brain on the functional connectivity between the site of electrical stimulation and the site(s) of recording. Using this approach, functional connectivity has been documented between core auditory cortex on HG and an auditory field on posterolateral STG, between that field and the inferior frontal gyrus (IFG), between the IFG and motor cortex of the precentral gyrus, and between subfields within the IFG. Connectivity has also been inferred from patterns of coherence between distant sites as revealed in the electrophysiological recording data (Oya et al., 2007; Gourevitch et al., 2008). Such inferences may be tested recording sound-evoked activity from auditory fields and employing electrical stimulation tract tracing in the same subject.

### *3.4.3 Electrical Stimulation Functional Mapping*

As described earlier, the first experiments carried out in the operating room to study the functional organization of human auditory cortex involved the use of electrical stimulation methods. This approach to create a "functional lesion" by briefly and reversibly disrupting cortical processing in a small cortical area beneath and adjacent to the stimulating electrodes has been further refined. Boatman and her colleagues at Johns Hopkins University have made some of the most effective use of this approach to systematically study auditory cortex functions on the lateral hemispheric surface (Boatman et al., 1995; Boatman, 2004; Sinai et al., 2005; Sinha et al., 2005). These studies are now performed not only in the operating room, but in a more controlled setting associated with chronic recording. Under these conditions, stimulating current (0.3 ms 10–15 mA alternating polarity square wave pulses, 50 Hz, 5–10 s duration) is directed through pairs of adjacent contacts in electrode arrays on the pial surface or in depth electrodes within the supratemporal plane. The approach now can include the use of simultaneous ECoG recordings both to correlate the effects of stimulation with physiological events (Sinai et al., 2005) and to ensure that stimulus intensity does not exceed after-discharge threshold. In chronically implanted subjects controlled psychophysical testing is performed before, and then during periods of electrical stimulation. These experiments have identified sites on lateral STG that appear to be involved in higher order, phonological and lexical-semantic processing of speech (Fig. 3.10), thus providing a framework for a cortical model of speech perception. Electrical stimulation of the STG may also suppress the perception of sound, a phenomenon described originally by Penfield

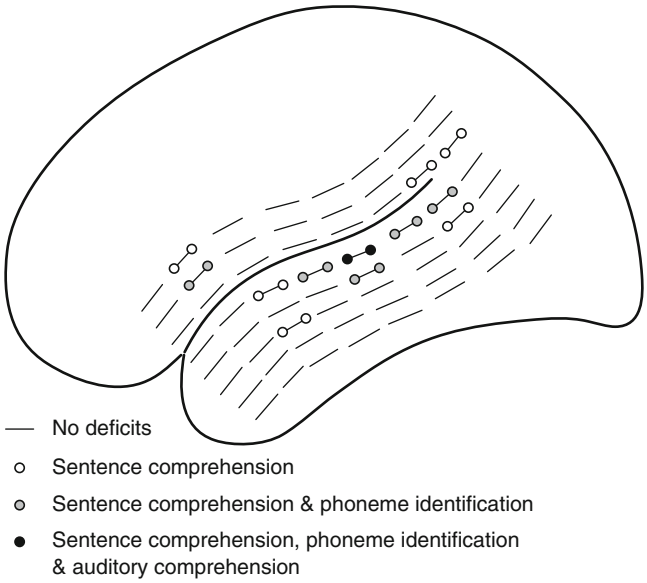


**Fig. 3.10** Schematic diagram of a cerebral hemisphere showing the locations of auditory discrimination deficits, phoneme identification errors and auditory sentence comprehension deficits induced during electrical stimulation mapping. Electrode locations have been normalized within a standard brain atlas. Lines represent sites where auditory discrimination was tested, but no deficits were induced. (Redrawn from Boatman, 2004.)

and his group as "deafening." Stimulation of the STG may attenuate ambient sound sensation (Sinha et al., 2005) and, surprisingly, also suppress tinnitus (Fenoy et al., 2006). Another method available to disrupt processing in localized regions of cerebral cortex is local cooling (Bakken et al., 2003). Unlike electrical stimulation, cooling blocks synaptic transmission in the area under the cooling probe. To date, its use is confined to acute experiments performed in the operating room.

## 3.5 Validity of Invasive Recordings

Although these invasive studies are intended to provide insights into the functional organization of normal human auditory cortex, interpreting the results obtained is done within the context of repeated seizure activity experienced by the study patients, often over periods of years, as well as the present and long-term use of multiple antiepileptic drugs. Surgical patients serving as research subjects are only those diagnosed with a focal seizure disorder. The seizure focus is typically localized to the mesial portion of the temporal lobe, including the hippocampus, where anatomical malformations have been well documented in individuals with drug resistant temporal lobe epilepsy (Gloor, 1991). Thalamic atrophy is reported to be most intense in thalamic nuclei having strong connections with limbic structures

(Bonilha et al., 2006). Epileptic discharges that occasionally invade cortex under study from a distant seizure focus are routinely detected and excluded from analyses. There is also evidence that in addition to mesial temporal malformations there is progressive atrophy of temporopolar, orbitofrontal, insular, and parietal areas (Bernhardt et al., 2009) as well as widespread thinning of neocortex, including lateral temporal regions (Bonilha et al., 2006; Bernhardt et al., 2010) that are considered to be auditory or auditory-related cortex. Thus, one cannot rule out the possibility that pathological processes associated with seizure disorders influence activity recording from distant cortical sites. We also note, however, that data obtained from the auditory core in particular bear a striking resemblance to those recorded from core cortex in the monkey (Fishman et al., 2001; Steinschneider et al., 2005; Ray et al., 2008; Brugge et al., 2009), suggesting that functional organization and certain stimulus–response relationships found in this area have been relatively spared.

## 3.6 Summary

The methodology of invasive research of human auditory cortex has made tremendous progress since the early studies of Penfield and his colleagues. These developments have paralleled the strides made in developing noninvasive imaging and electrophysiological recording methods. By employing invasive and noninvasive approaches in complementary ways to studies of the functional organization of auditory cortex, the knowledge gained promises to be far greater than that obtainable by relying on any one method alone.

Despite advances, however, technical shortcomings continue to impose limitations on invasive cortical electrophysiological recording and stimulation as research tools. Chronically implanted electrode arrays are tethered to head-mounted connectors that are, in turn, connected to external electronic instruments. Current data acquisition systems and surgical techniques allow for extensive (>200 contacts) electrode coverage making the external cables bulky and sometimes uncomfortable for the patient. External electrical (power line) noise easily coupled to wires often introduces unwanted interference during recording sessions. Wires can, and do, break, especially during seizures, resulting in loss of both clinical and research data. All of these considerations have a direct impact on the conduct and outcome of research, which in turn relate directly to patient safety and successful diagnosis of brain disorders and to successful development of neural prostheses.

Solutions will come through advances in engineering and material science. Miniaturization and tailoring of implanted arrays will be found in thin-film technology, currently in use for electronic circuit design and fabrication, as well as emerging nanotechnology coupled, perhaps, with the aid of magnetic navigation for implanting miniaturized and flexible depth electrodes. Bioactive conductive polymers may replace metal as material for electrode contacts, thereby eliminating concerns over potential electrochemical tissue damage. Finally, replacing bulky cables with wireless

transmission will allow clinical and research data to be obtained under a far wider range of environmental conditions. Taken together, these, and other, future technical advances will enhance patient comfort and safety, improve diagnosis and treatment, and open new opportunities for research.

**Acknowledgments** Preparation of this chapter was supported by NIH RO1-DC004290, UL1RR024979, and GCRC MO1-RR-59 and by the Hoover Fund.

## References

Bakken, H. E., Kawasaki, H., Oya, H., Greenlee, J. D., & Howard, M. A. (2003). A device for cooling localized regions of human cerebral cortex. *Journal of Neurosurgery*, 99, 604–608.

Bernhardt, B. C., Worsley, K. J., Kim, H., Evans, A. C., Bernasconi, A., & Bernasconi, N. (2009). Longitudinal and cross-sectional analysis of atrophy in pharmacoresistant temporal lobe epilepsy. *Neurology*, 72, 1747–1754.

Bernhardt, B. C., Bernasconi, N., Concha, L., & Bernasconi, A. (2010). Cortical thickness analysis in temporal lobe epilepsy: Reproducibility and relation to outcome. *Neurology*, 74(22), 1776–1784.

Bitterman, Y., Mukamel, R., Malach, R., Fried, I., & Nelken, I. (2008). Ultra-fine frequency tuning revealed in single neurons of human auditory cortex. *Nature*, 451(7175), 197–201.

Boatman, D. (2004). Cortical bases of speech perception: Evidence from functional lesion studies. *Cognition*, 92, 47–65.

Boatman, D., Lesser, R. P., & Gordon, B. (1995). Auditory speech processing in the left temporal lobe: An electrical interference study. *Brain and Language*, 51(2), 269–290.

Bonilha, L., Rorden, C., Appenzeller, S., Coan, A. C., Cendes, F., & Li, L. M. (2006). Gray matter atrophy associated with duration of temporal lobe epilepsy. *NeuroImage*, 32, 1070–1079.

Brugge, J. F., Volkov, I. O., Garell, P. C., Reale, R. A., & Howard, M. A. (2003). Functional connections between auditory cortex on Heschl's gyrus and on the lateral superior temporal gyrus in humans. *Journal of Neurophysiology*, 90, 3750–3763.

Brugge, J. F., Volkov, I. O., Reale, R. A., Garell, P. C., Kawasaki, H., Oya, H., et al. (2005). The posteriolateral superior temporal auditory field in humans. Functional organization and connectivity. In R. Konig, P. Heil, E. Budinger, & H. Scheich (Eds.), *The auditory cortex—toward a synthesis of human and animal research* (pp. 145–162). Mahwah, NJ: Erlbaum.

Brugge, J. F., Volkov, I. O., Oya, H., Kawasaki, H., Reale, R. A., Fenoy, A., et al. (2008). Functional localization of auditory cortical fields of human: Click-train stimulation. *Hearing Research*, 238(1–2), 12–24.

Brugge, J. F., Nourski, K. V., Oya, H., Reale, R. A., Kawasaki, H., Steinschneider, M., & Howard, M. A. (2009). Coding of repetitive transients by auditory cortex on Heschl's gyrus. *Journal of Neurophysiology*, 102(4), 2358–2374.

Catani, M., Jones, D. K., Donato, R., & Ffytche, D. H. (2003). Occipito-temporal connections in the human brain. *Brain*, 126(Pt 9), 2093–2107.

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology*, 57(1), 8–16.

Celesia, G. G. (1976). Organization of auditory cortical areas in man. *Brain*, 99, 403–414.

Celesia, G. G., & Puletti, F. (1969). Auditory cortical areas of man. *Neurology*, 19, 211–220.

Cohen, Y. E., Russ, B. E., Davis, S. J., Baker, A. E., Ackelson, A. L., & Nitecki, R. (2009). A functional role for the ventrolateral prefrontal cortex in non-spatial auditory cognition. *Proceedings of the National Academy of Sciences of the USA*, 106(47), 20045–20050.

Creutzfeldt, O., & Ojemann, G. (1989). Neuronal activity in the human lateral temporal lobe. III. Activity changes during music. *Experimental Brain Research*, 77(3), 490–498.

Creutzfeldt, O., Ojemann, G., & Lettich, E. (1989a). Neuronal activity in the human lateral temporal lobe. I. Responses to speech. *Experimental Brain Research*, 77(3), 451–475.

Creutzfeldt, O., Ojemann, G., & Lettich, E. (1989b). Neuronal activity in the human lateral temporal lobe. II. Responses to the subjects own voice. *Experimental Brain Research*, 77(3), 476–489.

Crone, N. E., Boatman, D., Gordon, B., & Hao, L. (2001). Induced electrocorticographic gamma activity during auditory perception. *Clinical Neurophysiology*, 112(4), 565–582.

Crone, N. E., Sinai, A., & Korzeniewska, A. (2006). High-frequency gamma oscillations and human brain mapping with electrocorticography. *Progress in Brain Research*, 159, 275–295.

Davis, P. A. (1939). Effects of acoustic stimuli on the waking human brain. *Journal of Neurophysiology*, 2, 494–499.

Edwards, E., Soltani, M., Kim, W., Dalal, S. S., Nagarajan, S. S., Berger, M. S., & Knight, R. T. (2009). Comparison of time-frequency responses and the event-related potential to auditory speech stimuli in human cortex. *Journal of Neurophysiology*, 102(1), 377–386.

Engel, A. K., König, P., Kreiter, A. K., Singer, W. (1991). Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. *Science*, *252*(5010), 1177–1179.

Engel, A. K., Moll, C. K., Fried, I., & Ojemann, G. A. (2005). Invasive recordings from the human brain: Clinical insights and beyond. *Nature Reviews Neuroscience*, 6(1), 35–47.

Engel, J. J. (2001). Finally, a randomized, controlled trial of epilepsy surgery. *New England Journal of Medicine*, 345, 365–367.

Fenoy, A. J., Severson, M. A., Volkov, I. O., Brugge, J. F., & Howard, M.A. (2006). Hearing suppression induced by electrical stimulation of human auditory cortex. *Brain Research*, 1118, 75–83.

Fishman, Y. I., Volkov, I. O., Noh, M. D., Garell, P. C., Bakken, H., Arezzo, J. C., et al. (2001). Consonance and dissonance of musical chords: Neural correlates in auditory cortex of monkeys and humans. *Journal of Neurophysiology*, 86(6), 2761–2788.

Flinker, A., Chang, E. F., Barbaro, N. M., Berger, M. S., & Knight, R. T. (2011). Sub-centimeter language organization in the human temporal lobe. *Brain and Language*. doi: S0093–934X(10)00155–0 [pii].

Freeman, W. J. (1978). Spatial properties of an EEG event in the olfactory bulb and cortex. *Electroencephalography and Clinical Neurophysiology*, 44, 586–605.

Fried, I., Wilson, C. L., Maidment, N. T., Engel, J., Jr., Behnke, E., Fields, T. A., et al. (1999). Cerebral microdialysis combined with single-neuron and electroencephalographic recording in neurosurgical patients. Technical note. *Journal of Neurosurgery*, 91(4), 697–705.

Geisler, C. D., Frishkopf, L. S., & Rosenblith, W. A. (1958). Extracranial responses to acoustic clicks in man. *Science*, 128, 1210–1211.

Ghovanloo, M., Otto, K. J., Kipke, D. R., & Najafi, K. (2004). In vitro and in vivo testing of a wireless multichannel stimulating telemetry microsystem. *Proceedings of the 26th Annual International Conference of the IEEE EMBS*, 6, 4294–4297.

Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cerebral Cortex*, 18(11), 2471–2482.

Gloor, P. (1991). Mesial temporal sclerosis: Historical background and an overview from a modern perspective. In H. O. Luders (Ed.), *Epilepsy surgery* (pp. 689–703). New York: Raven Press.

Gloor, P., Olivier, A., Quesney, L. F., Andermann, F., & Horowitz, S. (1982). The role of the limbic system in experiential phenomena of temporal lobe epilepsy. *Annals of Neurology*, 12, 129–144.

Gourevitch, B., Le Bouquin Jeannes, R., Faucon, G., & Liegeois-Chauvel, C. (2008). Temporal envelope processing in the human auditory cortex: Response and interconnections of auditory cortical areas. *Hearing Research*, 237(1–2), 1–18.

Gray, C. M., König, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature*, 338, 334–337.

Greenlee, J. D., Oya, H., Kawasaki, H., Volkov, I. O., Kaufman, O. P., Kovach, C., et al. (2004). A functional connection between inferior frontal gyrus and orofacial motor cortex in human. *Journal of Neurophysiology*, 92(2), 1153–1164.

Greenlee, J. D., Oya, H., Kawasaki, H., Volkov, I. O., Severson, M. A., 3rd, Howard, M. A., 3rd, & Brugge, J. F. (2007). Functional connections within the human inferior frontal gyrus. *Journal of Comparative Neurology*, 503(4), 550–559.

Griffiths, T. D., Kumar, S., Sedley, W., Nourski, K. V., Kawasaki, H., Oya, H., et al. (2010). Direct recordings of pitch responses from human auditory cortex. *Current Biology*, 20(12), 1128–1132.

Hackett, T. A. (2003). The comparative anatomy of the primate auditory cortex. In A. A. Ghazanfar (Ed.), *Primate audition: Ethology and neurobiology* (pp. 199–219). Boca Raton: CRC Press.

Hackett, T. A. (2007). Organization and correspondence of the auditory cortex of humans and nonhuman primates. In J. H. Kaas (Ed.), *Evolution of the nervous system* (pp. 109–119). Oxford: Elsevier.

Hackett, T. A. (2008). Anatomical organization of the auditory cortex. *Journal of the American Academy of Audiology*, 19(10), 774–779.

Hackett, T. A., Stepniewska, I., & Kaas, J. H. (1999). Prefrontal connections of the parabelt auditory cortex in macaque monkeys. *Brain Research*, 817(1–2), 45–58.

Howard, M. A., Volkov, I. O., Abbas, P. J., Damasio, H., Ollendieck, M. C., & Granner, M. A. (1996a). A chronic microelectrode investigation of the tonotopic organization of human auditory cortex. *Brain Research*, 724, 260–264.

Howard, M. A., Volkov, I. O., Granner, M. A., Damasio, H. M., Ollendieck, M. C., & Bakken, H. E. (1996b). A hybrid clinical-research depth electrode for acute and chronic in vivo microelectrode recording of human brain neurons. Technical note. *Journal of Neurosurgery*, 84, 129–132.

Howard, M. A., Volkov, I. O., Mirsky, R., Garell, P. C., Noh, M. D., Granner, M., et al. (2000). Auditory cortex on the posterior superior temporal gyrus of human cerebral cortex. *Journal of Comparative Neurology*, 416, 76–92.

Jenison, R. L., Rangel, A., Oya, H., Kawasaki, H., & Howard, M. A. (2011). Value encoding in single neurons in the human amygdala during decision making. *Journal of Neuroscience*, 31(1), 331–338.

Johnson, M. D., Otto, K. J., Williams, J. C., & Kipke, D. R. (2004). Bias voltages at microelectrodes change neural interface properties in vivo. *Proceedings of the 26th Annual International Conference of the IEEE EMBS*, 6, 4103–4106.

Kaas, J. H., & Hackett, T. A. (2005). Subdivisions and connections of auditory cortex in primates: A working model. In R. Konig, P. Heil, E. Budinger, & H. Scheich (Eds.), *Auditory cortex. A synthesis of human and animal research* (pp. 7–25). Mahwah, NJ: Erlbaum.

Kellis, S., Miller, K., Thomson, K., Brown, R., House, P., & Greger, B. (2010). Decoding spoken words using local field potentials recorded from the cortical surface. *Journal of Neural Engineering*, 7(5), 056007.

Lempka, S. F., Johnson, M. D., Barnett, D. W., Moffitt, M. A., Otto, K. J., Kipke, D. R., & McIntyre, C. C. (2006). Optimization of microelectrode design for cortical recording based on thermal noise considerations. *Proceedings of the 28th IEEE EMBS Annual International Conference*, 1, 3361–3364.

Leonard, C. M., Puranik, C., Kuldau, J. M., & Lombardino, L. J. (1998). Normal variation in the frequency and location of human auditory cortex landmarks. Heschl's gyrus: Where is it? *Cerebral Cortex*, 8, 397–406.

Liégeois-Chauvel, C., Musolino, A., & Chauvel, P. (1991). Localization of the primary auditory area in man. *Brain*, 114, 139–151.

Liégeois-Chauvel, C., Musolino, A., Badier, J. M., Marquis, P., & Chauvel, P. (1994). Evoked potentials recorded from the auditory cortex in man: Evaluation and topography of the middle latency components. *Electroencephalography and Clinical Neurophysiology*, 92, 204–214.

Liégeois-Chauvel, C., de Graaf, J. B., Laguitton, V., & Chauvel, P. (1999). Specialization of left auditory cortex for speech perception in man depends on temporal coding. *Cerebral Cortex*, 9, 484–496.

Liégeois-Chauvel, C., Lorenzi, C., Trebuchon, A., Regis, J., & Chauvel, P. (2004). Temporal envelope processing in the human left and right auditory cortices. *Cerebral Cortex*, 14(7), 731–740.

Lu, T., Liang, L., & Wang, X. (2001). Temporal and rate representations of time-varying signals in the auditory cortex of awake primates. *Nature Neuroscience*, 4(11), 1131–1138.

Matsumoto, R., Nair, D. R., LaPresto, E., Najm, I., Bingaman, W., Shibasaki, H., & Luders, H. O. (2004). Functional connectivity in the human language system: A cortico-cortical evoked potential study. *Brain*, 127(Pt 10), 2316–2330.

Matsumoto, R., Nair, D. R., LaPresto, E., Bingaman, W., Shibasaki, H., & Luders, H. O. (2007). Functional connectivity in human cortical motor system: A cortico-cortical evoked potential study. *Brain*, 130(Pt 1), 181–197.

Miller, K. J., Makeig, S., Hebb, A. O., Rao, R. P., denNijs, M., & Ojemann, J. G. (2007). Cortical electrode localization from X-rays and simple mapping for electrocorticographic research: The "Location on Cortex" (LOC) package for MATLAB. *Journal of Neuroscience Methods*, 162(1–2), 303–308.

Moriarity, J. L., Boatman, D., Krauss, G. L., Storm, P. B., & Lenz, F. A. (2001). Human "memories" can be evoked by stimulation of the lateral temporal cortex after ipsilateral medial temporal lobe resection. *Journal of Neurology*, *Neurosurgery and Psychiatry*, 71(4), 549–551.

Mukamel, R., Gelbard, H., Arieli, A., Hasson, U., Fried, I., & Malach, R. (2005). Coupling between neuronal firing, field potentials, and FMRI in human auditory cortex. *Science*, 309(5736), 951–954.

Nourski, K. V., Reale, R. A., Oya, H., Kawasaki, H., Kovach, C. K., Chen, H., et al. (2009). Temporal envelope of time-compressed speech represented in the human auditory cortex. *Journal of Neuroscience*, 29(39), 15564–15574.

Oya, H., Poon, P. W., Brugge, J. F., Reale, R. A., Kawasaki, H., Volkov, I. O., & Howard, M. A., 3rd. (2007). Functional connections between auditory cortical fields in humans revealed by Granger causality analysis of intra-cranial evoked potentials to sounds: comparison of two methods. *Biosystems*, 89(1–3), 198–207.

Penfield, W., & Perot, P. (1963). The brain's record of auditory and visual experience—a final summary and discussion. *Brain*, 86, 595–696.

Penfield, W., & Rasmussen, T. (1950). *The cerebral cortex of man—A clinical study of localization of function*. New York: Macmillan.

Pierce, A. L., Sommakia, S., Rickus, J. L., & Otto, K. J. (2009). Thin-film silica sol-gel coatings for neural microelectrodes. *Journal of Neuroscience Methods*, 180(1), 106–110.

Preuss, T. M. (1995). The argument from animals to humans in cognitive neuroscience. In M. S. Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 1227–1241). Cambridge, MA: MIT Press.

Rademacher, J., Caviness, V., Steinmetz, H., & Galaburda, A. (1993). Topographical variation of the human primary cortices; implications for neuroimaging, brain mapping and neurobiology. *Cerebral Cortex*, 3, 313–329.

Rauschecker, J. P., & Scott, S. K. (2009). Maps and streams in the auditory cortex: Nonhuman primates illuminate human speech processing. *Nature Neuroscience*, 12(6), 718–724.

Ray, S., Niebur, E., Hsiao, S. S., Sinai, A., & Crone, N. E. (2008). High-frequency gamma activity (80–150 Hz) is increased in human cortex during selective attention. *Clinical Neurophysiology*, 119(1), 116–133.

Reddy, C. G., Dahdaleh, N.S., Albert, G., Chen, F., Hansen, D., Nourski, K., et al. (2010). A method for placing Heschl gyrus depth electrodes. *Journal of Neurosurgery*, 112(6), 1301–1307.

Romanski, L. M. (2004). Domain specificity in the primate prefrontal cortex. Cognitive, Affective, & Behavioral Neuroscience, 4(4), 421–429.

Romanski, L. M., & Goldman-Rakic, P. S. (2002). An auditory domain in primate prefrontal cortex. *Nature Neuroscience*, 5(1), 15–16.

Romanski, L. M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P. S., & Rauschecker, J. P. (1999). Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nature Neuroscience*, 2, 1131–1136.

Rosen, S. (1992). Temporal information in speech: Acoustic, auditory and linguistic aspects. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 336(1278), 367–373.

Sinai, A., Bowers, C. W., Crainiceanu, C. M., Boatman, D., Gordon, B., Lesser, R. P., et al.(2005). Electrocorticographic high gamma activity versus electrical cortical stimulation mapping of naming. *Brain*, 128(Pt 7), 1556–1570.

Sinha, S. R., Crone, N. E., Fotta, R., Lenz, F., & Boatman, D. F. (2005). Transient unilateral hearing loss induced by electrocortical stimulation. *Neurology*, 64, 383–385.

Steinschneider, M., Reser, D. H., Fishman, Y. I., Schroeder, C. E., & Arezzo, J. C. (1998). Click train encoding in primary auditory cortex of the awake monkey: Evidence for two mechanisms subserving pitch perception. *Journal of the Acoustical Society of America*, 104(5), 2935–2955.

Steinschneider, M., Volkov, I. O., Fishman, Y. I., Oya, H., Arezzo, J. C., & Howard, M. A., 3rd. (2005). Intracortical responses in human and monkey primary auditory cortex support a temporal processing mechanism for encoding of the voice onset time phonetic parameter. *Cerebral Cortex*, 15(2), 170–186.

Steinschneider, M., Fishman, Y. I., & Arezzo, J. C. (2008). Spectrotemporal analysis of evoked and induced electroencephalographic responses in primary auditory cortex (A1) of the awake monkey. *Cerebral Cortex*, 18(3), 610–625.

World Health Organization (2005). *Atlas: Epilepsy care in the world*. Geneva: WHO.