Published in final edited form as:

Hear Res. 2007 July ; 229(1-2): 14–23. doi:10.1016/j.heares.2007.01.003.

Exploring the extent and function of higher-order auditory cortex in rhesus monkeys

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Abstract

Just as cortical visual processing continues far beyond the boundaries of early visual areas, so too does cortical auditory processing continue far beyond the limits of early auditory areas. In passively listening rhesus monkeys examined with metabolic mapping techniques, cortical areas reactive to auditory stimulation were found to include the entire length of the superior temporal gyrus (STG) as well as several other regions within the temporal, parietal, and frontal lobes. Comparison of these widespread activations with those from an analogous study in vision supports the notion that audition, like vision, is served by several cortical processing streams, each specialized for analyzing a different aspect of sensory input, such as stimulus quality, location, or motion. Exploration with different classes of acoustic stimuli demonstrated that most portions of STG show greater activation on the right than on the left regardless of stimulus class. However, there is a striking shift to left hemisphere “dominance” during passive listening to species-specific vocalizations, though this reverse asymmetry is observed only in the region of temporal pole. The mechanism for this left temporal pole “dominance” appears to be suppression of the right temporal pole by the left hemisphere, as demonstrated by a comparison of the results in normal monkeys with those in split-brain monkeys.

Keywords

monkey; vocalization; lateralization; multisensory; temporal pole; superior temporal gyrus

Introduction

According to the zeitgeist of the 1970s, the auditory system contained relatively little higher-order cortical processing areas compared to that in the visual and somatosensory systems. The explanation was that much of the processing in audition was completed before the cortex was reached. Auditory input is indeed transmitted along complex multisynaptic pathways composed of numerous subcortical nuclei. Nevertheless, considering the tremendous processing needs of the auditory system – with acoustic signals varying not only across multiple simultaneous frequencies but also across time in the millisecond range, with both the sequential order of these frequency modulations and completely derived spatial information constituting

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critical additional factors – even very extensive subcortical processing may not be sufficient to the task; it is therefore likely that, just as in the other exteroceptive sensory modalities, the auditory modality too makes use of elaborate cortical processing. The earlier view that the auditory system occupied a limited cortical territory may have arisen in part from the common use of anesthetized animals in neurophysiological research (Merzenich and Brugge, 1973; Brugge and Merzenich, 1973), as well as the systematic study of tonotopic mapping utilizing pure tones and frequency sweeps. As auditory research moved to the use of awake animals and an ever-widening array of sounds (Schwarz and Tomlinson, 1990; Ahissar et al., 1992; Bieser and Muller-Preuss, 1996), areas of cortex identified as auditory proved to be more extensive than originally thought. Defining the full extent and boundaries of auditory cortical regions thus became an important step toward a better understanding of auditory processing. In addition, because processing complex auditory stimuli is critical for identifying behaviorally relevant objects and, particularly for vocal communication, making use of complex acoustic stimuli in studies of nonhuman primates could help inform us about the mechanisms needed for the analysis of spectrotemporally varying sounds as well as the neural precursors, if any, of human language. Here we review our studies mapping the extent of auditory-related cortex during passive listening to a variety of both basic and complex acoustic stimuli, including monkey calls.

Visual system guides to higher-order auditory processing areas

Some of the questions that define the long-term goals of cognitive neuroscientists in the auditory domain include: How does the cortex represent auditory information; how is auditory information encoded and stored in memory; how is it associated with other information; and how is auditory information transformed into adaptive behavior. Some possible answers can be proposed from the knowledge base available for vision. There are considerable data now addressing how the cortical visual system represents the properties of objects and their locations, how these are encoded and retained in memory, and how that information is utilized to guide behavior (Ungerleider and Mishkin, 1982; Logothetis and Sheinberg, 1996; Bar and Biederman, 1999; Squire, 2004; Gattas et al., 2005). Even though the inputs through sensory receptors and subcortical pathways in vision and audition are markedly different, the organization of the cortical processing systems in these two modalities could still reflect similar principles, and this idea can serve as a guide to gathering and interpreting data on higher-order cortices in the auditory domain (e.g. Romanski et al., 1999).

Auditory thalamocortical connections are well documented in the rhesus monkey (Morel et al., 1993; Pandya et al., 1994). The primary auditory thalamic nucleus, the medial geniculate body (MGB), projects to the supratemporal plane and other posterior portions of the STG. Based on anatomical considerations, this projection territory has been divided into three main regions, core, belt, and parabelt (Hackett et al., 1998; Kaas and Hackett, 2000), thought to correspond to primary, secondary, and tertiary auditory cortices. Encircling the core, which consists of areas of A1, R, and RT, are at least seven belt areas; and the parabelt, located on the lateral edge of the belt, is subdivided into anterior and posterior parts. The MGB's ventral division projects mainly to the auditory core, whereas its medial and dorsal divisions, as well as the supragenulate nucleus, project primarily to the belt and parabelt. Besides the thalamic afferents to these two regions, the belt also receives large inputs from the core, and the parabelt receives large inputs from the belt. Many of these regions have been characterized in terms of their tonotopic maps as revealed initially through microelectrode recording (Brugge and Merzenich, 1973; Morel et al., 1993; Wang et al., 1995; Rauschecker et al., 1995; Rauschecker, 1998; Tian et al., 2001; Recanzone, 2000, 2001) and more recently through visualization with fMRI in awake monkeys (Petkov et al., 2006). These tonotopic regions, all of which can now be considered to be early auditory processing areas (see below), are known to project rostrally along the STG to the temporal pole, as well as into the prefrontal cortex (Galaburda and Pandya,

1983; Moran, et al., 1987; Romanski, et al., 1999; Kaas and Hackett, 2000). In an attempt to obtain functional maps of these and other regions to which the early auditory areas project, we adapted a metabolic mapping method used earlier in vision (Macko et al., 1982; Macko and Mishkin, 1985).

Metabolic mapping of auditory cortex

For the auditory study (Poremba et al., 2003), we first prepared monkeys with unilateral ablation of the inferior colliculus combined with transection of the corpus callosum and anterior, posterior, and tectal commissures to create a ‘deaf’ and a ‘hearing’ hemisphere (Figs. 1 and 2). A few weeks later, we injected 2-[14C]deoxyglucose (2-DG) intravenously while the awake animals listened passively to a wide variety of both basic and complex, stationary and moving sounds for a period of 45 minutes. The complex acoustic stimuli included monkey calls, vocalizations of other animals, human voices, environmental sounds, music, etc. After the brains were prepared histologically for quantitative autoradiography, we compared local cerebral glucose utilization in the acoustically activated and nonactivated hemispheres, thereby obtaining a relatively high resolution map of auditory-related tissue (Fig. 3). The results indicated that this tissue occupies the entire superior temporal gyrus including the temporal pole, large portions of the inferior parietal gyrus extending into the dorsal insula, parts of the parahippocampal gyrus, substantial portions of the inferior frontal and orbitofrontal gyri, and smaller areas in the anterior cingulate and dorsolateral prefrontal cortices. Areas activated subcortically included parts of the superior colliculus, medial geniculate nucleus, lateral amygdala, and ventrocaudal neostriatum (Figs. 3 and 4).

Comparison of auditory and visual maps

Differential metabolic activity in the temporal pole to the auditory input was limited to its dorsal half (Fig. 4, AP +20), its ventral half having been found earlier to be activated instead by visual stimuli (Macko et al., 1982; the activation map in that study was created by comparing 2-DG uptake to visual stimulation in a blind and a seeing hemisphere, prepared as illustrated in Fig. 5). Interestingly, these auditory and visual processing areas at the level of the temporal pole appear to be separated by tissue that is neither auditory nor visual (Figs. 4 and 7D), and so may contain neurons that respond only when both modalities are stimulated or perhaps only when another sensory modality is stimulated.

In addition to the nonoverlapping territories, there are also many cortical areas in which auditory and visual territories do overlap (see below). Together, these areas of overlap and nonoverlap support the proposal that there are at least three different cortical processing streams in audition (Fig. 6) paralleling the three streams that had previously been identified in vision (Ungerleider and Mishkin, 1982; Mishkin et al., 1983; Boussaoud et al., 1990). These appear to be: (i) a modality-specific ventral stream for processing acoustic stimulus quality or auditory ‘objects’, analogous to the one in the visual system for processing visual objects; (ii) a modality-nonspecific dorsal stream for processing the spatial source of acoustic stimuli, analogous to, and overlapping with, the one in vision for processing spatial location; and (iii) a second modality-nonspecific stream, this one coursing through the upper bank of the superior temporal sulcus and possibly processing auditory motion, by analogy to the visual stream in this same location that processes visual motion.

Evidence from both monkeys and humans had already suggested that there were multisynaptic corticocortical pathways in audition paralleling those in vision (Bruce et al., 1981; Wang et al., 1995; Andersen, 1997; Romanski et al., 1999; Rauschecker and Tian, 2000; Clarke et al., 2002; Kaiser et al., 2003; Rama et al., 2004; For review see, Shroeder and Fox, 2005). The metabolic mapping study not only lends strong support to that notion, but also allows simultaneous visualization of the territory occupied by all three of these proposed pathways.

The areas of overlap in the auditory and visual systems point not only to parallel cortical processing streams but also to potential areas of bimodal and even multisensory association and integration, processes that are prevalent in our everyday lives, as when viewing a favorite fruit evokes its aroma, taste, and texture, and the sound of biting into it. Locating and investigating the areas that could mediate these and other types of polymodal associations should help elucidate the neuronal mechanisms for multisensory integration, including those needed for communication and language.

Alignment of the auditory and visual metabolic maps reveals many bimodal and potentially polymodal association areas (Fig. 4). Included are areas previously shown by electrophysiological and connectational studies to be multisensory, such as the upper bank of the superior temporal sulcus (Fig. 7B; Yeterian and Pandya, 1989; Baylis et al., 1987; Bruce et al., 1981; Seltzer and Pandya, 1978; Jones and Powell, 1970), prefrontal cortex (Fig. 7A; Constantinidis et al., 2001), amygdala (Turner et al., 1980), lower bank of the intraparietal sulcus (area LIP; Fig. 7C; Mazzoni et al., 1996; Anderson, 1997), superior colliculus (Wallace et al., 1993), insula, and caudate nucleus (Nagy et al., 2006).

Besides confirming that the upper bank of the superior temporal sulcus is polysensory, the mapping experiment indicated that the density of 2-DG uptake decreases from medial to lateral for visual stimulation and from lateral to medial for auditory stimulation (Fig. 7B). These observations predict that the greatest convergence of neuronal activation is likely to be located midway along the upper bank.

Auditory cortical columns

In addition to revealing the wide expanse of cortical territory that serves audition, metabolic mapping with 2-DG also revealed some of the functional architecture within this territory, namely, acoustically responsive cortical columns within the rostral third of the STG. At the level of the temporal pole, these columns occupied its dorsal half (Fig. 8A). Measured in the coronal plane in animals with bilaterally intact auditory systems, most columns extended ~500-800 microns mediolaterally, while in the horizontal plane most of them extended ~160-700 microns rostrocaudally. Although the 2-DG uptake within each column could extend vertically from layers II to V (and only rarely to layer VI), the highest density was observed in layers III to IV, centered at layer IV.

In the hearing hemisphere of the unilaterally deafferented monkeys that had received commissurotomy, columns measured in the coronal plane were about 200 microns narrower than they were in the intact monkeys (i.e. extending ~330-600 microns mediolaterally compared with ~500-800 microns; Fig. 8A). This finding suggests that each relatively wide column, probably receiving its main auditory input from its own hemisphere, lies adjacent to a narrower column that normally receives its main auditory input from the opposite hemisphere (Fig. 8B). The existence of anatomically organized columns in higher-order auditory cortex was demonstrated recently in human brain tissue by means of postmortem tract tracing (Galuske et al., 2000). Applied to the intrinsic connections of Brodmann area 22, the technique disclosed an interconnected network of regularly spaced neuronal clusters; extending this finding to the monkey, the columns might be interconnected as depicted in the illustration (Fig. 8B).

The functional significance of the interdigitated columns without or with lesser 2-DG uptake in the intact monkeys remains unknown, but presumably these columns require for their activation either auditory stimuli of a type not utilized in our metabolic experiment, or perhaps more likely, since so many different classes of auditory stimuli were presented, stimulation of a different sensory modality. Given the functional significance of columns in other sensory systems, particularly the visual system, investigation of the auditory columns described here

in the dorsal temporal pole could yield important insights into how auditory object information is processed in cortex beyond the early auditory areas.

Metabolic activations by different sound categories

While the relatively high resolution 2-DG technique was useful for identifying precise functional boundaries between auditory and nonauditory tissue as well as for detecting auditory columns, we wished to measure possible differences in activation evoked by different classes of acoustic stimuli. Since this could not be accomplished with the single-assessment 2-DG method, we turned to the use of positron emission tomography, PET (Poremba et al., 2004). Although PET provides relatively poor spatial resolution, it has the distinct advantage of allowing repeated testing across days, thereby enabling replication within and comparison across different conditions in the same animal. In this study we measured local cerebral metabolic activity while the animals listened passively to five different sound classes (species-specific monkey calls, the same calls phase-scrambled, human speech, simple and complex nonvocal sounds, and ambient background noise), with each sound class presented in a separate session. The procedure began with an intravenous injection of 2-[¹⁸F]fluoro-deoxyglucose (FDG), followed by presentation of one of the sound categories for a period of 25 minutes, immediately after which the animal was anaesthetized and taken to the PET scanner where FDG uptake was measured while radioactivity levels were still fairly high.

The image analyses described here focused on the superior temporal gyrus, which showed high levels of activity especially within its caudal two-thirds. Within this posterior portion of the gyrus, in the region of the early auditory areas, all five sound classes evoked significantly greater metabolic activity on the right than on the left. More rostrally, however, this hemispheric difference tended to dissipate, with one striking exception. During the presentation of the rhesus monkey calls, there was a shift to significantly greater activation on the left than on the right, but only at the level of the temporal pole (Fig. 9, 10). In short, left-hemisphere 'dominance', at least in terms of functional activation, was specific to this region and to this specific sound class. And this hemispheric asymmetry in favor of the left appeared against the background of the reverse asymmetry posteriorly, even in response to the same sound class.

Comparison of the FDG uptake that had been evoked in the region of the temporal pole by the five different acoustic categories suggested that the category-specific asymmetry at this location was due more to a relative reduction in activity on the right during presentation of rhesus monkey calls than it was to a relative enhancement of activity on the left. This evidence led us to consider the possibility that the relative reduction of activity in the right temporal pole was due to active suppression, perhaps mediated by the forebrain commissures. Transcallosal suppression of activity in one hemisphere by activity in the other had already been demonstrated earlier in both the motor and visual systems (Ferber et al., 1992; Desimone et al., 1993). To test whether the same mechanism might have been at work in our auditory study, we repeated the FDG/PET experiment, this time in a new group of monkeys prepared with forebrain commissurotomies (Poremba et al., 2004).

The postoperative results were clearcut: the category-specific asymmetry at the level of the temporal pole disappeared, due specifically to a relative increase in metabolic activity on the right, indicating that this tissue had been released from interhemispheric suppression (Fig. 10). The findings imply that the perception of monkey vocalizations elicits interhemispheric interaction that directs and focuses the auditory processing of these species-specific calls within a specialized area of one hemisphere. This implication is consistent with lesion findings demonstrating that ablation of auditory cortex on the left but not on the right impairs the animals' ability to discriminate monkey calls (Heffner and Heffner, 1984). A similar mechanism for directing cortical processing to specialized areas in one hemisphere may

underlie left hemisphere dominance for language in humans. For example, it has been suggested that collateral inhibition in human language areas contributes to lateralization of function (Karbe et al., 1998), and only when this normal suppression is prevented by removal of a damaged, epileptogenic left hemisphere early in life does the right hemisphere become linguistically capable (e.g. Vargha Khadem et al., 1997; Hertz-Pannier et al., 2002). Left-hemisphere specialization for processing of species-specific vocalizations may have an evolutionary origin in non-primate mammals (Ehret, 1987), paralleling that in birds (George et al., 2002). Monkeys, with their extensive auditory system and large number of distinct vocal communicative signals could provide a useful animal model for uncovering the neural basis for such specialization.

An additional finding in the sound-category study suggests that, within the monkey's cortical auditory system, two different types of hemispheric lateralization coexist, one dependent on the interhemispheric interaction just described, but another based on *intra*hemispheric mechanisms. Although left temporal pole 'dominance' was absent in the commissurotomy monkeys, the reverse asymmetry in the posterior portions of the STG remained strong despite the commissurotomy. The latter form of asymmetry is thus apparently due to differences that are intrinsic to the two hemispheres. Whether these intrinsic differences reflect more effective processing of all types of auditory stimuli by early auditory areas on the right than by early auditory areas on the left is an open question. However, if this turns out to be the case, the results of the unilateral-lesion study (Heffner and Heffner, 1984) described above would weigh in favor of the notion that the determining factor for hemispheric specialization in auditory perception is the effectiveness of processing not in the early, but in the higher-order auditory areas.

Acknowledgments

Startup funds from the University of Iowa to A.P., and the National Institute of Mental Health, Intramural Research Program, Dept. of Health and Human Services to M.M. provided support for this research. The authors would also like to acknowledge the help, and support of Megan Malloy, Richard C. Saunders, Peter Herscovitch, Richard E. Carson, Louis Sokoloff, Michelle Cook, Alison Tannenbaum, and Mark Hauser.

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Isolation of One Hemisphere From Auditory Input

Figure 1.

Schematic diagram of the lesions performed to deprive one hemisphere of all auditory input, accomplished by aspirating the inferior colliculus in that hemisphere and then transecting the corpus callosum together with the anterior, posterior, and tectal commissures.

Figure 2.
MRI images showing six coronal sections from anterior (upper left) to posterior (lower right) for one monkey prepared with the lesion illustrated in Figure 1.

Figure 3.

Coronal sections, 50-microns thick, showing 2-DG autoradiographs from one monkey prepared with the lesion illustrated in Figure 1. Sections are arranged from anterior (upper left) to posterior (lower right). Compare the intact hemisphere, on the left of each coronal slice, with the deafferented hemisphere, on the right.

Figure 4.

Schematic summary of cortical areas related to the processing of auditory, auditory plus visual, and visual stimuli, based on a comparison of the results from the auditory and visual unilateral-deafferentation studies (see text). Data have been transferred to a lateral surface view (top) of the right hemisphere and coronal sections (arranged from posterior to anterior) of a standard brain. AP levels of the sections are indicated by the vertical lines on the lateral surface view, and numerals refer to the number of millimeters anterior (+) or posterior (-) to the interaural plane. The frontal pole surrounded by a dashed line on lateral surface view was not available for assessment in the 2-DG visual experiment. Boundaries were determined by visual inspection followed by quantitative examination of the autoradiographs for the individual

cases, and the boundary positions were averaged across all monkeys in the study. Sulcal abbreviations: ai, inferior limb of arcuate; as, superior limb of arcuate; ca, calcarine; ce, central; ci, cingulate; ip, intraparietal; l, lunate; la, lateral; oi, inferior occipital; orm, medial orbital; ot, occipitotemporal; p, principal; rh, rhinal; tma, anterior middle temporal; tmp, posterior middle temporal; and ts, superior temporal.

Isolation of One Hemisphere From Visual Input

Figure 5. Schematic diagram of the lesions performed to deprive one hemisphere of all visual input, accomplished by unilateral transection of the optic tract combined with a forebrain commissurotomy.

Auditory processing streams?

Figure 6.

Putative cortical processing streams in the auditory system, by analogy to the processing streams in the visual system. All auditory streams begin in early auditory areas depicted by the dashed yellow line in the posterior part of the STG. The three putative streams, from dorsal to ventral, are: (i) a temporo-parieto-dorsoprefrontal pathway specialized for processing the location of sound sources, (ii) a temporo-ventroprefrontal pathway specialized for processing sound quality or auditory objects, and (iii) a second temporo-ventroprefrontal pathway coursing through the upper bank of the superior temporal sulcus, possibly specialized for processing auditory motion.

Figure 7.

Examples of overlapping and nonoverlapping activation effects in monkeys deprived unilaterally of either visual or auditory input and presented with visual and auditory stimuli, respectively. First note left-right differences in 2-DG uptake in the “seeing” versus the “blind” hemisphere (top section in each pair), and in the “hearing” versus the “deaf” hemisphere (bottom section in each pair). Then compare top and bottom sections within pairs A-C to identify affected areas that overlap in the two cases. Specifically, both cases show greater activation on the left than on the right in parts of: A) inferior and orbital prefrontal cortices; B) upper bank of the superior temporal sulcus; and C) inferior parietal cortex; D) Example of the nonoverlapping activation effects in the temporal pole. See also Figure 4.

Figure 8.

Coronal sections from PET scans of four different normal monkeys listening to species-specific vocalizations. Note in each case the greater activation of the left than of the right temporal pole (temporal poles outlined by the red squares).

Figure 9.

Coronal sections from PET scans of four different normal monkeys listening to species-specific vocalizations. Note in each case the greater activation of the left than of the right temporal pole (temporal poles outlined by the red squares).

Figure 10.

Mean metabolic activity evoked by rhesus monkey calls in the left and right temporal poles of normal ($n=8$) and commissurotomed ($n=3$) monkeys. The left-right difference in the normal animals appears to be due to interhemispheric suppression of the right temporal pole, as indicated by the increase in activation on the right – to a level matching the activation on the left – in the animals with commissurotomy. Asterisk, left hemisphere activity significantly greater than right with correction for multiple comparisons.