Relationships between human auditory cortical structure and function

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ABSTRACT

The study of the functional organization of the human auditory cortex has flourished in the last few years, thanks largely to the advent of functional neuroimaging. Functional magnetic resonance imaging (fMRI) in particular is making significant contributions to our understanding of the organization of the auditory cortex. Given the spatial resolution of fMRI (under 6 mm), an understanding of cortical architectonics and neurophysiology is becoming increasingly necessary for interpreting the imaging data in an informative and meaningful way. The human auditory cortex comprises multiple areas, largely distributed across the supratemporal plane. Although the precise number and configuration of auditory areas and their functional significance are not yet clearly established in humans, architectonic and neurophysiological studies in non-human species can provide a broad conceptual framework for interpreting functional specialisation within human auditory cortex. Furthermore, researchers can, in part, overcome the uncertainties of human auditory anatomy by defining auditory regions by their functional characteristics within individuals and relating these to visible macro-anatomical structures. In this paper, we discuss recent research concerning architectonic and functional organisation within the human auditory cortex. We review the pattern in human auditory cortex of the functional responses to various acoustic cues, such as frequency, pitch, sound level, temporal variation, motion and spatial location, and we discuss their correspondence to what is known about the organization of the auditory cortex in other primates.

KEYWORDS

Human auditory cortex, neuroimaging, cortical architecture, functional organisation.

INTRODUCTION

The advent of tools for imaging human brain function has revolutionized the field of cognitive neuroscience. Detailed anatomical images, acquired using magnetic resonance imaging (MRI), can now be combined with information from functional imaging with spatial resolution of a few centimetres or less. These imaging techniques include positron emission tomography (PET), functional MRI (fMRI), electroencephaolography (EEG) and magnetoencephalography (MEG). Each

technique affords certain advantages and limitations. PET and fMRI provide good spatial maps of brain activation, and the identification of activation foci is methodologically straightforward (although their interpretation may be more difficult, see Brett et al., 2002). These two techniques have relatively poor temporal resolution because they reflect changes associated with blood flow. PET and fMRI are thus indirect measures of brain activity, and are fundamentally limited by the characteristics of the haemodynamic response on which the activation signal is based. In contrast, EEG is sensitive to scalp surface measurements of electrical activity produced by synchronous neural firing in the brain and MEG is sensitive to scalp magnetic fields directly generated by this electrical activity. Both measures thus provide information about the millisecond time course of brain activity. Modelling techniques are used to estimate the source of the electrical generators giving rise to the surface fields. However, there is no unique solution to solving the number of sources and location of each source: the location cannot be well estimated unless the number of contributory sources is known [Lütkenhöner et al., 2001). Thus, EEG and MEG data complement the spatial maps derived from PET and fMRI data.

The last few years have seen a shift away from the use of PET towards fMRI. Although PET retains certain advantages, particularly in terms of the quiet experimental environment and the lack of signal loss in the anterior and inferior portions of the temporal lobe [see Johnsrude et al., 2002], fMRI is more widely available, has no radiation burden, and has superior temporal and spatial resolution particularly at high field strengths. fMRI is suitable for research use with children as well as adults, and can also be used with clinical populations such as the hearing impaired. Since multiple observations can be made on the same individual, fMRI permits the investigation of longer-term dynamic processes, such as functional plasticity after disease or damage. In addition, the need for averaging data across individuals is reduced, further improving the accuracy with which activations can be mapped onto brain structure.

Current research seeks evidence in humans of the anatomical and physiological systems known from studies in other mammals (particularly primates). In the occipital cortex, PET and fMRI have been used to delineate functional specialisation of different visual fields [see Wandell, 1999 for a review]. These

techniques are clearly also important in exploring the functional organisation of the auditory system. However, functional and anatomical specialisations have not been revealed in the auditory system as readily as they have in the visual system. Anatomical and functional homologies between humans and other primates have also been unexpectedly difficult to find. Auditory cortical function is particularly difficult to assess because the exact number and precise location of different auditory fields is still largely unknown. In addition, input to the primary auditory cortex is likely to be more complex than the frequency- and sound-level -based information that is represented in the cochlear nerve, because a good deal of processing takes place in the brainstem and midbrain nuclei. Furthermore, cortical afferents from the medial geniculate nucleus of the thalamus project in parallel to multiple auditory fields and are suggestive of a highly parallel system [Rauschecker et al., 1997]. A consequence of the incomplete decussation of the auditory pathway and the multiple projections to the cortex is that bilateral lesions of the brainstem or the STG are required to disrupt auditory processing [see Griffiths et al, 1999 for a review]. Thus, the lesion literature has also proved to be less informative for understanding audition, than for vision or somatosensory modalities.

This review describes some recent research into the functional and anatomical organisation of the human auditory cortex. We report key issues that have emerged over the last few years and discuss what PET, fMRI, EEG and MEG, in conjunction with recent architectonic studies, reveal about the general organization of human auditory cortex. We review only that research pertaining to the processing of basic (i.e., non-linguistic) acoustic features in sound, since auditory cortical regions that respond to the phonetic cues in speech also respond to spectral change and temporal regularity in non-speech sounds [for a review see Scott and Wise, 2002]. Thus, the early stages of speech processing can be attributed to aspects of the acoustic complexity in the signal. In addition, with the exception of spatial sound processing, we restrict our discussion to the organisation of unimodal auditory cortex on the supratemporal plane rather than the entire auditory network, which involves parietal and prefrontal cortices, in addition to temporal regions [e.g., Romanski et al., 1999; Kaas and Hackett, 2000; Romanski and Goldman-Rakic, 2002].

ARCHITECTONIC ORGANISATION OF THE AUDITORY CORTEX

** Table **

Architectonic mapping techniques have been used for more than 100 years to differentiate among cortical fields in the human brain [e.g., Brodmann 1909]. Architectonic divisions are based on the connectivity, neuro-chemical characteristics and cell morphology and composition of the layers of the cortex. Cortical areas can differ along all of these dimensions, as has been shown using markers for cyto-architecture, (e.g. Nissl staining), myelo-architecture (e.g., Gallyas method), connectivity (e.g. parvalbumin heavily stains thalamocortical projection zones) and metabolic activity (cytochrome oxidase staining). In mammals, such as cat and macaque monkey, architectonic borders correspond well with physiological borders [Wallace et al., 1991; Kosaki et al., 1997; Morel et al., 1993]. Therefore, the functional properties of neurons may provide clues about the spatial distribution of anatomical fields.

Organisation of auditory cortex in non-human primates

The organisation of auditory cortex in the macaque monkey has been reviewed in several recent papers [Hackett, 2002; Kaas and Hackett, 1998, 2000; Rauschecker, 1998; Rauschecker and Tian 2000], and this is thought to be a good model for the organisation of auditory cortex in the human brain. Kaas and Hackett [1998; 2000] present a model of auditory cortical organisation in non-human primates in which a primary ‘core’ field, located upon the lower bank of the transverse (Sylvian) sulcus, is encircled by non-primary belt fields and on the lateral aspect by parabelt fields. In Figure 1, core regions are shown in white, belt regions are shaded light grey and parabelt regions are shaded darker grey. The core has a highly granular and densely myelinated appearance and is highly metabolically active. The core receives ascending inputs from the ventral medial geniculate body and projects to ipsilateral and contralateral core areas, as well as to adjacent belt areas. Neurons in the core respond well and with short latencies to pure tones, with narrow frequency tuning at their characteristic frequency [Rauschecker et al., 1995; 1997]. Neurons with a similar characteristic frequency are arranged in rows that are organised along a frequency gradient [e.g., Merzenich and Brugge, 1973]. Three distinguishable frequency gradients have been reported in the core region of the macaque monkey. These subdivisions are referred to as A1 (primary area), R (rostral area) and RT

(rostrotemporal area). A1 and R share a common low-frequency border, and R and RT may share a high-frequency border [Morel et al., 1993]; see Figure 1.

** Figure 1 **

The surrounding belt region includes 7 or 8 non-primary fields. Relative to the core, belt areas have reduced cell density and columnar spacing, larger pyramidal cells and less dense myelination. Each belt field receives major inputs from the adjacent core field and from the dorsal and medial divisions of the medial geniculate body. Belt neurons respond less well to pure tones, but sufficiently to indicate tonotopic gradients [Kosaki et al. 1997; Rauschecker et al., 1995; Merzenich and Brugge, 1973]. Neurons in the belt region generally have broader frequency tuning than those in the core [Kosaki et al., 1997; Recanzone et al., 2000]. Neurons in belt have more complex receptive field properties than those in the core, probably reflecting integration over convergent inputs. For example, in the lateral belt region, neurons respond vigorously to spectrally complex stimuli such as vocalisations [e.g., Rauschecker et al., 1995; Rauschecker and Tian, 2000; Tian et al., 2001].

The parabelt receives afferents largely from neurons in the belt [Hackett et al., 1998; Kaas & Hackett, 2000], but it also receives projections from dorsal and medial divisions of the medial geniculate nucleus. The physiological characteristics of the parabelt are not established and subdivisions are not obvious using architectonic markers. Rather, the definition of parabelt borders is made on the basis of differences in cortico-cortical connectivity [e.g., Kaas and Hackett, 2000], with rostral (anterior) parabelt receiving afferents from anterior belt areas and projecting anteriorly to multiple sites within the temporal lobe and into ventrolateral frontal cortex, and caudal (posterior) parabelt receiving input from posterior belt, and projecting posteriorly and dorsally into the temporoparietal junction and dorsolateral prefrontal cortex [Hackett, et al. l999; Romanski et al., 1999; Kaas & Hackett, 2000]. Belt areas project to the same areas as do their adjacent parabelt areas. Nevertheless, the hierarchical organization suggests at least three levels of processing within primate auditory cortex.

Organisation of primary auditory cortex in humans

The extent to which the primate scheme generalises to humans is not established, and comparisons will undoubtedly be limited by phylogenetic differences

in brain organisation. There are some limitations in directly applying the same methodology used in primate research to human research. For example, not all histochemical markers used for identifying auditory fields in the macaque brain are equally useful for the human brain [Kaas and Hackett, 2000] and so the combined use of cyto- and myelo-architectonic and histochemical markers are required to provide a more reliable determination of anatomical borders. In addition, human tissue is difficult to obtain, is usually acquired after a variable postmortem delay, is generally from elderly people and thus shows tissue degeneration (including metabolic and cytochemical changes) characteristic of normal ageing. Electrophysiological studies of human auditory cortex are rare, since they can only be performed in individuals undergoing invasive evaluation or surgical treatment of focal neurological disease [Howard et al., 1996]. Connectivity analyses are still extremely difficult, although magnetic resonance (MR) techniques, such as diffusion tensor imaging, are developing rapidly [e.g., Poupon et al., 1999]. Despite these methodological constraints some progress has been made to identify the organisation of human auditory cortex, but establishing correspondences with the primate work is difficult [Hackett, 2001; 2002].

In humans, the primary auditory field has a distinctly dense cytochrome oxidase staining in layer IV [Rivier and Clarke, 1997; Clarke and Rivier, 1998], a high cell density, especially in layers II-IV, and relatively thick layers V and VI [Galaburda and Sanides, 1980; Wallace et al., 2002]. Generally speaking, the architectonic classification of primary auditory cortex overlaps substantially with the location of the anterior transverse temporal gyrus of Heschl (HG). The transverse temporal gyrus (or gyri; many individuals have more than one) are located on the plane of the superior temporal gyrus (STG) within the Sylvian fissure. Specifically, the primary area is an elongated field that overlaps with approximately two-thirds of HG (or the anteriormost HG when more than one is present) [Rademacher et al., 2001]. Like the morphology of HG itself [e.g., Campain and Minckler, 1976; Leonard et al., 1998; Penhune et al., 1996], the position and extent of the primary field with respect to the gross morphology of the auditory region is variable across individuals [Hackett et al., 2001; Rademacher et al., 2001]. A recent study has quantified the inter-subject variability by detailing the relationship between structural landmarks and the cytoarchitectonic boundaries of the primary field in 27 human brains [Morosan et

al., 2001; Rademacher et al., 2001; see Figure 2 for a depiction of a subset of these data]. The primary field did not extend to the lateral convexity of the STG, but often extended beyond HG anteriorly and posteriorly into the bordering sulci and onto the walls of the neighbouring gyri (although it did not extend to the crown of adjacent gyri). Furthermore, although the volumes of HG and the primary field differed substantially across individuals, they were not correlated with each other. Studies using implanted electrodes in surgical patients confirm the localization of primary auditory cortex in humans to HG, particularly its middle part [Howard et al., 1996; Liegeois-Chauvel et al., 1991]. Evoked potentials from this recording site typically have a short latency and sharp frequency tuning, with an orderly frequency progression.

** Figure 2 **

Rivier and Clarke [1997] defined a single primary field on HG in 10 hemispheres. However, the primary field is not uniform cytoarchitectonically. For example, Clarke and Rivier [1998] have reported bands of cytochrome oxidase and acetylcholinesterase staining parallel to the long axis of HG. In some studies, architectonic criteria have been used to subdivide the primary region. By staining 6 hemispheres for cyto- and myelo-architecture, Galaburda and Sanides [1980] distinguished medial and lateral fields, while Morosan et al. [2001] identified three fields in 20 hemispheres, using a marker for cyto-architecture. In both studies, boundaries were perpendicular to the long axis of HG. Wallace et al. [2002] used cyto- and myelo-architectonic and histochemical markers in 8 hemispheres to identify two parallel strips of primary-like tissue, one strip on HG and one immediately posterior to it (Figure 3). Thus, Wallace identified a boundary between primary fields that was parallel to the long axis of HG. In addition, Wallace et al. [2002] defined a belt area, the anterolateral area (ALA), located in the lateral third of HG, that partly coincided with the most lateral subdivision of the primary field in the Morosan et al. [2001] parcellation. Unlike the primary field, ALA lacked the clear band of high metabolic activity (identified by a cytochrome oxidase marker) in layer IV. Thus, it is uncertain whether the most lateral primary field identified by Morosan et al. [2001] is indeed a primary field or represents a transitional zone. Hackett et al. [2001] have also suggested that the anatomical characteristics of the most medial zone in Morosan's scheme may correspond most closely to the caudomedial field (CM) in macaques and chimpanzees - a subdivision of the belt region.

In summary, the morphology of HG provides a reasonable guide to the location of the primary field, being on the middle two-thirds of the anterior-most HG and bordered anteriorly and posteriorly by visible sulci. However, the number and location of subdivisions within the field are uncertain.

** Figure 3 **

Organisation of non-primary auditory cortex in humans

Homologies of the belt and parabelt subdivisions defined in the macaque have not yet been ascertained in the human brain and so we simply refer to areas surrounding the primary auditory cortex as non-primary auditory cortex. In humans, the non-primary auditory cortex extends across the undulating surface of the supratemporal plane into the insula [Rivier and Clarke, 1997] and the frontal and parietal operculum [Galaburda and Sanides, 1980]. Using morphological criteria, much of this non-primary region has been segregated into planum polare (anterior to HG) and planum temporale (posterior to HG), but borders are not clearly and uncontroversially defined [see Westbury et al., 1999]. Planum polare and planum temporale are classical terms and have no apparent architectonic or functional analogues.

Architectonic parcellations of human auditory cortex identify multiple non-primary auditory fields surrounding the primary auditory area [Brodmann 1909; Galaburda & Sanides, 1980; Rademacher et al., 1993; 2001, Hackett et al., 2001; Rivier & Clarke, 1997; von Economo and Koskinas, 1925; Wallace et al., 2002]. Galaburda and Sanides [1980] described a pattern of non-primary cytoarchitecture similar to that in the macaque and rhesus monkey in terms of a transitional zone (belt cortex) surrounded by association (parabelt) zone that has a large pyramidal layer III and granular layer IV and a distinct radial columns from layer VI to layer II. Using a range of markers, at least six non-primary fields have been distinguished to date in humans [Rivier & Clarke, 1997; Wallace et al., 2002]. Figure 3 depicts the spatial layout of human non-primary auditory fields across the superior surface of the STG. At least two fields (the anterior area, AA and the medial area, MA) are located on the planum polare immediately anterior to HG, two (the lateral area, LA and the posterior area, PA) on the planum temporale just posterior to HG, one (ALA) on the lateral third of HG and one (the superior temporal area, STA) on the posterior lateral convexity of the STG.

There is little information about the connectivity of non-primary regions. Howard et al. [2000] have employed a functional technique to measure cortico-cortical connections between HG and a posterolateral superior temporal area, which might correspond to STA. They measured by evoked potentials recorded from two sets of electrodes implanted in humans undergoing surgery for medically intractable epilepsy. Recordings from the electrode arrays indicated that HG and putative STA differed in their sensitivity to anaesthesia and to changes in the rate of stimulus presentation suggesting that the areas are functionally distinct. Direct electrical stimulation of HG resulted in short-latency evoked potentials in posterolateral STG, indicating that it receives cortico-cortical input either directly or indirectly from HG. Tardif and Clarke [2001] report preliminary results using injections of a lipophilic antero- and retro-grade tracer at 30 points throughout the auditory cortex in four human brains. Within the primary field and adjacent non-primary fields LA and MA, the tracer spread less than 2.5 mm from the injection perimeter. Wider axonal connectivity patterns, indicated by projections up to 7 mm, were found in other non-primary fields (notably PA and AA). In summary, human auditory cortex comprises at least six non-primary fields that probably receive input from the primary field and have more widespread projections to surrounding fields.

MAPPING AUDITORY CORTICAL FUNCTION IN HUMANS

One of the key research aims in human auditory neuroimaging is to seek evidence for the anatomical and physiological systems known from studies in other animals (particularly primates). From animal research, we know that the peripheral auditory system represents a number of features of the sound stimulus, such as its distribution across the frequency spectrum and the energy of each frequency component. Dynamic variations in spectrum, sound level, spatial position and motion of a sound source are characteristic of all real-world sounds, and influence the activity patterns within the auditory system.

In humans, fMRI and PET have been widely used to study the patterns of brain activation associated with processing these sound features. The poor temporal resolution of these techniques has resulted in an emphasis on the spatial extent, magnitude and topographical distribution of brain activation. On the other hand, EEG and MEG have been used to map the cortical topography at prominent periods in the

temporal pattern. For example, a steep increase in the magnetic field at around 20 ms can be traced to the primary auditory cortex [Lütkenhöner et al., 2002]. The general approach is to average neuroimaging data across subjects to provide a general description of the links between structure and function. Individual differences are observed in the activation patterns, but it is not possible to know to what degree this reflects inter-subject variability in functional organisation or in anatomical structure (such as cytoarchitecture). Given that it is not yet possible to map anatomical structure in vivo in humans, researchers can, at best, parcellate the auditory cortex according to its functional characteristics with reference to key morphological landmarks.

Sound frequency

Frequency is the prime organising feature throughout the auditory pathway. Within the mammalian auditory cortex, core and some belt fields show a tonotopic organisation. In humans, tonotopy has been sought using a variety of imaging methods. Electrophysiology has provided the most direct demonstration of a frequency gradient along HG. Using electrodes implanted in epileptic patients to detect the foci of seizures, a lateral progression in frequency sensitivity from high frequency (3360 Hz) to lower frequency (1480 Hz) has been found [Howard et al., 1996]. Using MEG and EEG, a systematic relationship has been shown between dipole sources and stimulus frequency in the auditory cortex [e.g., Romani et al., 1982a, 1982b; Pantev et al., 1988, 1995; Yamamoto et al., 1992; Huotilainen et al., 1995; Lütkenhöner and Steinsträter, 1998; Rosburg et al., 2000]. Lütkenhöner and Steinsträter [1998] demonstrated a lateral shift in the location of the response within HG as tone frequency was presented at steps of 2000, 1000, 500 and 250 Hz. More recently, Lütkenhöner et al. [2001] claim that the single medial-lateral tonotopic arrangement of dipole sources places too simplistic an interpretation on the data. The auditory evoked field represents a complicated spatial pattern that changes over time and dipole locations are also partly dependent on the stimulation paradigm and filtering techniques used.

** Figure 4 **

Two PET studies have reported more laterally located auditory activation by a 500-Hz tone than by a 4000-Hz tone [Lauter et al., 1985; Lockwood et al., 1999]. However, the precise locations cannot be determined due to the low resolution of the technique. FMRI has also revealed spatially separate responses to high and low

frequency tones [Bilecen et al., 1998; Wessinger et al., 1997]. A detailed fMRI investigation of frequency organisation has revealed multiple tonotopic fields encompassing both HG and surrounding fields on the STG in 6 individual listeners [Talavage et al., 2000]. Within each field, differential responses were elicited to a variety of low- and high-frequency signals including pure tones, instrumental music, and amplitude-modulated (AM) tones. Broadband signals were bandpassed and had at least a 2-octave wide frequency separation between low- and high-frequency conditions so that the spectral separation would be detectable at the resolution of fMRI. By directly contrasting high- and low-frequency stimulation, eight frequency-dependent areas (4 low and 4 high) were identified. These areas were arranged in a consistent position relative to one another and to anatomical landmarks, and all four were observed in at least six of the eight datasets. Although the direction of frequency gradients joining high and low areas could not be ascertained in this study, it does suggest that there might be at least 4 tonotopic areas on the STG in humans. The location of the frequency-dependent areas was determined by overlaying the individual functional map onto a high-resolution anatomical image for that subject. The location of each focus was defined according to its position relative to particular anatomical landmarks. An example of such functional localisation is shown in Figure 4. A low-frequency fMRI focus was seen on the superior crown of HG – a position that was roughly two-thirds of the length of HG from its medial root and two neighbouring high-frequency foci were found; one anteriorly near the first transverse temporal sulcus and another posteriorly near Heschl's sulcus. The low-frequency fMRI focus may indicate a region where two tonotopic maps abut at their low isofrequency contours. Given that the core areas, A1 and R, in the macaque also share a low-frequency border, the tonotopic arrangement in humans could possibly be a homologue of these core fields. However, an alternative proposal by Schönwiesner et al. [2002] posits that these foci correspond to different auditory fields rather than to endpoints of tonotopic gradients. Thus, a consensus has yet to emerge about the spatial representation of frequency within human auditory cortex. The design of neuroimaging studies may not yet be adequate to resolve tonotopicity in the human auditory cortex. For example, studies have not probed the full range of human hearing, nor have fMRI studies done this in the absence of the background scanner noise (which has peaks of acoustic energy that overlap with the test frequencies). Another consideration is the broad frequency tuning of cortical neurones at higher

sounds levels. The presentation levels used in neuroimaging studies are well above threshold, thus any tonotopic relationship is likely to be spread at these higher intensities.

** Figure 5 **

Bandwidth

Whereas single-frequency tones may activate focal areas within an auditory field, broadband sounds should activate larger neuronal populations, particularly within those non-primary auditory areas that correspond to belt cortex [Rauschecker et al., 1995; Rauschecker, 1998]. Using fMRI, Wessinger et al. [2001] contrasted responses to single-frequency tones at 0.5, 2 or 8 kHz with one-octave wide, bandpassed noise at the same centre frequencies. Bandpassed noise clearly generated more widespread activation than did the single-frequency tones (Figure 5). Hall et al. [2002] also reported greater activation beyond HG when activation by a single-frequency tone was subtracted from that by a harmonic-complex tone of the same pitch (Figure 6). An attractive parsimonious interpretation, consistent with electrophysiological predictions, is that the single-frequency tone activation indicates the core field, while the broadband sound activation indicates surrounding belt and parabelt fields. However, this view is unlikely to provide an accurate method for distinguishing anatomical areas because the borders were determined by simple statistical criteria, applied to smoothed functional image data. Spatial smoothing makes ‘true’ tissue boundaries of activation impossible to judge since smoothing smears activation over an area that can exceed that which is physiologically responsive. The extent of the smearing effect is proportional to the magnitude of the activation peak and hence, probability thresholding defines a region of activation whose size is highly correlated with the height of the peak at the activation centre. Activation maps only define functional areas approximately and do not provide precise information about either their shape or size. For instance, activation by the single-frequency tones in these two studies did not consistently reach the significance threshold in all subjects and hence yielded either an absent or a small “core” field, which is physiologically unlikely.

** Figure 6 **

Pitch

The pitch of a sound is determined by its periodicity or the rate of fluctuation of the envelope of the sound waveform. The pitch of a complex sound can arise from temporal autocorrelation, for example, by taking a random noise, delaying it by a few milliseconds, and adding it to itself. As this delay-and-add process is repeated, the sound maintains its noise-like spectrum, but comes to have a pitch with a frequency at the inverse of the delay time [Yost et al., 1996; Patterson et al., 1996]. When high-pass filtered at frequencies of 500 Hz or above, delay-and-add noise effectively excites all frequency channels in the same way as random noise, with no resolved spectral peaks. Thus, the perception of pitch elicited by these stimuli must rely on extraction of regular time intervals of a few milliseconds, rather than extraction of any prominent spectral features. Recent PET and fMRI studies have used this manipulation to reveal that the extraction of pitch based on temporal cues recruits auditory cortex on HG bilaterally [Griffiths et al., 1998; 2001; Patterson et al., 2002 data, see Figure 7]. In these studies, listeners were presented with random noise bursts, a series of sounds with a fixed pitch, and a series of sounds with a pitch excursion between successive items. Sounds with a pitch generated greater activation than did the random noise within a confined region on HG (shown in red in Figure 7), in an area most likely corresponding with ALA. Moreover, Griffiths et al. [1998] demonstrated that activity within HG increased with the temporal regularity of the stimulus (and hence the strength of the pitch). Thus, pitch extraction based on temporal cues may engage parts of HG.

** Figure 7 **

Sound level

PET and fMRI studies have reported systematic changes in activation of the auditory cortex with changing sound level [e.g., Millen et al., 1995; Strainer et al., 1997; Jäncke et al., 1998; Lockwood et al., 1999; Mohr et al., 1999; Hall et al., 2001; Hart et al., 2002; Brechmann et al., 2002]. There is lack of a clear consensus on the exact pattern of the increase in activation; some studies report a systematic increase in both extent and magnitude of activation [Lockwood et al., 1999; Brechmann et al., 2002], whereas others report an increase only in extent [Jäncke et al., 1998] or only in magnitude [Mohr et al., 1999]. The inconsistency between extent and magnitude is

surprising given that these measures are highly correlated for spatially smoothed image data. At least some of these inconsistencies may be due to the narrow and different ranges of sound levels presented. Only two fMRI studies have investigated the differential sensitivity to sound level across subregions of the auditory cortex. Brechmann et al. [2002] found that, out of four different regions of the human auditory cortex, area T1b showed the most robust increase with sound level. T1b includes primary auditory cortex on HG, as well as the lateral part of HG which is likely to be a non-primary auditory field (possibly ALA). Hart et al. [2002] estimated the border between these two parts of T1b, and revealed that the putative location of primary auditory cortex was more sensitive to sound level (see Figure 8).

** Figure 8 **

EEG recordings show that the amplitude of the main response progressively increases with sound level [Rapin, 1966; Beagely et al., 1967]. These findings are consistent with the increase in activation measured by neuroimaging studies, although the dipole merely represents the centre of activity, and does not determine the spatial extent of a source. Using MEG, Gutschalk et al. [2002] have shown that modelling their data using two sources fitted the data more accurately than a single source. A source posterior to HG, on the border between HG and planum temporale, exhibited an increase in response amplitude as the stimulus sound level was increased. It is possible that the posterior source corresponds to the fMRI activation in T1b [Brechmann et al., 2002].

Temporal variation in sound

Communication signals and other everyday sounds change in frequency and amplitude on a moment-to-moment basis. Convenient stimuli for studying the effect of changing the temporal characteristics of sounds are frequency and amplitude sinusoidally modulated tones: these are well-controlled stimuli in which the temporal characteristics are determined by the modulating waveform. Neuroimaging has been used to determine which brain areas are involved in processing spectrotemporal patterns in sound. Imaging has also been used to localise those brain regions involved in processing dynamic spectrotemporal changes happening over a longer timescale.

fMRI studies have investigated brain responses to sounds that are sinusoidally modulated in frequency [Hall et al., 2002] and in amplitude [Giraud et al., 2000], by contrasting them against their unmodulated counterparts. Hall et al. [2002] reported a

significant effect of 5-Hz frequency modulation in bilateral HG, and the anterolateral and posterolateral parts of STG, for both single-frequency and harmonic-complex carrier tones. These regions of differential activation are shown in pink in Figure 6. The posterolateral STG region displayed an especially high response to the FM harmonic-complex tone. Giraud et al. [2000] also reported a significant effect of amplitude modulation in bilateral primary and non-primary areas, strongest in the posterolateral regions of the STG. This study used a white noise carrier modulated at rates between 4 and 256 Hz. There is little neuroimaging evidence for any segregation between amplitude and frequency modulation processing because fMRI studies have favoured the use of a sequence of pulsed tone bursts, thus incorporating AM components within the FM stimulus [e.g. Binder et al., 2000; Hall et al., 2002]. Mäkelä et al. [1987] investigated the issue of separate processing channels by measuring auditory cortical evoked magnetic fields to each type of modulation, presented in four pair-wise combinations (FM-AM, FM-FM, AM-FM, AM-AM). The N100 component of the response to the second stimulus was generally smaller than to the first, indicative of shared neuronal processing. However, the N100 attenuation was significantly smaller when the second stimulus was different to the first (e.g. AM-FM) suggesting that the encoding of AM and FM, do not involve identical neuronal populations. Source localisation of the MEG signals for AM and FM tones revealed no systematic differences across the STG, consistent with the hypothesis that the activated populations partly overlapped or were interdigitated; or that the coding differences occurred at a more peripheral auditory site.

The effects of temporal variation have been investigated using other types of temporal manipulation. For example, Thivard et al. [2000] used synthetic sounds that were similar to vocal sounds in structure, with spectral maxima that were modulated in time. Relative to matched signals that had a stationary spectral profile, these spectrally varying sounds generated bilateral auditory cortical activation located posterior and lateral to HG. Binder et al. [2000] used sequences of single-frequency tones, presented at 1.5 tones per second, in which the frequency increased by at least 10 Hz between successive tones. This tone sequence produced greater activation in non-primary posterolateral areas than did an unmodulated white noise. Zatorre and Belin [2001] independently manipulated the frequency and timing information in sequences of single-frequency tones. Spectral variation involved tone sequences in

which the frequency separation was stepped at a range from 1 octave to 1/32 octaves, but with a fixed rate of change between tones. Temporal variation involved tone sequences that varied in the rate of change (from 1.5 Hz to 48 Hz) between two fixed frequencies. This parametric study is conceptually different from the studies of Giraud et al. [2000], Hall et al. [2002] and Thivard et al. [2000] because the activation by each type of modulated sound was assessed by comparing them with each other, not by contrasting each against their unmodulated control. A greater response to spectral changes (compared to temporal changes) was found in bilateral non-primary auditory areas, but in anterior, not posterior, STG. Griffiths et al. [1998; 2001; Patterson et al., 2002] contrasted a sequence of sounds with a fixed pitch, with a sequence of sounds in which the pitch changed from burst to burst to create a melodic pitch sequence. In the fMRI study, relative to the fixed-pitch stimuli, the melodic pitch sequence generated a greater response at the lateral-most extremity of HG and on the convexity of the STG in the right hemisphere [Patterson et al., 2002]; see the green activated regions in Figure 7. In the PET study, an effect of the pitch melody was found in both anterior and posterior non-primary auditory areas [Griffiths et al., 1998]. The results from these many different studies converge on the importance of non-primary auditory cortex, particularly the posterolateral region of the STG, in the analysis of spectrotemporal patterns in sound. The center of activity moves anterolaterally away from HG as the processing of melodic sounds proceeds.

Spatial attributes of sound: motion and location

Three cues contribute to the perception of sound source location and motion. First, monaural spectral cues are important for vertical location and for the discrimination of front from back. Second, a difference in the level of the sound reaching the two ears is used to localise high-frequency sounds (>2-3 kHz). Third, a difference in the arrival time of the sound at the two ears is used to localise low-frequency sounds (<1-2 kHz). Sound movement is signalled by continuous temporal variation of these cues.

Sound motion When compared with a silent baseline, moving sounds produce bilateral activation in primary and nonprimary regions of the auditory cortex [Bremmer, 2001; Lewis, 2000], as do stationary sounds. Thus, when activation by stationary sounds is subtracted from that by moving sounds, often the difference in the auditory cortex does not reach significance. However, by using a low-noise imaging sequence,

Baumgart et al. [1999] have identified a lateral area in the right planum temporale that was more activated by a moving than by a stationary sound. Warren et al. [2002] have also reported bilateral activation in planum temporale for moving versus stationary sounds; see Figure 9.

** Figure 9 **

Using MEG, responses to both moving and stationary tones can be fitted using dipole sources in bilateral auditory cortex, but only moving sounds are best fitted with an additional source located in the right parietal cortex [Xiang et al., 2002]. An EEG study directly comparing auditory location and motion perception has revealed a divergent topography between motion discrimination and spatial localisation [DuCommun et al., 2002], with moving sounds specifically involving the right parietal cortex, at about 300 and 750 ms after stimulus offset. The evoked responses thus suggest partly segregated networks for auditory location and motion processing.

Numerous PET and fMRI studies have revealed selective activation by sound motion in the inferior and/or superior parietal regions [Griffiths et al., 1998; 2000; Griffiths and Green, 1999; Warren et al., 2002]. Griffiths et al. [1998] mapped the response to the same moving sounds using both PET and fMRI techniques. The moving sound was a binaural 500-Hz tone in which congruent inter-aural level and time differences created the percept of auditory motion. Compared with a stationary sound, in which these binaural cues were present but cancelled one another out, both PET and fMRI revealed activation in the right superior parietal cortex. The fMRI study identified additional areas of activation in the right insula, bilaterally in premotor cortex and inferior parietal cortex, and in left superior parietal cortex [see also Griffiths et al., 2000]. Griffiths speculated that the recruitment of additional activation in the fMRI study could arise from the background MR scanner noise adding a requirement for auditory streaming. Indeed, there were fewer differences between the networks identified by PET and fMRI when a sparse imaging sequence [Hall et al., 1999] was employed to reduce the interference of the scanner noise on stimulus perception during the fMRI [Warren et al., 2002].

Sound localisation At least part of the inferior parietal lobule, particularly in the right hemisphere, appears to be involved in sound localisation. For example, parietal cortex was more activated by a sound localisation task than by either a frequency discrimination task [Alain et al., 2001; Weeks et al., 1999] or a sound identification task [Maeder et al., 2001]. Compared with midline reference sounds, deviant

lateralised sounds generated MEG signals in right posterior parietotemporal areas [Kaiser et al., 2000]. This evidence supports the notion that information about sound location is separate from that of non-spatial acoustic cues and that the former may be projected along a posterior auditory route [e.g., Rauschecker & Tian, 2000].

The results do not provide a completely consistent pattern across studies, but generally speaking, processing the spatial properties of sound involves a network of non-primary posterior auditory cortex and inferior parietal lobule bilaterally and superior parietal cortex, greater in the right hemisphere.

HAS NEUROIMAGING BEEN SUCCESSFUL IN CONFIRMING PHYSIOLOGICAL FEATURES ?

Although the population of neurones sensitive to specific sound features may in some cases be lower than the spatial resolution of the haemodynamic response, PET and fMRI techniques have been able to show evidence for gross functional distinctions across the STG. Neuroimaging techniques have been used to demonstrate the cortical representation of frequency, pitch, bandwidth, spectrotemporal modulation and sound location and motion. The arrangement of functional responses to these sound properties has been mapped across different auditory cortical fields in human auditory cortex and a consistent topography is becoming apparent. The primary auditory cortex, located on medial HG, is more involved than non-primary auditory areas in processing basic sound properties, such as frequency and sound level. Multiple frequency gradients have been reported in the auditory cortex of primates and other animals, these being most clearly demonstrated in the primary fields. In humans, neuroimaging evidence indicates that the primary auditory cortex may contain at least one pair of mirror-reversed frequency gradients, suggesting functional subdivisions within this region. Evidence also suggests that several surrounding non-primary auditory fields are tonotopically arranged, but the number and orientation of these frequency gradients are unknown. Sounds with a broad frequency spectrum activate widespread regions of the supratemporal plane extending from HG across the planum polare and planum temporale. By analogy with what is known in primates, this pattern may reflect the broader frequency tuning of neurons in non-primary auditory fields. In humans, the planum temporale has been described as a “computational hub” involved in processing many types of sound that have more

complex spectrotemporal patterns than do single-frequency tones [Griffiths and Warren, 2002]. Indeed, it is observed that no matter what spectrotemporal sound pattern is presented, when activation is contrasted with a silent baseline condition, the pattern of activation often resembles a “crescent shape” involving HG and adjacent parts of the planum temporale. Within the planum temporale, a broad distinction can be made between the localisation of activation by moving sounds from that by modulated sounds perceived ‘in the middle of the head’; i.e., with no dynamic spatial component. Both types of sounds engage the planum temporale, but modulated sounds specifically involve a more lateral subdivision. This broadly supports the theory, derived from primate neurophysiology, of two parallel auditory cortical pathways; one recruiting posterolateral areas, involved in sound localisation, and one recruiting anterolateral areas, involved in the analysis of spectral and temporal features of sounds and auditory recognition [e.g., Kaas and Hackett, 2000; Rauschecker, 1998 Rauschecker and Tian, 2000; Tian et al., 2001; Romanski and Goldman-Rakic, 2002]. While a gross outline of the functional organisation is emerging, we still have a relatively poor understanding of the fine-grained subdivisions within non-primary auditory cortex. For example, it is not known what are the functionally specialised roles of the multiple non-primary fields that have been identified by anatomical techniques.

There are a number of explanations for why it has been so difficult to map functional specialization in the auditory cortex. In discussing these issues, we look to the physiological response characteristics, cortical anatomy, neuroimaging methodology and analysis. First, the anatomical organization of human auditory cortex is uncertain and the homologies with non-human primates, such as the macaque, are poorly understood. Without the necessary framework provided by the anatomy, it is difficult to interpret rich and complex neuroimaging datasets. Second, the auditory stimuli typically presented in cortical studies may not be optimal for eliciting the strongest or the most area-specific responses. Pure tones generally elicit weak activation relative to rest in fMRI and PET [e.g., Wessinger et al., 2001]. Where tonotopy has been demonstrated, investigators have used stimuli with broad frequency spectra, or time-varying components, which generate more robust patterns of activation [see Harms and Melcher, 2002]. However, the precise mapping of tonotopy might be blurred by using sounds that activate widespread regions of cortex, not all of

which will play a role in sound frequency encoding. The issue of stimulus attributes is also important for MEG. For example, Lütkenhöner et al. [2001] report that the type of acoustic stimulus influences the source location of MEG-based tonotopic maps. Third, intense acoustic noise, often exceeding 110 dB SPL, is generated by gradient coil vibration during fMRI [Foster et al., 2000]. The noise has dominant spectral peaks at frequencies up to 3000 Hz. Unless steps are taken to reduce scanner noise, it affects the pattern of brain activation that is measured within the auditory cortex and can mask the perception of stimuli whose frequencies overlap with the spectral peaks in the background noise. The confounding effects of the background noise can be reduced by using a sequence which acquires each brain slice more slowly thereby generating lower levels of noise [e.g., Baumgart et al., 1999]. Alternatively, one can interleave rapid image acquisition with a period of silence [e.g., Hall et al., 1999]. Researchers now more routinely implement variants of these protocols for better reliability in mapping stimulus-dependent responses in auditory cortex. Fourth, the highly convoluted surface of the superior temporal gyrus makes it difficult to segregate the different tonotopic fields in 3-dimensional space. In some circumstances, cortical flattening may help in the visualization of functional maps, but may distort the absolute sizes of cortical fields. Fifth, spatial smoothing of images blurs activation across adjacent (possibly differentially specialized) anatomical fields, and the extent of the blurring is proportional not only to the spatial width of the filter applied, but also to the peak magnitude of the response. Spatial blurring is especially problematic for PET data which have a poorer intrinsic spatial resolution than fMRI and require averaging across multiple subjects [e.g., Lauter et al., 1985; Lockwood et al., 1999]. The type of frequency filtering applied to MEG data also affects the source locations [Lütkenhöner et al., 2001]. Sixth, for tonotopic mapping, PET and fMRI analyses have reported only one or two maximal responses to each frequency, instead of numerous local maxima as might be expected given the multiple tonotopically organized areas observed in macaques and other primates [e.g., Lockwood et al., 1999]. This limitation is also true for MEG, where the data are often modelled by a single equivalent-current dipole [see Lütkenhöner et al., 2001 for a review]. Some PET and fMRI analyses have also contrasted different stimulus conditions with a silent condition, rather than directly with one another [e.g., Alain et al., 2001; Bilecen et al., 1998; Wessinger et al., 1997]. Comparisons with a common baseline do not identify the locus of the greatest stimulus-dependent difference. Finally, one might

speculate whether or not the neural substrates of complex sound processing are actually organised into modules that are functionally and anatomically independent. As we have already highlighted, sound-induced activation often involves common areas of the auditory cortex, irrespective of the type of sounds used. These common areas include HG, the lateral tip of HG and a region posterolateral to HG on the planum temporale and may indicate the obligatory involvement of populations of neurons with general response properties.

CONCLUSIONS

One of the principle advantages of fMRI and PET techniques over other imaging methods, such as EEG and MEG, is their ability to localize changes in brain activity with an increasingly high degree of spatial resolution. However, new findings about the functional organisation of the auditory cortex, as demonstrated by functional neuroimaging, have not been wholly consistent; either with one another or with the neurophysiological literature for non-human primates. In this review, we have highlighted a number of limitations in the field; principally, the paucity of our current understanding of the architectonic organisation of the human and non-human primate auditory cortex, the large degree of individual variability, and the poor spatial separation of the representation of different acoustic cues. The evidence discussed in this review might imply that functional neuroimaging data have a limited use in robustly defining functional borders between auditory cortical fields However, neuroimaging is still in its infancy and is evolving rapidly. New techniques that offer better spatial and temporal resolution are on the horizon, particularly for fMRI. With current methods, progress might still be made by determining patterns of functional activation for individual subjects and by relating this to their individual cortical morphology. Not only could the data be more lightly spatially smoothed but perhaps also more precise links could be ascertained between individual structure and function. Further progress may be achieved with fMRI by measuring the temporal patterns of the response, as well as its spatial localisation. For example, rather than the cortical representation of different acoustic features being in the absolute presence or absence of activation in a particular area, it may involve subtle changes, in the magnitude or shape of the response. One of the challenges for neuroimaging is to

determine whether these other approaches to data analysis will prove to be informative.

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FIGURE LEGENDS

Figure 1. Dorsolateral view of the human and macaque cerebral cortex after removal of the overlying parietal cortex. This view exposes the ventral bank of the lateral sulcus and insular cortex and the superior surface of the STG, but the medial portions of the auditory cortex are not visible. The dashed line defines the portion of the cortex that has been cut away. In the human brain, the outline of HG is depicted in black, with the primary auditory cortex (in white) on the medial part of the gyrus. Surrounding non-primary regions on the lateral part of HG, the planum polare and planum temporale are shown in light grey. In the macaque brain, the approximate region of the core (in white), posterior and lateral portions of the belt (in light grey) and parabelt (in dark grey) regions are shown. Subfields (A1, R, RT) within the auditory core are denoted and high-frequency (H) and low-frequency (L) response regions indicate the orientation of the tonotopic gradients in these core fields. The estimated subdivisions within the belt and parabelt regions are shown. CS central sulcus; PAC primary auditory cortex; STS superior temporal sulcus; STG superior temporal gyrus. Macaque brain adapted from Hackett et al. (2001).

Figure 2. Probability map of cytoarchitectonically defined core region, Te1, from 10 brains superimposed on an axial slice of a single computerised reference brain. The outer blue contour represents 10% overlap (i.e. present in only 1 specimen), while the inner red contour represents 100% overlap (i.e. present in all 10 specimens) [Figure reproduced from Rademacher et al., 2001].

Figure 3. Multiple auditory areas on the superior surface of the temporal lobe of the left hemisphere in humans as described by Rivier and Clarke [1997] and Wallace et al. [2002]. Primary auditory cortex is shown in blue with the principal region being located on Heschl's gyrus, bounded posteriorly in Heschl's sulcus by a further primary-like field. HA (the first transverse temporal sulcus) marks the anterior border

to Heschl's gyrus, while H1S (Heschl's sulcus) marks the posterior border of Heschl's gyrus. A further primary-like field may lie within H1S. Surrounding the primary cortex, six putative non-primary areas have been identified on the basis of their laminar structure. These fields are shown in yellow.

Figure 4. A schematic interpretation of the relationship between frequency-dependent region and Heschl's gyrus reported by Talavage et al. [2000] for three subjects using a noise stimulus that has been amplitude modulated at 10 Hz. The top diagram shows a canonical coronal view of the brain indicating the location of Heschl's gyrus (HG) in the left hemisphere. The summary diagrams were obtained by outlining the individual's left HG and their activation map ($P<0.05$). The region on the superior aspect of HG (vertical stripes) showed greater activation by low than by high frequencies. The two regions inferomedial and inferolateral to this (horizontal stripes) showed greater activation by high than by low frequencies.

Figure 5. Axial slices for two subjects showing their individual auditory activation as a function of frequency spectrum [Wessinger et al., 2001]. Activation is plotted for all voxels exceeding $Z > 4.2$. Areas shown in blue represent activation by pure tones, yellow represents activation by bandpassed noise and green represents the overlap between the two activation patterns.

Figure 6. Regions of group activation ($P<0.05$ corrected for multiple comparisons) produced by two different types of auditory stimulation. Brain regions more activated by harmonic tones than by single tones are shown in yellow. Regions that were more activated by frequency-modulated tones than by static tones are shown in red. There are areas of overlap between the two activation maps where there is an additive (i.e. combined) response to both harmonicity and frequency modulation. Activation is overlaid onto the mean structural image and, for anatomical reference, the intersection of the crosshairs occurs within Heschl's gyrus at the voxel location x –54 mm, y –20 mm, z 4 mm. Axial, coronal and sagittal sections brain views are displayed through this point. Data are from Hall et al. [2002].

Figure 7. Group activation for three hierarchical comparisons using a fixed-effects model, rendered onto the average structural image of the group. The height threshold

for activation was t=5.00 (p<0.05 corrected for multiple comparisons). Greater activation to the random noise than to silence is shown in blue. Red shows greater activation by the fixed-pitch sound than by the noise. Green shows greater activation by the melodic pitch sequence than by the fixed-pitch sound. Activation is displayed on sagittal and axial slices at the point of intersection of the crosshairs and is superimposed on an average of the HG maps for the group (marked in white). The position and orientation of the activations are denoted by the whole brain images. Data are from Patterson et al. [2002].

Figure 8. The mean extent of activation for three auditory regions (primary, ALA and PT) as a function of sound level for a monaural 300-Hz tone. The locations and extents of the three regions were estimated from the literature [Rivier & Clarke, 1997; Wallace et al., 2002] with reference to gross morphological landmarks. These are overlaid on an outline of the mean structural image. Extent of activation is expressed as a percentage of the total number of voxels in the region. Solid black lines represent data for the hemisphere contralateral to the stimulated ear and dashed grey lines data for the ipsilateral hemisphere. Error bars represent 95% confidence intervals. Data plotted are taken from Hart et al. [2002].

Figure 9. Activation maps for motion sound conditions minus stationary sound conditions. Maps from two experiments have been rendered on coronal (top) and axial (bottom) sections of a canonical structural template. Axial sections have been tilted in the pitch plane to produce oblique axial views parallel to the supratemporal plane at the two levels A and B indicated on the coronal view. Insets indicate the relationship of activations to Heschl's gyrus (HG). Both the PET data (red) and fMRI group data (yellow) show that all activations in the supratemporal plane occur posterior to HG, in the planum temporale. Voxels conjointly activated by PET and fMRI experiments are indicated in orange. All voxels significant at the P<0.05 level (corrected for multiple comparisons) are shown. Figure taken from Warren et al. [2002].

Abbreviations

A1	primary area (primate core)
AA	anterior area
ALA	anterolateral area
HG	Heschl’s gyrus
LA	lateral area
MA	medial area
PA	posterior area
R	rostral area (primate core)
RT	rostrotemporal area (primate core)
STA	superior temporal area
STG	superior temporal gyrus
STP	supratemporal plane

Table

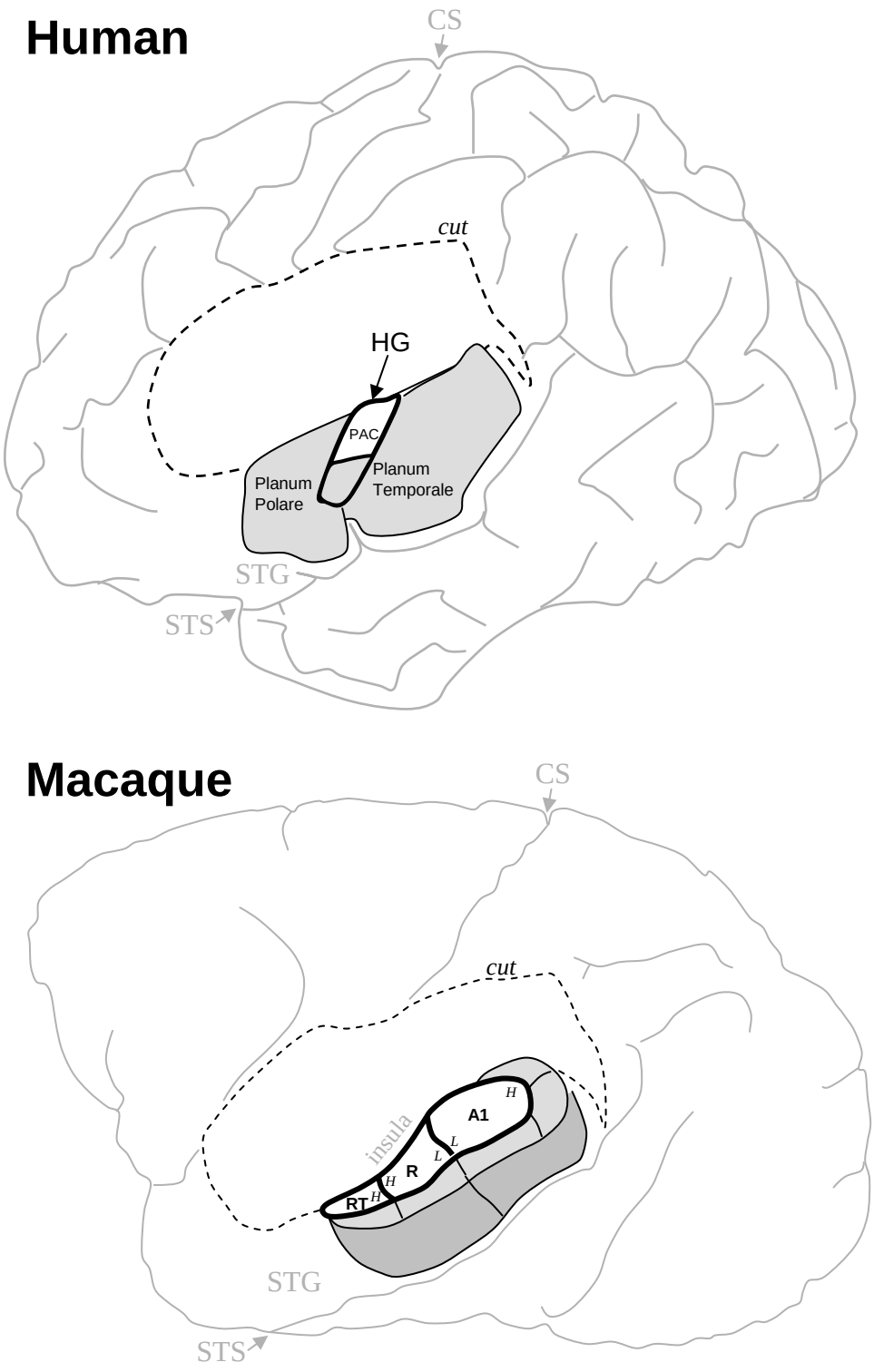
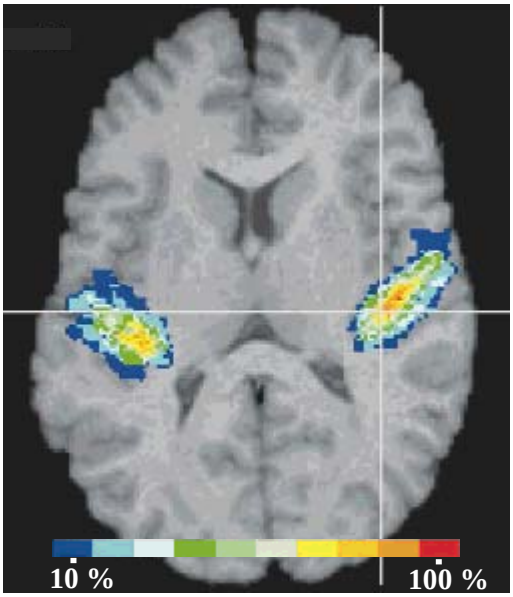

Human
CS
cut
HG
PAC
Planum
Temporale
Planum
Polare
STG
STS
Macaque
CS
cut
insula
A1
H
L
L
R
H
RT
H
STG
STS

Figure 1.



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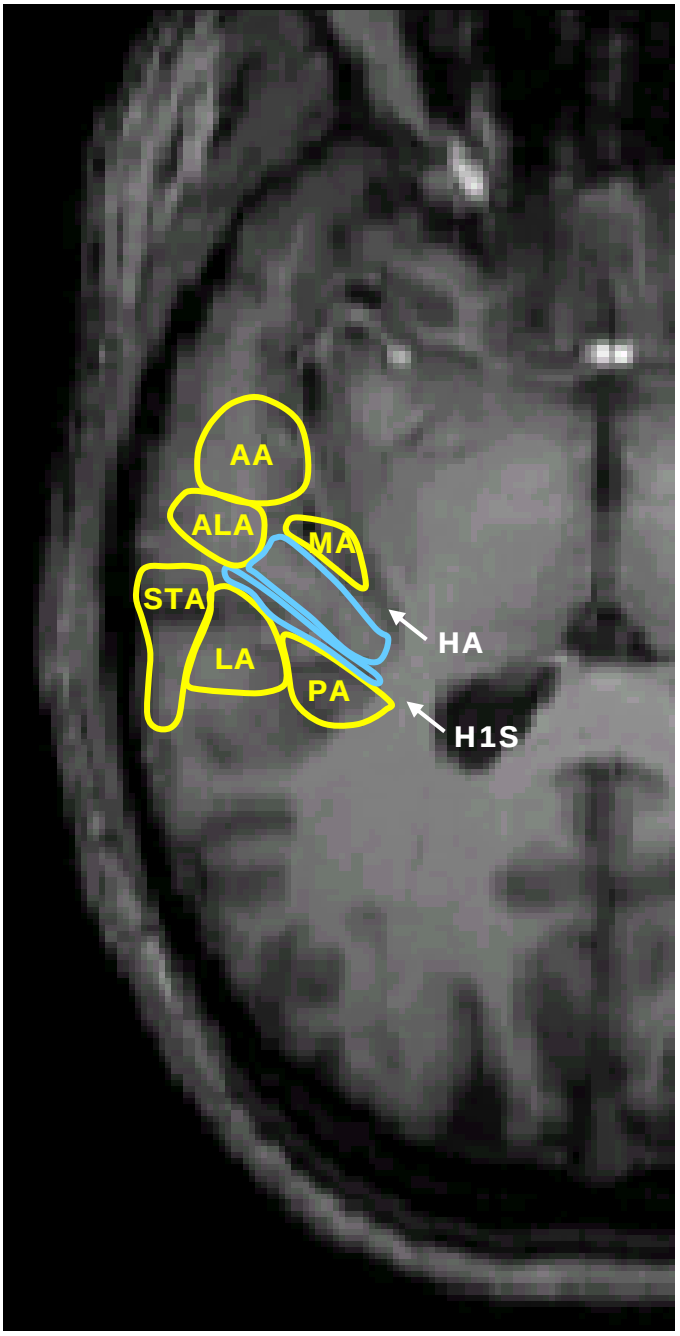

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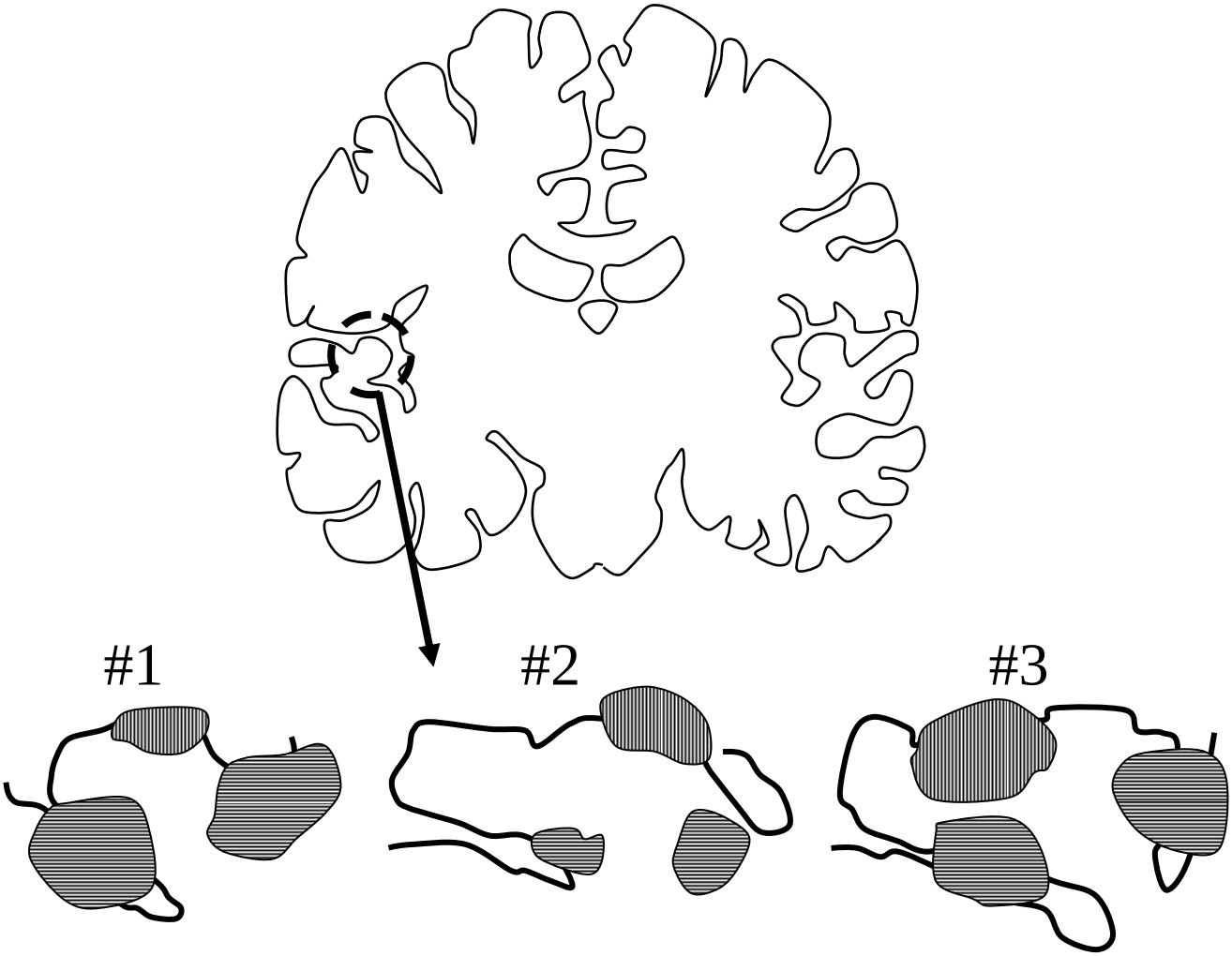

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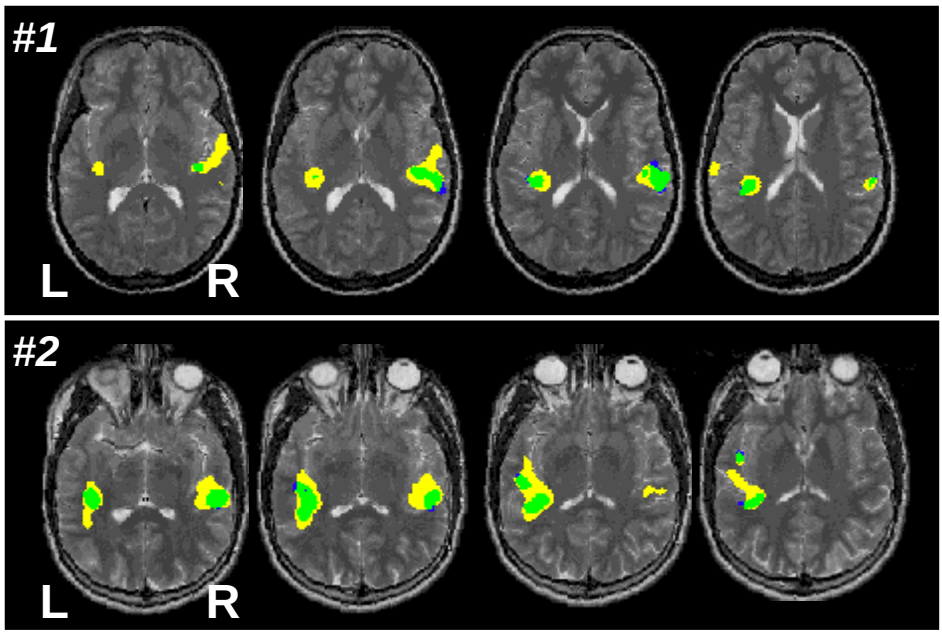

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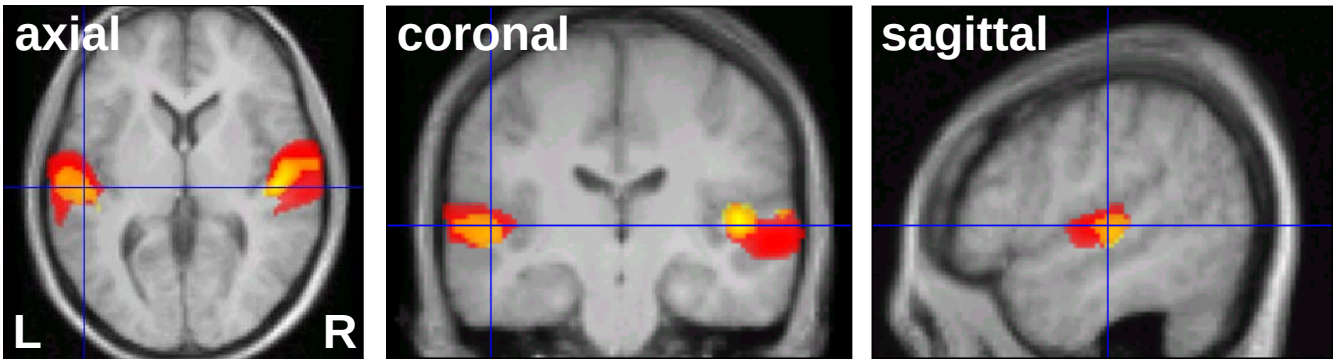

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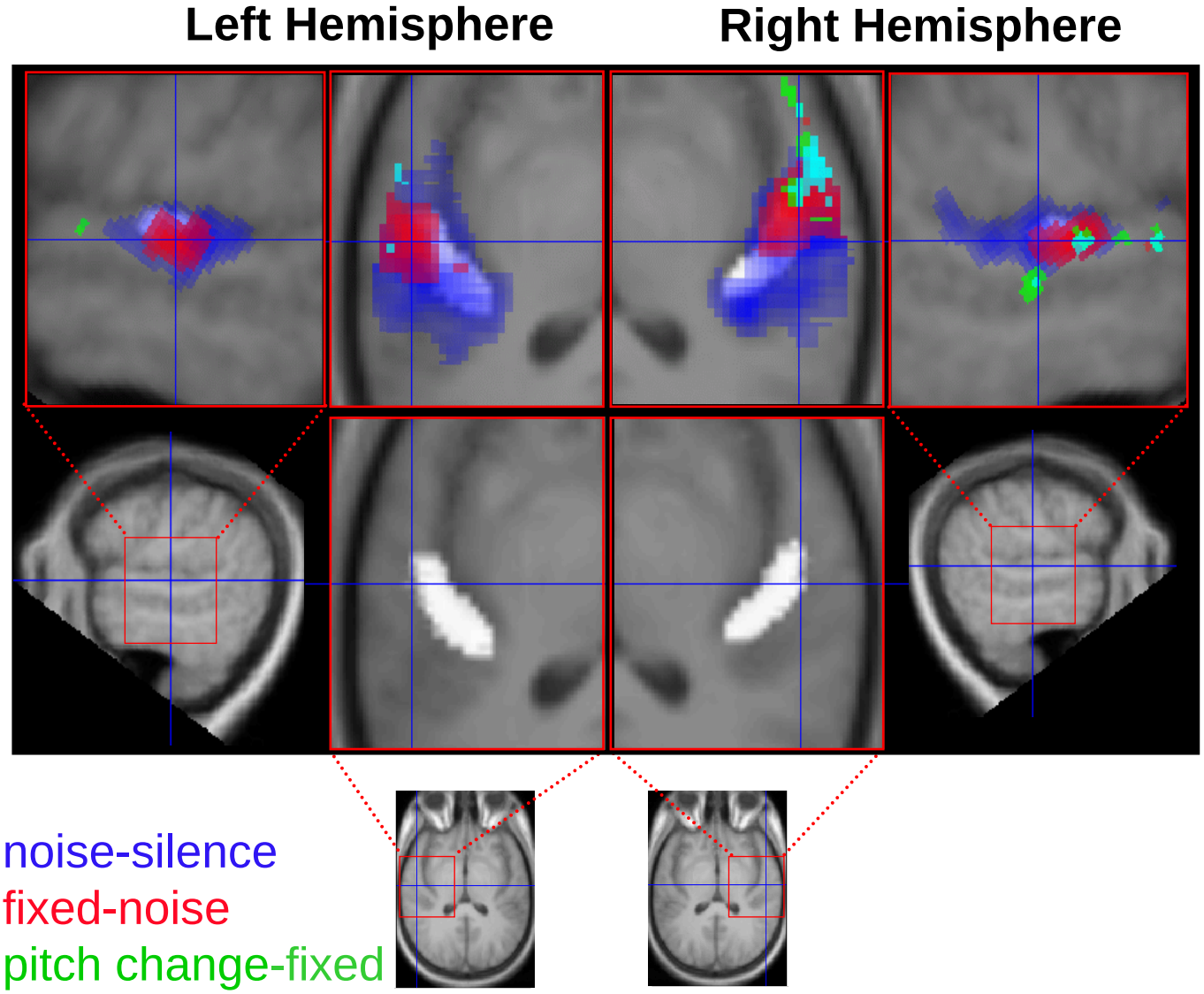
Left Hemisphere
Right Hemisphere
noise-silence
fixed-noise
pitch change-fixed

Figure 7.

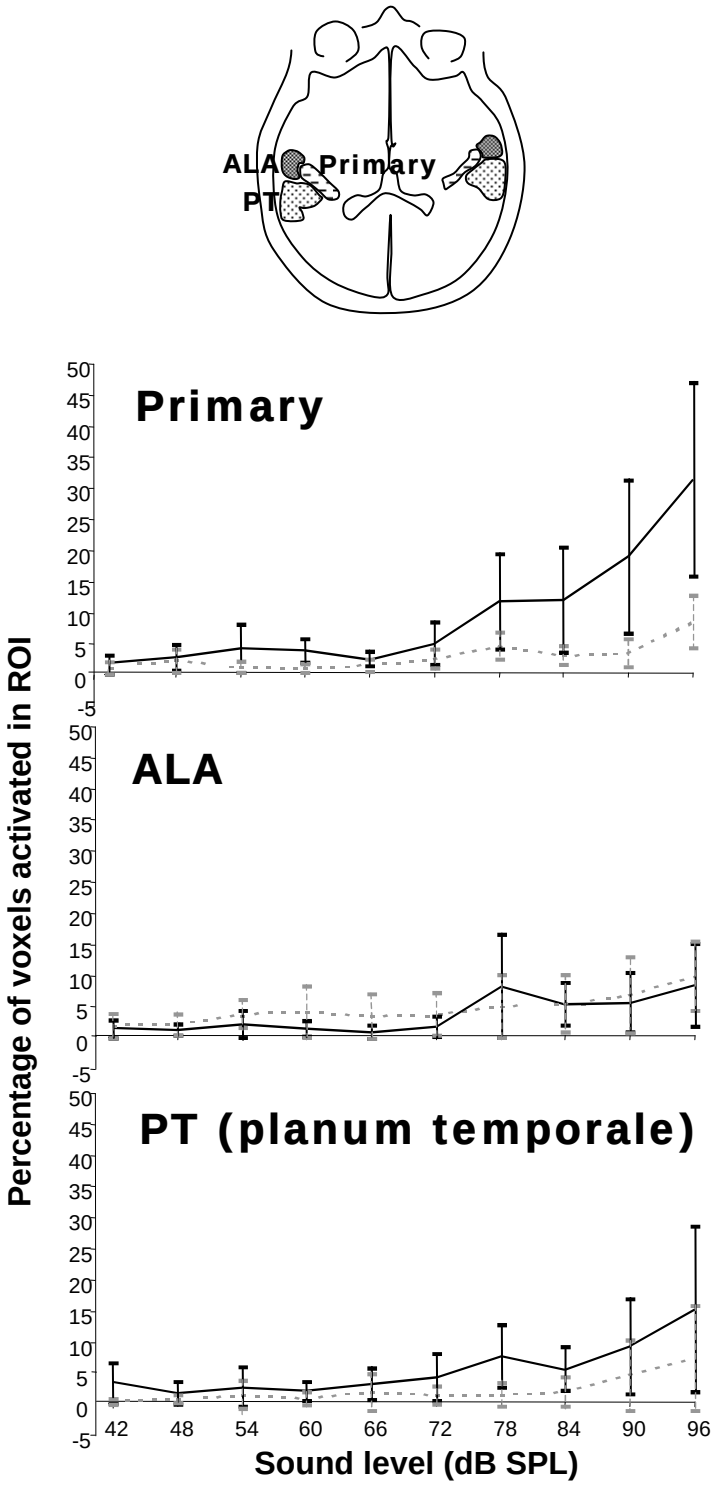
ALA
Primary
PT
Primary
ALA
PT (planum temporale)
Percentage of voxels activated in ROI
50
45
40
35
30
25
20
15
10
5
0
-5
42
48
54
60
66
72
78
84
90
96
Sound level (dB SPL)

Figure 8.

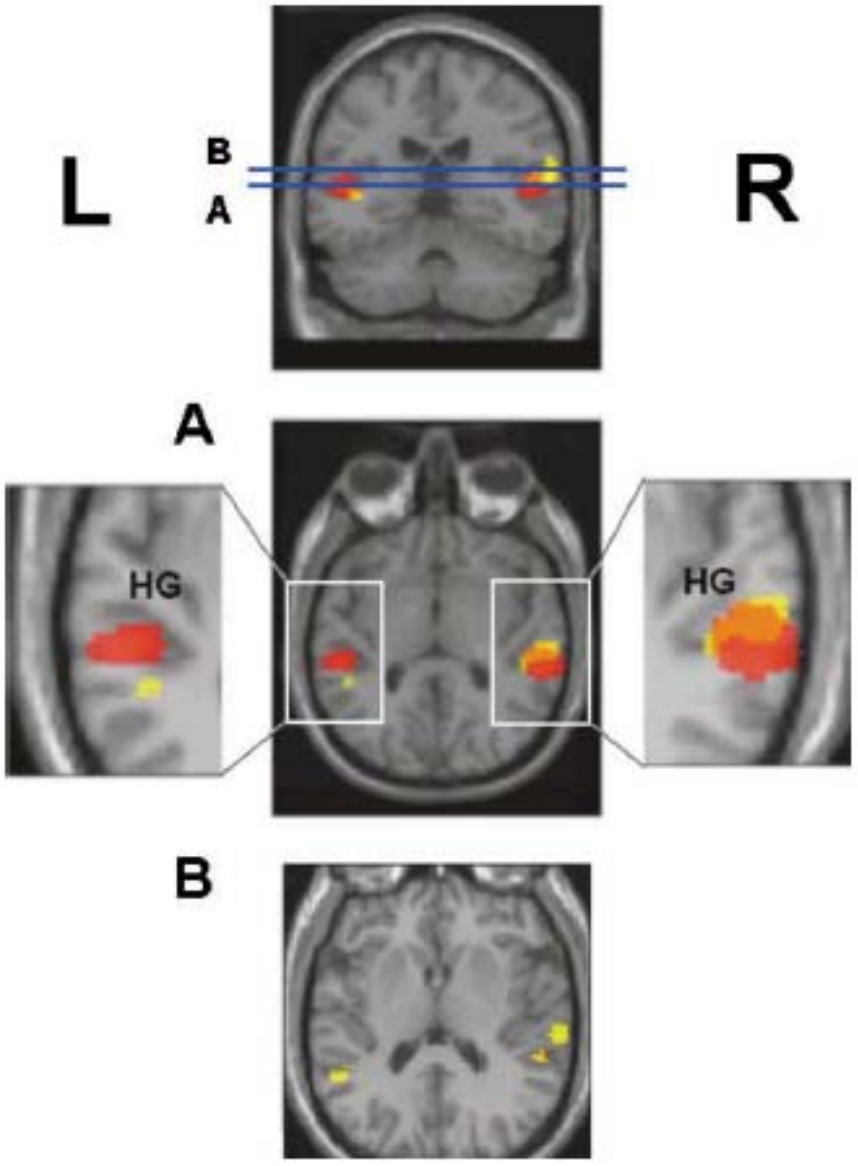

Figure 9.