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Anatomy of the auditory cortex then and now

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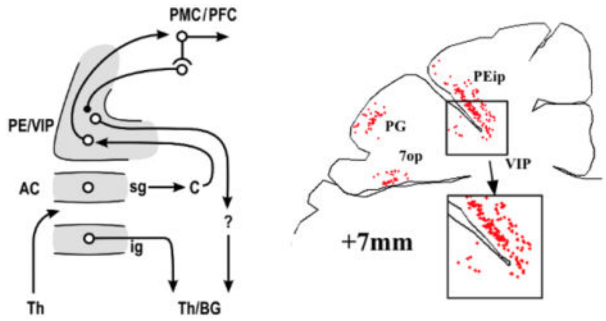
Abstract

Using neuroanatomical investigations in the macaque, Deepak Pandya and his colleagues have established the framework for auditory cortex organization, with subdivisions into core and belt areas. This has aided subsequent neurophysiological and imaging studies in monkeys and humans, and a nomenclature building on Pandya's work has also been adopted by the Human Connectome Project. The foundational work by Pandya and his colleagues is highlighted here in the context of subsequent and ongoing studies on the functional anatomy and physiology of auditory cortex in primates, including humans, and their relevance for understanding cognitive aspects of speech and language.

Graphical Abstract



Keywords

Auditory cortex; Parietal cortex; Premotor cortex; Internal models; Anatomical tracers

1. Introduction

With his review on the "Anatomy of the auditory cortex" (published 1995 in English with a resumé in French), Deepak Pandya created a body of knowledge about the auditory cortex by summarizing his own ideas and the work that he and his colleagues had done up to that point (e.g., Pandya et al., 1994; Pandya & Sanides, 1973; Pandya & Seltzer, 1982). Beyond

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When I began my neurophysiological work on the auditory cortex of the macaque in the 1990s (Rauschecker, 1998b, 1998a; Rauschecker et al., 1995, 1997), I relied to a large extent on Pandya’s insight into the organization of the thalamo-cortical auditory system. Relatively few studies (compared to the flamboyant visual cortex work which dominated the scene since the late 1950s) had been done on the auditory cortex (with notable exceptions, such as the studies by Aitkin et al., 1988; Imig et al., 1977; Merzenich & Brugge, 1973; Miller et al., 1972; Pfingst & O’Connor, 1981); it took a while until the top journals (as well as the funding agencies) took notice of the turning tide. Meanwhile, studies of the anatomical and physiological basis of speech perception and production were very much ‘en-vogue’, and the anatomical studies by Pandya’s group, as well as those of Jon Kaas and Ted Jones (Jones et al., 1995; Morel et al., 1993), opened the door for such physiological studies to be undertaken.

2. Serial and Parallel Processing in the Auditory System

Another motivation for work on auditory cortex in primates was the desire to discover generalized principles of cortical organization across sensory systems. In this context, Schmahmann and Pandya (2006) made an enormous contribution to this understanding through their studies of long association fiber bundles. Another important body of work going back to Pandya was established by Petrides and his colleagues on language areas of the brain (Frey et al., 2008; Petrides & Pandya, 1999, 2009), summarized in a beautiful monograph (Petrides, 2014).

Parallel Processing in the Auditory Brainstem and Thalamus

The organization of hearing for two different purposes is already set up in the brainstem: 1) a linear, narrowband high-fidelity system for transmission of frequency information and the identification of sounds originates in the ventral cochlear nucleus (VCN), and 2) a broadband system for determining the position and direction of movement of sounds in space originates in the dorsal cochlear nucleus (DCN) (Rauschecker, 2021). This functional and anatomical division continues into the inferior colliculus (ICC and ICX, respectively) and the auditory thalamus. The medial geniculate nucleus (MGN) of old-world primates and humans (as well as most other mammals) is divided into three main subnuclei (Jones, 2007; Winer & Schreiner, 2011): the ventral (MGv) division is strictly tonotopically organized and projects to primary core areas of auditory cortex, and must be considered the principal auditory relay nucleus for tonal analysis of sounds; a dorsal (MGd) division, which has broadly tuned neurons and projects to nonprimary regions of auditory cortex involved in auditory space processing; and a medial (MGm) subdivision, which projects to supragranular layers of multiple cortical targets, suggesting a mostly modulatory influence (Sherman & Guillery, 2006). MGm also targets the amygdala, basal ganglia, and limbic association areas of the brain, which are associated with emotional and mnemonic aspects of sounds (LeDoux, 2000).

Hierarchical Organization of Core, Belt, and Parabelt

One could argue that work on the anatomy of auditory cortex began when a specific location within primary auditory cortex of humans was discovered by Richard Ladislaus Heschl (1824–1881), an Austrian-Polish anatomist. “Heschl’s gyrus”, as it was later referred to, stands out by one or more transverse gyri (in Heschl’s words, a ‘complex of gyri’) across the superior temporal cortex. Ferrier, who used stimulation and lesion approaches in monkeys (both published in 1876; see S. Finger, 1994), ultimately proved the auditory function of Heschl’s gyrus. Although primary auditory cortex (A1) in nonhuman primates does not form a discrete transverse gyrus, there is a noticeable thickening (or ‘bump’), indicating the increased density of layer-4 neurons that receive input from principal thalamic relay cells.

Later studies invariably found that the superior temporal cortex contained more than one koniocortical (or primary-like) area, which led to the definition of a ‘core’ region. This was followed by the foundational proposal of Pandya and Sanides (1973) that these primary core regions are generally surrounded by secondary areas, which they termed “root” areas on the medial and “belt” areas on the lateral side. This anatomical scheme was elaborated in great detail for the auditory cortex in the superior temporal gyrus (STG) of the rhesus monkey (Galaburda & Pandya, 1983; Pandya, 1995). Nissl staining of histochemical markers for acetylcholinesterase, parvalbumin, myelin and calbindin subsequently permitted the refinement and expansion of the distinction between core and belt areas (Hackett et al., 1998b, 1998a; Jones et al., 1995; Morel et al., 1993). Architectonic similarities between root and belt led to the term ‘root’ being dropped in favor of ‘medial belt’ by later investigators, and the simplified concept of a ‘belt’ surrounding the core was introduced. The terms ‘LBelt’ and ‘MBelt’ have recently been adopted by the Human Connectome Project (HCP) (Glasser et al., 2016).

Thalamo-Cortical Organization

Concomitant neurophysiological and lesion evidence confirmed that neurons in the core areas, such as the primary auditory cortex (A1) and the rostral area (R), respond well to pure tones (PTs) and are narrowly tuned to frequency, whereas normal responsiveness at later stages of auditory cortical processing (area CM) depends on the integrity of the core (Rauschecker et al., 1997; see Figure 2). Three cochleotopically organized areas on the STG, the antero-lateral (AL), middle lateral (ML), and caudo-lateral (CL) areas, were identified on the basis of their responses to band-passed noise bursts (Rauschecker et al., 1995) (Figure 1A). Such stimuli greatly enhance the response of neurons in these lateral belt areas compared to pure tones. Further, these neurons are tuned to the center frequency as well as bandwidth of the noise bursts. Given that lateral belt areas receive their major input from core areas (Hackett et al., 1998b, 1998a) (Figure 1B), these physiological findings support the notion of a hierarchical organization within the auditory cortex of primates (Kaas et al., 1999; Rauschecker, 1998b), similar to that found in the visual cortex (Desimone & Ungerleider, 1989; Felleman & van Essen, 1991; Zeki & Shipp, 1988).

Human Imaging Studies

Triggered by the findings in the macaque, auditory cortical organization was also investigated with functional imaging techniques in humans. Organization into core and belt was confirmed (Chevillet et al., 2011; Wessinger et al., 2001) and later expanded by demonstrating tonotopic organization and responsiveness to natural complex sounds, including segregated regions for speech and music (Leaver & Rauschecker, 2010; Norman-Haignere et al., 2015). Architectonic analysis of auditory areas using Nissl staining had previously demonstrated some structural differences between the rhesus monkey and human, but functional differences were not identified (Fullerton & Pandya, 2007). Despite various attempts to demonstrate fundamental differences between auditory cortical organization in monkeys and humans, for instance in harmonic perception, only quantitative differences have been found (Kikuchi et al., 2014; Norman-Haignere et al., 2019).

3. Processing Streams in the Auditory Cortex: The Early Years

Having identified several core and belt areas, the question arose whether fibers projecting from these areas had differential targets at the next level, termed parabelt by Kaas and Hackett (2000). Indeed, it turned out that the anterolateral area (AL) projects to rostral parabelt (RB), and the caudolateral area (CL) projects to caudal parabelt (CB). In addition, a middle lateral area (ML) was found that projected to both RB and CB (Rauschecker, 1998b, 1998a; Rauschecker & Tian, 2000). Already at this early stage, it became evident that anatomical processing streams were forming that conveyed different types of information: AL neurons were narrowly tuned for the type of species-specific calls, whereas CL neurons were specific for location in space (Tian et al., 2001).

Next, fluorescent tracers were injected into physiologically identified regions of the lateral belt, and anterograde label was observed in areas of prefrontal cortex (Romanski et al., 1999; Rauschecker & Tian, 2000). Injections into area AL led to label in the ventrolateral prefrontal cortex (VLPFC), whereas injections into area CL led to label in the dorsolateral prefrontal cortex (DLPFC). This result was highly informative, because VLPFC and DLPFC relate to different functions in lateral prefrontal cortex (Barbas, 1988): VLPFC contains neurons that represent visual object working memory, whereas DLPFC neurons convey visual spatial working memory (Wilson et al., 1993). Hence, the logical conclusion was that the projection from AL in the auditory belt to VLPFC subserves the same purpose of object working memory as in the visual domain; and the projection from CL conveys auditory spatial information to support auditory spatial working memory (Romanski et al., 1999).

What, Where and How in the Auditory Cortex

Our studies of auditory processing pathways in the macaque led to the proposal that an anteroventrally directed pathway from rostral belt projects to VLPFC and provides the anatomical-physiological substrate for the identification of auditory objects: a ventral or ‘what’-stream (Rauschecker & Tian, 2000; Romanski et al., 1999). Reminiscent of the dual-stream model of Ungerleider and Mishkin (1982) for the visual cortical system, a postero-dorsal pathway from the caudal belt projects to DLPFC, providing the substrate for auditory spatial analysis: a ‘where’-stream. Complementary to that, there has been the suggestion of a ‘how’-stream involved in the programming of actions and their perception (Goodale & Milner, 1992; Milner & Goodale, 2008), but it has been argued that the ‘where’-

and 'how'-streams can be subsumed under a common concept of sensorimotor processing (Rauschecker, 2018).

Participation of posterior superior temporal and parietal cortex in processing space and motion

Human functional imaging and stroke studies were consistent with the participation of posterior superior temporal and parietal cortex in spatial hearing (Ahveninen et al., 2006; Alain et al., 2001; Arnott et al., 2004; Deouell et al., 2007; Maeder et al., 2001; Spierer et al., 2009; Warren et al., 2002). Transcranial magnetic stimulation studies further corroborated the participation of posterior temporal and parietal cortices in auditory space processing (At et al., 2011). Some of these and other studies also demonstrated a participation of DLPFC in spatial hearing (Belin et al., 2002; Lewald et al., 2008; Weeks et al., 2000), thus completing the extent of the auditory dorsal stream in humans to the same regions that were identified in the monkey (see Rauschecker, 2007, 2015 for prior reviews).

The auditory dorsal stream as an internal model of the outside world

The dorsal-stream model of auditory and speech processing postulates that connections between auditory and motor regions of the brain are crucial for relating motor commands to their sensory outcomes (Rauschecker, 2011). Evidence from functional imaging studies in humans has shown that the pathway is implicated in speech and musical production (Rauschecker & Scott, 2009; Figure 4). Recent nonhuman primate studies with functional MRI in our lab have demonstrated that motor regions, including dorsal and ventral premotor cortex (PMC), are activated when rhesus macaques are listening to auditory sequences they had previously learned to produce by pressing levers on a special-built "monkey piano" (Archakov et al., 2020; Figure 5). Indeed, prior anatomical tracer studies have shown direct connectivity between the superior temporal gyrus and sulcus (STG/STS) and the dorsal and ventral PMC (Luppino et al., 2001; Morecraft et al., 2012, 2015). Additionally, direct connections between the auditory belt cortex and prefrontal cortex (PFC) have previously been demonstrated (Romanski et al., 1999) (see above). However, no previous study has specifically shown direct or indirect anatomical connectivity between auditory cortex and identified regions of the PMC that physiologically respond to auditory input.

To further investigate the pathways connecting auditory and motor areas of the cortex, we injected Cholera Toxin B subunit (CTB) tagged with Alexa Fluor (AF) 488 and 594 fluorophores into anterior and posterior regions of the PMC, respectively, in two adult rhesus macaques (Macaca mulatta). The anterior injection was made at the junction between the F2 and F4 premotor areas, inferior to the spur of the arcuate, while the posterior injection was made at the junction between areas F1, F2, and F4. These locations were specifically chosen based on the activations found in our previous fMRI study (Archakov et al., 2020).

The study provides evidence for motor regions to be in communication with the auditory cortex through posterior parietal areas. Both tracers were taken up by axon terminals near the corresponding injection sites and retrogradely transported to cell bodies in other parts of the cortex, with the highest concentration of labeled cells in the posterior parietal region, including area PEip, the ventral intraparietal area (VIP), the posterior supramarginal gyrus (pSMG), and the parietal operculum (7op). Specifically, label within the parietal cortex was bilaminar - both supragranular (layer 3) and infragranular (layers 5 and 6), demonstrating feedforward and feedback connectivity within the dorsal stream. Additional label was found in the supplementary motor area (SMA), the anterior cingulate cortex (ACC), and in PMC areas F2 and F4 (Afsahi et al., 2022; Figure 6). The current dorsal-stream model postulates that posterior parietal areas may serve as a relay station between auditory centers and the PMC. This includes area VIP, which was previously assumed to play a role in auditory processing by Lewis and van Essen (2000). Future studies recording from posterior parietal sections PG, operculum, and PEip will assist in confirming whether additional relay stations exist between the PMC and auditory cortex.

4. Connectivity of Human Auditory Cortex

The classical anatomical approach of Pandya and colleagues using neuroanatomical tracers (culminating in the monograph by Schmahmann & Pandya, 2006, which covers the fiber pathways of the brain for virtually every major system) conveys a vast amount of information about brain connections, as they provide the substrate for the information super-highway system of our most important organ. The downside of this approach is that the information can only be gained by invasive work in animal models. Developments in the field of neuroimaging, in particular magnetic resonance imaging (MRI), have begun to replace the classical anatomical approach using tracers, first by diffusion tensor imaging (Basser et al., 2000; Le Bihan et al., 2001) and now by effective connectivity techniques based on data from the Human Connectome Project (HCP) (Glasser et al., 2016).

The specific research described in this final section goes beyond the previous sections by estimating causal connectivity between 15 auditory cortical regions in the human brain with a multimodal atlas with 360 cortical areas. Strengths of this investigation are that it utilized the HCP-MMP atlas (Glasser et al., 2016); HCP data from the same set of 171 participants imaged at 7T (Glasser et al., 2016) in which we could calculate the connections, functional connectivity, and effective connectivity; and that it utilized a method for effective connectivity measurement between all 360 cortical regions investigated here. The Hopf effective connectivity algorithm is important for helping to understand the operation of the computational system, for it is calculated using time delays in the signals between 360 or more cortical regions, and the use of time is an important component in the approach to causality (Rolls, 2021). We hope that future research using the same brain atlas (Glasser et al., 2016; Huang et al., 2022) will benefit from the human auditory cortical connectome described here.

The following conclusions can be drawn from the study by Rolls et al. (2022):

1. Measurements of effective connectivity, complemented by functional connectivity and diffusion tractography, provide evidence consistent with a hierarchy of auditory cortical processing in humans inferred from anatomical tracer studies in nonhuman primates (Kaas & Hackett, 2000; Pandya, 1995): from a Core region (A1) to Belt regions LBelt and MBelt, then to PBelt, and finally on to higher regions (A4 and A5; see also Rauschecker & Scott, 2009).

2. A4 has connectivity to TA2 in the anterior temporal lobe, which makes it part of a ventral auditory stream implicated in semantic object processing (Rauschecker & Scott, 2009; Rauschecker & Tian, 2000).
3. A4 also has effective connectivity to A5, which then connects to dorsal bank superior temporal sulcus (STS) regions STGa, STSda, and STSdp. These STS regions also receive visual inputs about moving faces and objects, and the auditory and visual streams are combined to help in multimodal object identification, such as who is speaking, what is being said, what the object is, etc. This system can thus also be considered as an important part of the ventral auditory 'what' stream.
4. Consistent with the dorsal-bank STS regions being part of a ventral auditory stream, the dorsal-bank STS regions then have effective connectivity to TPOJ1, STV, PSL, TGv, TGd and PGi, which are language-related regions involved in semantic representations about objects, faces, etc using multimodal information, and which then connect to Broca's area, especially to area 45.
5. Diffusion tractography indicated connections of PBelt, RI, A4 and A5 with Broca's area 44, and this may be how the dorsal 'how' language stream (Rauschecker, 2018; Rauschecker & Scott, 2009) is reflected in the analysis (Rolls, Rauschecker, et al., 2022). Corresponding effective or functional connectivity was not identified in the present analysis, perhaps because it is relatively weak, or perhaps because the data were acquired in the resting state. In the monkey there is a rostral and a caudal parabelt (Kaas & Hackett, 2000), and that distinction is not made in the HCP-MMP (Glasser et al., 2016), but if such a separation can be made in humans, that might provide further evidence about dorsal and ventral language-related streams.
6. A4 and A5, and some earlier cortical regions, have in addition effective connectivity to regions including MT and MST which in turn have effective connectivity to intraparietal and thereby parietal area 7 regions. This connectivity might be considered as part of the dorsal auditory 'where' stream (Rauschecker, 2018; Rauschecker & Tian, 2000) involved in actions in space that utilize auditory information.

The upshot of this line of work, using the example of the auditory cortical system, demonstrates that connectivity techniques can be extremely useful and can complement the classical tracer techniques. It does not mean that the classical techniques become obsolete; they still serve an important role in the study of brain connections and confirm the validity of the new approach in humans. It is actually astounding that anatomical techniques, developed decades ago, are as robust as they are, validating the results gained through them (Rockland, 2004). Even if the concepts of Root, Core, and Belt, as originally termed by Pandya and colleagues, are undergoing yet another name change (into Core, LBelt, and PBelt, with an MBelt to be expected), they are transforming into the most appropriate concept for describing and understanding sensory systems in general, and auditory cortex in particular.

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Key Findings:

Using neuroanatomical investigations in the macaque, Deepak Pandya and his colleagues have established the framework for auditory cortex organization, with subdivisions into core and belt areas. This has aided subsequent neurophysiological and imaging studies in monkeys and humans, and a nomenclature building on Pandya's work has also been adopted by the Human Connectome Project. The foundational work by Pandya and his colleagues is highlighted here in the context of subsequent and ongoing studies on the functional anatomy and physiology of auditory cortex in primates, including humans, and their relevance for understanding cognitive aspects of speech and language.

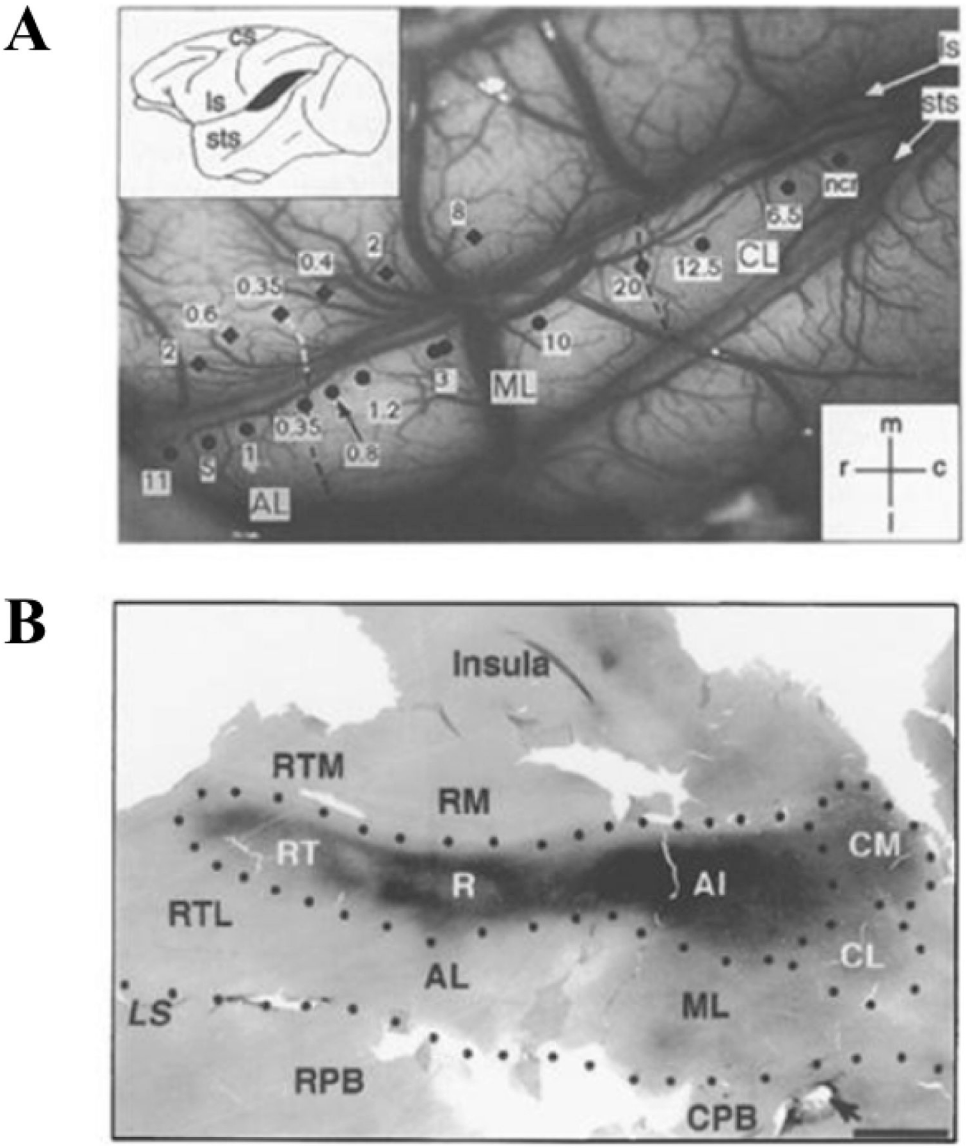

Figure 1:

(A) Neurophysiological map of best frequencies (BFc; in kHz) along the lateral sulcus (ls) (Rauschecker et al., 1995). The posterior part of the STG is seen in the center; electrode tracks that entered directly into its lateral surface and tracks that entered the STP after traveling through the overlying parietal cortex are also shown. All electrode tracks were verified by histology. Values of BFc were determined for each penetration from averages of at least three recordings at different depths. AL, anterolateral area; ML, middle lateral area; CL, caudolateral area; sts, superior temporal sulcus; ls, lateral sulcus; cs, central sulcus. Upper inset: Lateral view of the left hemisphere of a rhesus monkey brain, with the explored area emphasized by stippling. Lower inset: m, medial; l, lateral; r, rostral; and c, caudal. **(B)** The histochemistry of auditory cortex (Hackett, Stepniewska and Kaas, 1998a). Brain sections were cut parallel to the surface of artificially flattened cortex and processed for parvalbumin. A large, dark oval corresponding to the core auditory area I

(AI) is apparent. The rostral core area (R) is also apparent as a dark oval. Note also slight differences in the darkness of the caudomedial (CM), caudolateral (CL), middle lateral (ML), and anterolateral (AL) areas of the auditory belt. Dots outline these areas, as well as the lip of the lateral sulcus (LS). Additional abbreviations include the rostrotemporal area (RT), lateral rostrotemporal auditory belt (RTL), medial rostrotemporal auditory belt (RTM), rostromedial region (RM), caudal auditory parabelt (CP), and rostral auditory parabelt (RP). An arrowhead marks a diamidino yellow injection site. Scale bar = 5 mm.

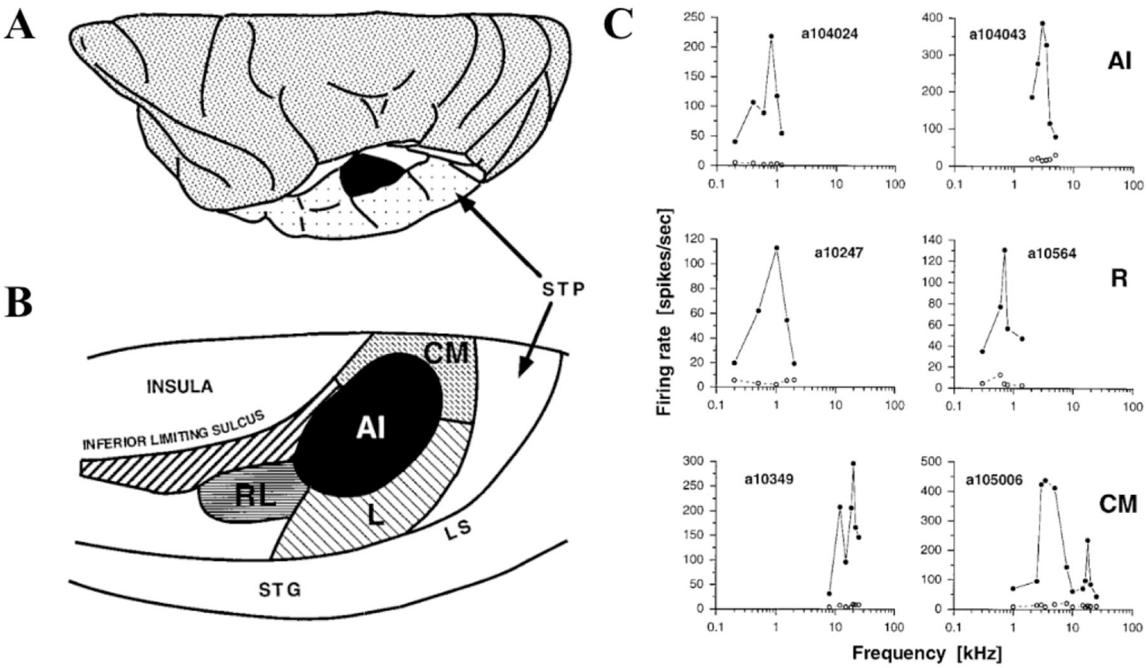

Figure 2:

(A) Dorsal view of the macaque brain (left hemisphere). The supratemporal plane is shown exposed after removal of the overlying frontoparietal operculum, a procedure used by Rauschecker, Tian, Pons and Mishkin (1997). The approximate position of primary auditory cortex (A1) is indicated in black. **(B)** Locations of auditory areas on the supratemporal plane. **(C)** Representative rate-frequency tuning curves of single neurons in A1, R, and CM. The stimuli were tone bursts of varying frequencies with 50 ms duration (5 ms rise/fall time) and an amplitude of 75 dB. The numbers in each panel refer to individual units. Responses were determined quantitatively from peristimulus time histograms (PSTHs) at five or more different frequencies. Level tolerance of best frequency and of frequency of tuning was assured in most neurons by varying the intensity of the stimulus. Note the relatively narrow tuning in A1 and R compared to the wider-band responses, often with more than one peak, found in CM.

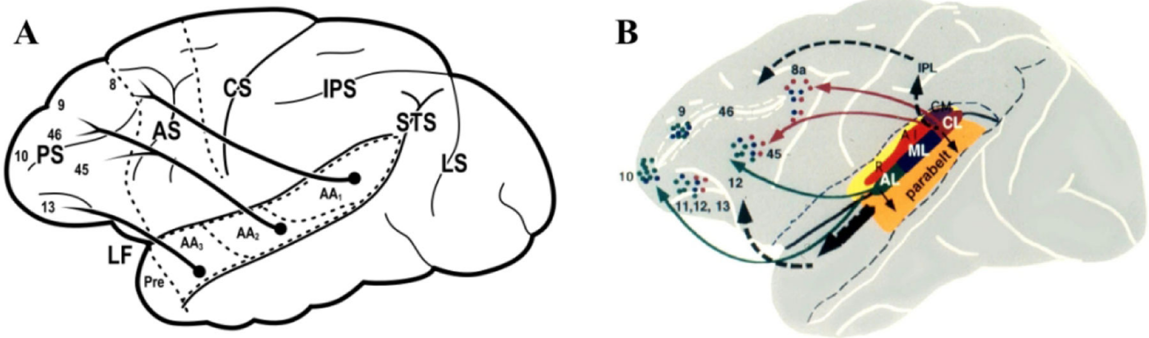

Figure 3:

(A) The three divisions of the auditory association areas of the STG and their long association connections to the prefrontal cortex, terminating in Brodmann areas 8, 46/45, and 13 (Pandya, 1995). **(B)** Tracer injections into physiologically identified areas of lateral auditory belt. Anterograde and retrograde labeling in the prefrontal cortex in three monkeys. Lateral brain schematic shows color coding of the lateral belt injections. Projections are summarized with arrows. CL projections form a dorsal stream; AL injections result in a ventral stream (Romanski et al., 1999).

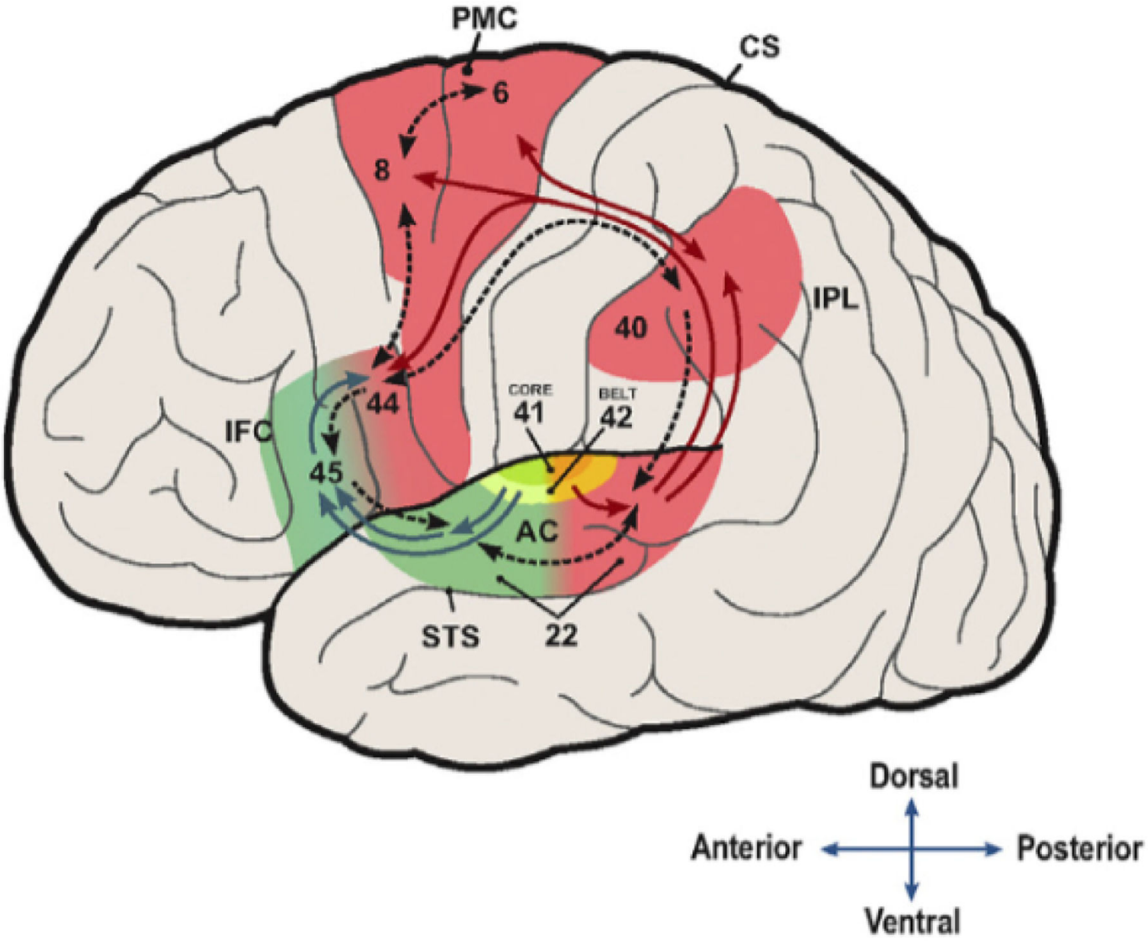

Figure 4:

Dual-stream model of auditory processing in the human brain (Rauschecker & Scott, 2009). The ventral processing stream is shown in green, and the dorsal stream is shown in red. Brodmann area 44 constitutes the target area of the dorsal stream while Brodmann area 45 is the endpoint of the ventral stream, with both regions interacting (as depicted by the reciprocal connections between them). Other abbreviations [Brodmann area (BA) in parentheses]: AC = auditory cortex (BA 41, BA 42), CS = central sulcus, PMC (BA 6), DLPFC (BA 8), IFC = inferior frontal cortex (BA 44, BA 45), IPL = inferior parietal lobule (BA 40), STS = superior temporal sulcus (BA 22).

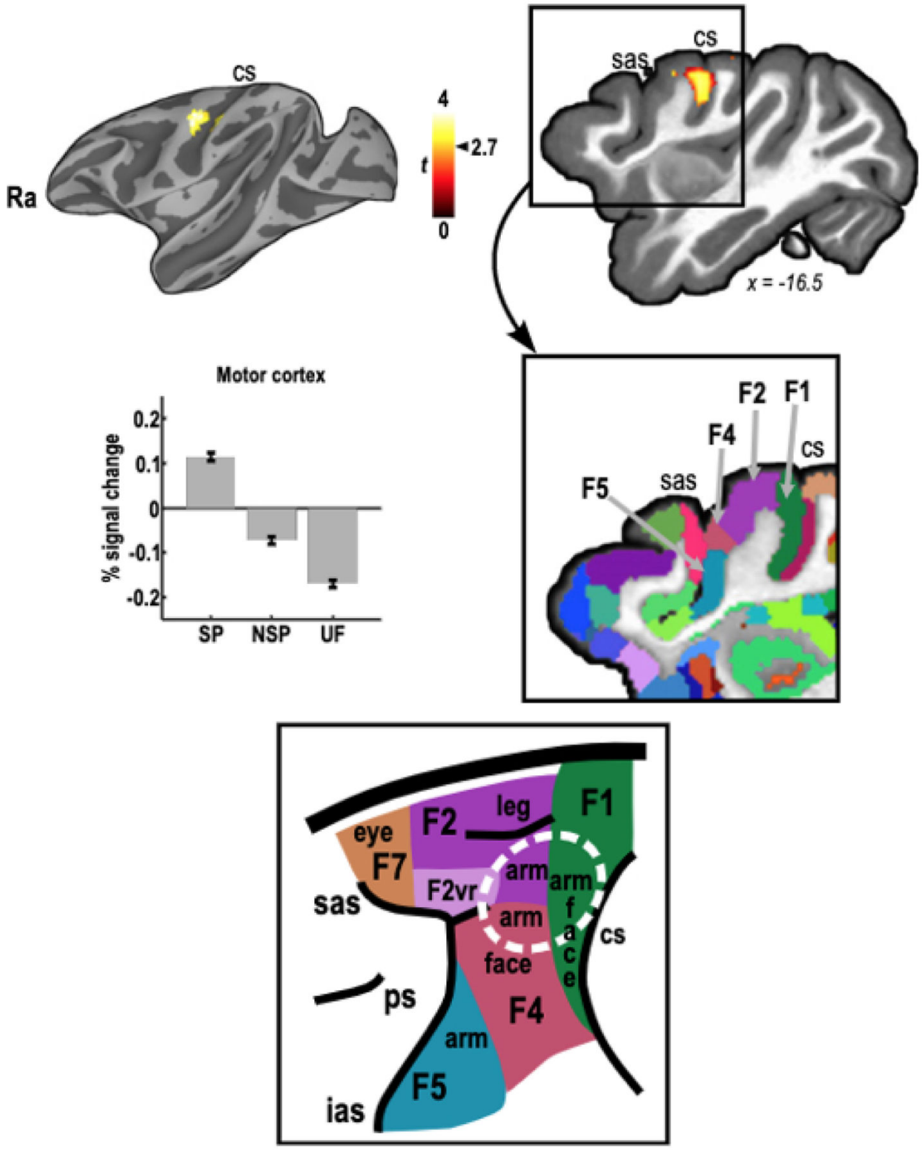

Figure 5:

In our previous fMRI study (Archakov et al., 2020), we used a novel "monkey piano" apparatus to train macaques to play sound sequences in their home cage. Comparison of responses evoked by learned self-produced (SP) sound sequences vs. sound sequences with passive familiarity (non-self-produced [NSP]) or complete unfamiliarity (UF). There was noticeable activation in the motor cortex as well as the putamen. Specifically, the activation was mapped to primary motor cortex (F1/M1), dorsal premotor area (F2), and ventral premotor cortex (F4). Abbreviations for sulci include central sulcus (cs), inferior arcuate sulcus (ias), principal sulcus (ps), and superior arcuate sulcus (sas).

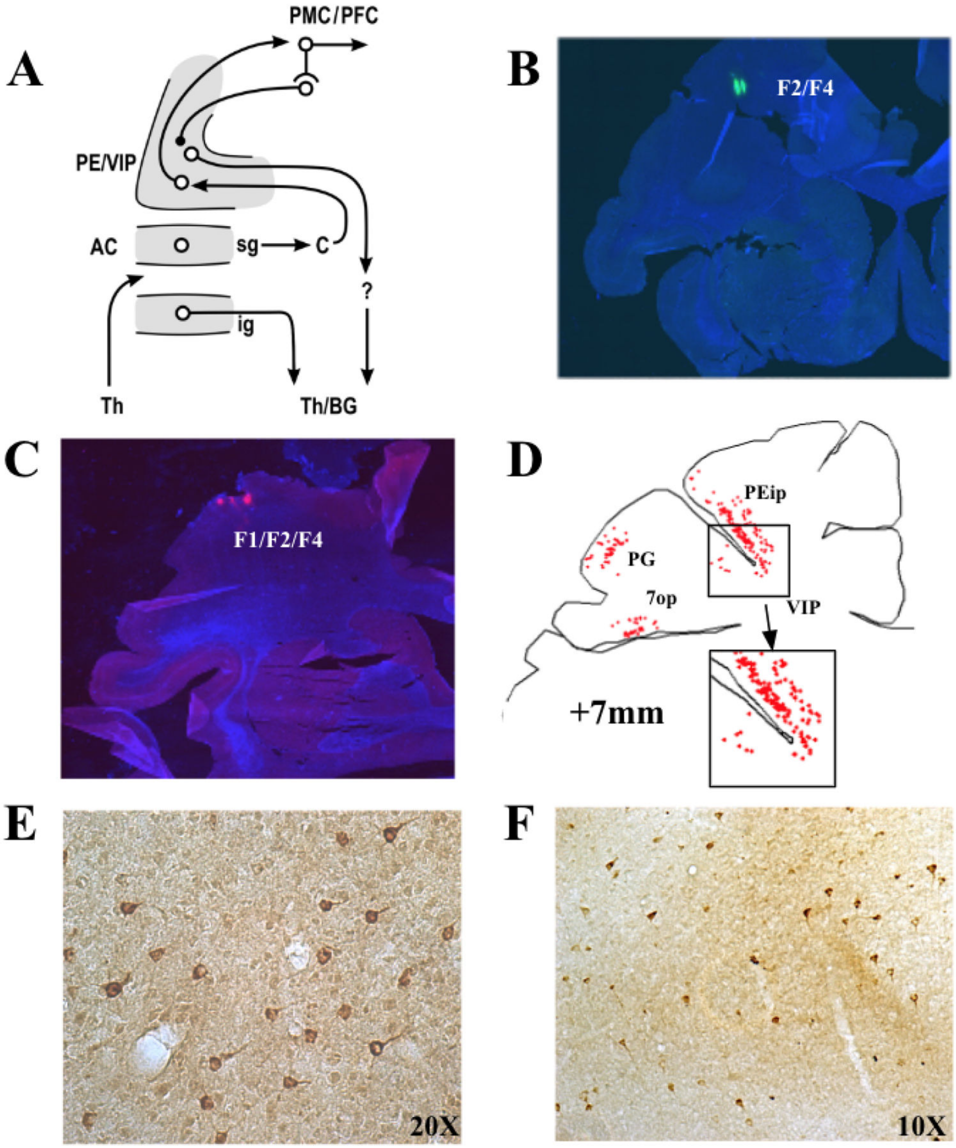

Figure 6:

(A) Schematic of feedforward and feedback connectivity between the auditory cortex (AC) and prefrontal cortex (PFC) and premotor cortex (PMC), with relay signals synapsing within the parietal cortex (PE/VIP). Additional abbreviations include basal ganglia (BG), infragranular layer (ig), supragranular layer (sg), and thalamus (Th). **(B-C)** To further investigate the anatomical pathways connecting motor and auditory areas, we injected Cholera toxin B subunit (CTB) tracers tagged with an Alexa Fluor (AF) 488 fluorophore (green, panel B) and 594 fluorophore (red, panel C). The anterior injection was made at the junction between premotor areas F2 and F4, inferior to the spur of the arcuate, while the posterior injection was made at the junction between premotor areas F1, F2, and F4. These locations were specifically chosen based on the activations found in our previous fMRI study (Archakov et al., 2020). Two different primary antibodies were used for immunohistochemical staining: anti-cholera toxin B (anti-CTB), which recognizes both tracers, and a polyclonal antibody raised against the AF488 fluorophore, which recognizes only that tracer. **(D)** Results showed a dense CTB+ cell cluster in the superior parietal lobule with cells appearing in both the supragranular and infragranular layers, demonstrating feedforward and feedback connectivity within the auditory dorsal stream. **(E)** Retrogradely labeled neurons appeared in the superior parietal lobule; viewed in 20X. **(F)** In addition, retrogradely labeled neurons appeared in the anterior cingulate cortex (ACC); viewed in 10X (Afsahi et al., 2022). The results provide evidence for the existence of forward and inverse models of auditory-motor processing (Borra et al., 2021; Fogassi et al., 2005).