Physiology of Higher Central Auditory Processing and Plasticity

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Abstract

Binaural cue processing requires central auditory function as damage to auditory cortex and other cortical regions impairs sound localization. However, the mechanisms through which the cerebral cortex supports spatial perception remain unknown. Sound localization cues are initially extracted by brainstem nuclei. However, localizing a sound within the complex auditory scenes that make up every-day acoustic environments requires integrating information across sound frequencies and localization cues. This chapter reviews evidence that spatial encoding within, and beyond auditory cortex supports sound localization. In particular, this chapter discusses the role of brain regions across the cerebral cortex that may be specialized for extracting and transforming spatial aspects of sounds and extends from sensory to parietal and prefrontal cortices. The chapter considers how the encoding of spatial information changes with attention and how spatial processing fits within the broader context of auditory scene analysis by cortical networks. The importance of neural plasticity in binaural processing is outlined, and how changes in the mapping of localization cues to spatial position allow listeners to adapt to changes in auditory input throughout life and how the brain is able to compensate following hearing loss. The chapter ends by summarizing some of the open questions about central processing of binaural cues and how they may be answered.

1 Introduction

Sound waves are encoded within the cochlea according to their frequency, meaning that spatial location of sound sources must be computed from acoustic features that are encoded as binaural (two ears) and monaural (one ear) localization cues (see Hartmann, Chap 2). While sound localization cues are extracted by specialized brainstem nuclei, no single cue defines the sound location unambiguously; instead, information must be integrated across cue types and frequencies to robustly compute spatial position. While the precise role of auditory cortex in sound perception has remained somewhat elusive, an observation that is highly consistent across methods and species is that a deficit in sound localization results from removal or silencing of auditory cortical activity (e.g., Whitfield et al. 1972; Heffner and Heffner 1990). Animals lacking an intact auditory cortex can detect a change in source location and can still accurately discriminate left from right (i.e., lateralize) sound locations; however, they show impairments in their ability to compute the precise source location in the side of space contralateral to the lesion. These observations from animal models mirror deficits in humans observed after brain damage in clinical case studies. However, despite work spanning several decades demonstrating a critical requirement for auditory cortex in sound localization, our understanding of how neural circuits in (and beyond) auditory cortex generate spatial perception remains limited.

This chapter begins by reviewing the cortical representation of space and our current understanding of spatial processing within auditory cortex (Sect. 2). The role of auditory cortex is then discussed within the context of larger scale brain networks, where regions such as auditory, parietal, and frontal cortex may form a specialized spatial processing stream (Sect. 3). This section also examines how task demands shape neural processing so that listeners can actively and dynamically sense their environment (Sect. 3.3). Flexible sound localization is then considered within the context of plasticity and reorganization of cortical function, with a particular focus on the role of descending connections in facilitating this plasticity (Sect. 4). Finally, the chapter discusses some of the open questions that remain regarding central processing of binaural cues. These include whether neurons in auditory cortex represent acoustic localization cues or an integrated representation of space

(Sect. 5.1), and how the brain represents sound location in multiple coordinate systems (Sect. 5.2). To answer these, and other important questions about central processing of binaural cues, significant technical and theoretical challenges must be overcome (Sect. 6).

2 Auditory Cortex

The auditory cortex encompasses a number of distinct cortical fields, with core (also known as primary) areas innervated directly by the lemniscal thalamus (medial geniculate body, MGB - see Table 1 for a list of all acronyms), belt (secondary) areas innervated directly by core areas (and also by MGB), and finally parabelt (tertiary) areas that receive cortical input but no direct connections from auditory thalamus (Hackett 2015). In humans, auditory cortex lies along the superior temporal gyrus (Fig. 1A) with the core area located in the caudal two thirds of Heschl's Gyrus (HG)(Hackett et al. 2001). HG is surrounded by belt areas that extend anterior, to the planum polare), and caudal, to the planum temporale (PT). Finally, parabelt areas lie beyond belt regions, eventually emerging on the superior temporal gyrus (Hackett 2015). Non-human primates, carnivores, and rodents share an analogous core-belt-parabelt organization (Fig. 1B) (Hackett 2015). In addition to the classical auditory cortex, a number of further cortical areas are critical for auditory processing and sound localization in particular - including parietal and frontal regions such as dorsolateral prefrontal cortex and posterior parietal cortex (Sect. 3.2).

Auditory cortex is divided into six layers that differ in their neuronal morphology and connectivity and, potentially, in their contribution to spatial hearing. . Inputs from the ventral division of the thalamus terminate in layers III and IV. From here, information is relayed to the supragranular layers (I and II) where information is combined with inputs from other cortical fields. Finally, infragranular layers (V and VI) receive input from layers I-IV and act as the major output of auditory cortex, containing large pyramidal neurons that send long-range connections across cortex, thalamus, midbrain, and striatum (Linden and Schreiner, 2003; Hackett, 2015).

PLACE FIGURE 1 ABOUT HERE

2.1 Cortical Areas Necessary for Sound Localization

To identify cortical areas with a causal role in spatial hearing, deficits in sound localization must be identified either through targeted inactivation using animal models in the laboratory or studies of patients with brain injuries. Profound and lasting sound localization deficits in primates (Heffner and Heffner 1990) and carnivores (Whitfield et al. 1972) result from lesioning the auditory cortex. Later studies using thermal or pharmacological methods to reversibly silence auditory cortex have also shown that primary and specific non-primary auditory cortical fields are critical for normal localization in both horizontal (Malhotra et al. 2004, Wood et al. 2017) and vertical (Bizley et al. 2007) dimensions. Here, thermal inactivation is achieved by passing chilled ethanol through a steel "cooling loop" on the cortical surface to reduce the temperature of neurons, temporarily disabling their spiking ability. Pharmacological inactivation may involve the application of muscimol to the brain; muscimol mimics the action of the inhibitory neurotransmitter GABA, and therefore silences the region in which it has been applied. Lesion, thermal, and pharmacological inactivation data all point to a role for auditory cortex in integrating binaural and spectral cues. Animals with primary auditory cortex inactivation show decreased localization accuracy, with front-back confusions accounting for a large proportion of the errors (Nodal et al. 2010). Such front-back confusions are thought to result from the ambiguity known as the "cone of confusion," whereby sound sources at multiple locations generate the same binaural cues (see Hartmann, Chap 2 and Takahashi et al., Chap 3). Resolving front-back confusions relies upon integrating of binaural and monaural spectral cues. Therefore, the inability of animals with auditory cortical inactivation to resolve these front-back confusions suggests that integration of different localization cues relies on auditory cortex. Beyond auditory cortex, a network of brain regions process sound and in particular sound location. While laboratory studies seeking to perturb activity in these areas during sound localization are limited, sound localization deficits have also been reported following lesions of prefrontal cortex in monkeys (Wegener 1973).

Spatial listening deficits in human patients are also associated with damage to frontal, inferior parietal, and superior temporal areas (Clarke et al. 2002), supporting the conclusion from animal studies that a cortical network contributes to sound localization. In particular, damage to parietal cortex produces spatial deficits, including impairments in the judgment of the relative location of two sounds sources (Griffiths et al. 1997; Pavani et al. 2001) and distorted sensitivity to interaural timing cues (Tanaka et al. 1999).

The study of behavioral deficits following stroke and other forms of traumatic brain injury in patients has played a vital role in developing models of neural processing and cognitive function. Such studies offer vital insights into how the human brain works: by studying the consequences of long-term neurological damage in small clinical populations, the brain regions critical for a given function may be elucidated. However, recovery of function following trauma may mask functional links between brain and behavior in listeners without brain damage. To complement studies in patients, approaches such as transcranial stimulation allow the study of causal mechanisms in large cohorts of healthy subjects over a relatively rapid time-course, where the perturbation is under experimenter control. Using such approaches, investigators have demonstrated that repetitive focal transcranial magnetic stimulation of posterior parietal cortex (PPC) can induce systematic errors in a subject's estimation of sound azimuth and elevation. In particular, stimulation of right PPC shifts subject's estimates of sound location down in elevation and to the left (i.e., the contralateral hemisphere) (Lewald et al. 2004). Broadly speaking therefore studies in patients and healthy listeners highlight a role for cerebral cortex in spatial perception.

2.2 How is Sound Location Represented by Neurons in Auditory Cortex?

Typically, experiments investigating the representation of sound location in auditory cortex use either free-field stimulus presentation from a loudspeaker or series of loudspeakers, or dichotic presentation over headphones. Dichotic presentation introduces spatial cues by altering the relative timing or intensity of the signals in each ear to create interaural timing differences (ITDs) or interaural

level differences (ILDs, see also Hartmann, Chap 2). An alternative is to present sounds over headphones using Virtual Acoustic Space (VAS) stimuli that are constructed from recordings of free-field sounds made with a microphone placed in the ear canal. VAS recreates both the binaural and spectral cues present in real world sounds and mostly reproduces a perception of a localized sound source in the world (Wightman and Kistler 1989; Middlebrooks 1999). This is in contrast to studies that only manipulate binaural cues over headphones, where sounds appear to move left to right within the head (i.e., sounds differ in lateralization). As well as offering practical advantages by allowing stimulus presentation over headphones, VAS offers the potential to independently manipulate (Wightman and Kistler 1992) or eliminate variation in particular spatial cues (Macpherson and Middlebrooks 2002; Campbell et al. 2006a). In contrast, free-field stimulation can only constrain the type of acoustic cue presented by limiting the frequency spectrum (e.g., Wood et al. 2019).

2.2.1 Encoding Interaural Level Differences

Historically, one of the earliest phenomena to be investigated at the neuronal level within auditory cortex was the difference in responses of neurons to sounds presented over headphones (e.g., Imig and Adrian 1977). In these animal studies, neural responses to sounds coming from one ear were compared with neural responses to sounds delivered to both ears. Neurons in auditory cortex were then classified based on whether their responses to monaural and binaural sounds were excitatory (E) or inhibitory (I): "EE" neurons produce excitatory responses to sounds at both ears, "EI" neurons produce excitatory and inhibitory responses to sounds at the contralateral and ipsilateral ear respectively, and "EO" neurons only produce excitatory responses to sounds at the contralateral ear and do not respond to sounds at the ipsilateral ear. Over time the stimulus parameter space has increased, such that auditory cortical neurons can be tested with sounds containing the entire physiological range of ILDs [±35 dB in humans (Middlebrooks et al, 1989), ±25 dB in ferrets (Carlile, 1990)] at a range of sound levels or "average binaural levels". Expanding the stimulus space has led to a concomitant increase in the complexity of reported receptive fields, with individual units tuned (i.e., most strongly responsive) to different ILDs. The majority of units in primary auditory cortex are

tuned to ILDs associated with contralateral sounds, although across the neural population the full range of physiological ILDs are represented (Campbell et al. 2006b). In some cases, neural responses have been reported to have a topographic distribution, with tuning to many different ILDs observed along isofrequency contours (Nakamoto et al. 2004). Two-photon imaging studies that allow visualization of neural activity through the use of voltage or ion sensitive dyes have provided an unprecedented ability to observe spatial structure in the representation of ILDs, but (at least in mice) have failed to reveal any systematic organization of ILD response preference type across primary auditory cortex (Panniello et al. 2018).

2.2.2 Encoding Interaural Time Differences

Although more studies have focused on the processing of ILDs than ITDs, many auditory cortical neurons are tuned to ITDs presented through earphones, as first shown by Brugge et al. (1969). ITDs and ILDs are dependent on sound frequency, and studies investigating the physiological representation of ITDs are probably less numerous, in part, because common animal models such as the mouse do not hear the low frequency sounds that convey ITDs (see Tollin and Owrutsky, Chap 4). While midbrain responses to sounds varying in ITD (or interaural phase difference (IPD) for ongoing tones) are strongest to ITD/IPDs corresponding to contralateral source locations (Shackleton et al, 2003), cortical tuning appears more heterogeneous. Most studies of cortical neurons report some degree of contralateral bias in tuning (Reale and Brugge 1990; Scott et al. 2009), although in gerbils (*Meriones unguiculatus*), each hemisphere of primary auditory cortex contains neurons tuned to ITDs that correspond to locations in both contralateral and ipsilateral sides of space (Belliveau et al. 2014). This study recorded predominantly in Layer V and raises the possibility that ipsilateral tuning might emerge through intracortical processing. Nevertheless, in humans, electroencephalography (EEG) and magnetoencephalography (MEG) adaptation studies suggest a strong bias in the neural representation for ITDs corresponding to contralateral sound locations (Magezi and Krumbholz 2010; Salminen et al. 2010). Investigations using functional magnetic resonance imaging (fMRI) also suggest that a bias

of neural activity for contralateral ITDs is present, but weaker than for contralateral ILDs (Higgins et al. 2017b).

2.3 Spatial Receptive Fields in Auditory Cortex

In everyday listening, broadband sounds with energy at many frequencies offer multiple, redundant cues (e.g., ITDs and ILDs) for computing sound location. The spatial tuning of individual neurons can be measured by varying the position of sounds (e.g., noise bursts) while recording the spiking response of neurons with microelectrodes. The sound source can be moved in space, either by presenting free-field sounds from a speaker array, or by presenting sounds in VAS. A spatial receptive field (SRF) can then be constructed by comparing the strength of the neuron's response (i.e., the number of action potentials elicited) to sounds at different positions (Fig. 2A) (Brugge et al. 1969; Eisenman, 1974). SRFs in primary auditory cortex are relatively broad and typically tuned to contralateral locations, with a minority of neurons tuned to ipsilateral space or the midline (Harrington et al. 2008).

Spatial tuning is refined as sound signals ascend the auditory pathway, from primary to non-primary auditory cortex. When presented with complex sounds varying in position or identity, neurons in the caudolateral belt show strong tuning to sound location but weak tuning to identity; whereas neurons in anterolateral belt are sensitive to sound identity but are weakly modulated by location (Tian et al. 2001). Spatial tuning of neurons in caudolateral belt regions of secondary auditory cortex is enhanced relative to primary auditory cortex, and only in the caudolateral belt do firing rates of populations of neurons convey sufficient spatial information to account for sound localization ability (Miller and Recanzone 2009).

Further evidence that processing of sound location and identity are separated within auditory cortex is provided by reversible inactivation studies in animals (Lomber and Malhotra 2008). Transiently cooling some auditory cortical fields (primary auditory cortex, posterior auditory field (PAF), anterior ectosylvian sulcus (AES)) of the domestic cat during a sound localization task results

in behavioral deficits. In contrast, inactivation of other areas (the anterior auditory field (AAF) and secondary auditory field (A2)) leaves performance intact (Malhotra et al. 2004). When cooling either anterior or posterior cortical fields during a localization task or a (non-spatial) temporal pattern discrimination task, a double dissociation was described: cooling posterior (but not anterior) auditory cortex resulted only in impaired localization, whereas cooling anterior (but not posterior) cortex impaired only temporal discrimination (Lomber and Malhotra 2008). Thus, spatial tuning is refined from primary to non-primary auditory cortex, with specific subfields of secondary auditory cortex playing a key role.

2.4 Spatial Receptive Fields during Behavior

Studies of the neural representation of space in auditory cortex have typically recorded neural responses in anesthetized or passively listening animals. This leaves open the possibility that the broad spatial tuning often observed in individual neurons - which stands in contrast to the fine discrimination of sound location behaviorally (see Hartmann, Chap 2) - might reflect the limits of the anesthetized state rather than the auditory system's true capabilities. To address this issue, Lee and Middlebrooks (2011) recorded spatial receptive fields in primary auditory cortex of cats that were either listening passively, performing a non-spatial task, or performing a task which required attention towards sound location. Spatial tuning of individual neurons narrowed when the animals actively listened to sounds, with the greatest contrast seen between passive listening and engagement in the localization task. Thus, even at the earliest stages of auditory cortical processing, ongoing task demands shape the way that neurons process spatial information. One might expect such changes to arise from enhanced selectivity of spatially tuned neurons for their preferred sound locations; in contrast, improvements in spatial tuning came principally from omnidirectional units (i.e., those with little to no spatial preference) becoming broadly tuned to contralateral space.

A follow-up study demonstrated that neurons in non-primary fields also sharpened during behavior (Lee and Middlebrooks 2013). Across subfields, neurons in the dorsal zone (area DZ)

appeared mostly tuned for midline sounds; whereas PAF neurons were mostly tuned for more lateral locations, including those behind the cat. Both these anatomical regions are necessary for sound localization (Malhotra et al. 2004) and so might play complementary roles in spatial hearing. Receptive fields of spatially tuned units in primary and non-primary auditory cortex were not dramatically sharper during task performance, indicating that single unit tuning was not responsible for behavioral thresholds. In contrast, behavioral sensitivity to sound location is most likely to arise from the activity of neuronal populations.

2.5 How is Spatial Information Extracted from Auditory Cortical Responses?

If listeners can accurately localize sounds with a precision of a few degrees, yet SRFs in auditory cortex are broadly tuned to contralateral space, then information must be combined across populations of neurons to yield a precise neural representation of sound location (Middlebrooks et al. 1998; Miller and Recanzone 2009). Inspired by studies of binaural cue encoding in the midbrain (see Tollin and Owrutsky, Chap. 4), at least two models have been proposed to account for integration of spatial information across neurons: A *distributed model* would represent the location of a sound source through the activation of a particular neural sub-population, with sounds originating from different locations eliciting distinct patterns of neural activity across the cortical population (Stecker and Middlebrooks, 2003; Day and Delgutte, 2013). In contrast, a two-channel or opponency model proposes that the relative activity of two broadly-tuned neural populations determines perceived location (Stecker et al. 2005b).

Recordings from single neurons provide support for a distributed model: While SRFs are typically tuned to contralateral space; their best positions are distributed throughout auditory space, rather than being restricted to two contralateral positions as predicted by the two-channel model (Woods et al. 2006; Wood et al. 2019). Neural activity can also be decoded using two-channel models (Stecker et al. 2005a) but such models are outperformed by distributed models (Day and Delgutte 2013; Wood et al. 2019).

In contrast to the support for distributed systems provided by single neuron recordings, functional imaging studies in primates (including humans) support a two-channel model when neural activity is measured with high temporal and low spatial resolution using MEG (Salminen et al. 2009), or at higher spatial resolution and lower temporal resolution using fMRI. These fMRI investigations reveal a strong bias for contralateral locations indicative of a two-channel representation, which is observed across cortical fields and hemispheres in both macaques (Ortiz-Rios et al. 2017) and humans (Higgins et al. 2017b).

The conflicting support for the two-channel and distributed models, from primate and non-primate studies, respectively, suggests a difference across species or methodologies. Most neural recording studies report that individual neurons have strong contralateral biases, but there is heterogeneous spatial tuning that shows little systematic organization of sound location across the cortical surface (also known as a topographic map, observable in primary visual and somatosensory cortices). Therefore, it is possible that measuring signals over the thousands of neurons within a voxel averages out the variability in individual SRFs producing the appearance of a two-channel representation, even when distributed codes exist. This would be particularly likely if each hemisphere represents contralateral space using a distributed code (Wood et al. 2019). Lastly, these models only attempt to account for azimuthal localization when we are able to pinpoint a sound accurately in at least two dimensions (Blauert 1996). In the future, expanded models of spatial tuning will be required that account for our behavioral ability to perform multi-dimensional localization.

3 Spatial Processing in Brain Networks

3.1 The Dual Stream Theory

Insights from animal studies (Sect. 2) suggest that spatial processing is refined in ascending pathways from primary to non-primary auditory cortex. This implies that spatial processing may be further enhanced higher up the auditory system to ultimately give rise to spatial perception. Inspired

by studies in vision (Ungerleider and Mishkin 1982), the dual-stream model formalizes this idea, proposing that information about sound location is processed independently to the non-spatial features (such as pitch and timbre) that allow us to identify a sound source. This has led to the two streams being described as the "what" and "where" pathways, with significant discussion about the nature and independence of spatial and non-spatial processing. Within the model, spatial and non-spatial information streams are processed in parallel pathways originating in auditory cortex, with the spatial stream then extending to parietal and prefrontal cortices (Fig. 2A) (Rauschecker and Tian 2000; Rauschecker and Scott 2009).

Evidence for the dual stream model comes from converging anatomical, neurophysiological, and neuropsychological studies. In addition to the early evidence that spatial processing was refined in primate caudal auditory cortex (see Sect. 2.4), key evidence for this model was provided by anatomical experiments. Romanski and colleagues (1999) injected neural tracers into physiologically identified regions of belt auditory cortex in macaque monkeys. They found that anterior belt cortex was reciprocally connected with several areas of the frontal cortex, including ventral prefrontal regions involved in processing non-spatial attributes of sound. In contrast, the caudal belt was mainly connected with the caudal principal sulcus and frontal eye fields: both areas involved in spatial processing. Thus distinct pathways from auditory to frontal cortex were found, indicating that information about sound travelled in parallel spatial and non-spatial processing streams.

Functional imaging studies in humans also support the dual stream model: Posterior auditory cortical fields are consistently activated during spatial processing in humans (Maeder et al. 2001) and only in these areas is activity correlated with spatial perception (Higgins et al. 2017a). Additional evidence for the dual stream model has included reports of functionally independent brain networks for spatial and non-spatial processing (Ahveninen et al. 2006; Retsa et al. 2018). Ahveninen et al. (2006) compared neural responses to sound location and identity when subjects attended to either spatial or non-spatial features of sound. Consistent with dual stream models, posterior STG showed greater sensitivity to changing sound location, while anterior STG and planum polare were more sensitive to sound identity. When listeners attended to changes in sound location (that were present in

all stimuli, but could be attended or ignored), activity was enhanced in posterior but not anterior regions. In contrast, attention to sound identity modulated activity in anterior but not posterior areas.

3.2 Cortical Processing of Space Outside Auditory Cortex

The spatial and non-spatial streams originating in auditory cortex (Sect. 3.1) each target distinct brain networks that include frontal and parietal cortex. In humans and other primates, frontal cortex is divided into the prefrontal cortex (PFC) and the precentral gyrus that contains motor cortex. PFC has several sub-regions including the dorsolateral (dlPFC) and ventrolateral prefrontal cortex (vlPFC), as well as the Frontal Eye Fields (FEF) (Fig 1). Dorsolateral and ventrolateral PFC receive distinct inputs from spatial and non-spatial auditory pathways (Romanski et al. 1999), although there are also connections between ventrolateral and dorsolateral regions within PFC (Petrides and Pandya 2001). Similarly, motor cortex has been divided into primary motor cortex, the supplementary motor area, and premotor cortex – all of which are important in coordinating a subject's behavioral response to sounds, with the ventral premotor area (vPM) sensitive to sound location (Graziano et al. 1999).

In PPC, several areas have been identified in spatial hearing, including the lateral intraparietal sulcus (LIP) and parietal reach region (PRR). Parietal cortex receives auditory input via connections from caudal temporoparietal cortex to ventral intraparietal area (VIP) and ventral LIP (Figure 1; Lewis and Van Essen 2000; Rozzi et al. 2006). Auditory signals processed within parietal areas may then be sent to prefrontal cortex via direct connections from PPC (Pandya and Kuypers 1969; Divac et al. 1977).

Human neuroimaging and neurophysiology complement the evidence from animal work for a role for prefrontal and parietal cortex in spatial auditory processing. While studies of individual neurons in animals are often limited to a single brain region, neuroimaging allows investigators to study neural processing across the entire brain. Thus, approaches like PET (positron emission tomography) imaging and fMRI revealed that spatial auditory processing activates not only specific regions of auditory cortex, but also widespread networks including other cortical areas.

Using PET imaging while subjects localized sounds, Bushara and colleagues (1999) found bilateral activation of superior and inferior parietal lobules, bilateral middle frontal gyrus, and right medial frontal gyrus. When localizing free-field stimuli, PET activation in right inferior parietal cortex specifically was predictive of sound localization performance (Zatorre et al. 2002). Similar results were found using fMRI, when subjects detected changes in virtual location of sounds (Alain et al. 2001) or identified sound location using ITDs (Maeder et al. 2001). An important question is whether the activated areas are involved in hearing generally, or in spatial hearing specifically. Maeder and colleagues addressed this by contrasting activation when subjects localized or identified the same test sounds: Localization produced greater activation of inferior parietal lobule, posterior-middle frontal gyri, and inferior frontal gyri, whereas identification activated middle temporal gyrus, precuneus, and left inferior frontal gyrus. Thus separate dorsal and ventral auditory pathways appear to be specialized for the analysis of sound location and identity respectively.

One constraint of fMRI and PET imaging is the relatively slow temporal resolution of the measurements, which limits insight into the time-course of auditory processing. This is particularly problematic for studies of audition, where signals unfold rapidly over time. Other approaches such as EEG and MEG can track neural signals with millisecond resolution, although it is much harder to pinpoint the source of these signals. These techniques have also shown the importance of parietal and frontal cortices: EEG studies where subjects listened passively to noise bursts found that binaural cues modulated activity in the temporal-parietal and inferior frontal cortices (Tardif et al. 2006). Using MEG, Kaiser et al. showed that posterior parieto-temporal and supratemporal areas respond to shifts in sound location (Kaiser et al. 2000; Kaiser et al. 2002). These effects differed across hemispheres, with right cortex responding to shifts in both ipsilateral and contralateral directions, whereas corresponding regions in the left hemisphere were responsive only to contralateral shifts in sound location (Kaiser et al. 2000). This observation fits with a model of spatial attention in which the right hemisphere controls shifts in attentional focus in both directions, whereas the left only controls shifts to the right (Mesulam 1981). Other studies using similar approaches, but focusing on early sensory responses, have found an opposite asymmetry (Salminen et al. 2010), so it remains unclear to what

extent auditory spatial processing is asymmetrically distributed in humans. What is clear across these studies, however, is that a broad network of parietal and frontal areas is active during sound localization.

3.2.1 Frontal Cortex

A role for PFC in sound localization was first indicated by lesion studies which demonstrated deficits in task performance following bilateral PFC lesions (Wegener 1973). Neurophysiological recordings in PFC of awake monkeys also demonstrated that neurons in the dlPFC were responsive to sounds, and often tuned to contralateral locations (Azuma and Suzuki 1984). Sound-driven responses in dlPFC occurred later in time than in auditory cortex and were less tightly locked to the onset of sounds. Contralateral tuning suggests that auditory cortex and dlPFC may share functional properties; however, later results indicated such similarities were limited (Vaadia et al. 1986; Vaadia 1989). In dlPFC, relatively few units responded to unisensory auditory stimuli, and those that were sound-responsive were also highly sensitive to the animal's behavior. When monkeys were engaged in a task (either sound detection or localization), a larger proportion of PFC units were responsive. While the largest proportion of responsive cells were reported during sound localization, these cells were also active during a visual localization task. This suggests that behaviors that required analysis of stimulus position in either modality engage these neurons, rather than only localization of sounds. In contrast to dlPFC, most units in the superior temporal plane around auditory cortex were sound-responsive and relatively few of these cells were modulated by behavior (Benson et al. 1981).

Neuroimaging results in humans also indicate that spatial behaviors engage frontal cortex: both visual and auditory localization tasks activate medial frontal cortex and IPL bilaterally (Bushara et al. 1999). In contrast, regions such as the SPL and middle frontal gyrus were activated only by visual or auditory localization. Together these results indicate that these brain regions use cues that are relevant to achieve the subject's goal, rather than any fixed physical features or modality. In the case of sound localization, binaural cues are relevant for behavior and thus selected for further

representation. However, this selection is flexible and binaural cue processing can be dynamically engaged or ignored when necessary.

Neurons encode selection rules for directing behavior towards task-relevant spatial information within rodent medial prefrontal cortex (mPFC). For example, Rodgers and DeWeese (2014) trained rats to flexibly switch between two tasks in which subjects reported the lateralization (i.e., whether sounds came from the left or right) or frequency of sounds (Fig. 2B). Stimuli contained spatial and non-spatial information on all trials, but subjects switched between decisions using (in the case of lateralization) or ignoring (in frequency discrimination) binaural cues (Fig. 2C and 2D). In mPFC (and auditory cortex), neurons showed task-dependent modulation of baseline neural activity in the anticipatory period preceding stimulus onset, as well as sound evoked activity during stimulus presentation. Thus, an example mPFC neuron might be more active before and during sound presentation when subjects used binaural cues to guide behavior than when those cues were ignored (Fig. 2E).

The idea that prefrontal cortex combines binaural cues with the goals of the listening subject is also supported by causal evidence showing that disruption of mPFC impairs flexible switching between using and ignoring binaural cues. For example, electrical stimulation of mPFC impaired alternation between lateralization and frequency discrimination tasks, and thus rats' ability to select binaural cues for behavior (Rodgers and DeWeese 2014). Similarly, optogenetic stimulation of prelimbic cortex (an area thought comparable to primate dorsolateral PFC) prevents mice from flexibly switching between lateralization of auditory and visual targets within an audiovisual stimulus (Wimmer et al. 2015). Intriguingly, optogenetic stimulation was only effective in the anticipatory window prior to sound onset, suggesting that subjects' use of binaural cues is determined *before* sounds are experienced, and that behavioral priorities may shape auditory processing prospectively. Mice have relatively poor spatial acuity for sounds compared to humans (Behrens and Klump 2016) and lack sensitivity to low sound frequencies that we use to access ITDs. In future research, it will thus be critical to test how cortical modulation of spatial processing occurs in other species with low frequency hearing and high spatial acuity.

Findings from human neuroimaging mirror results from rodent studies. Expectation of a sound produces enhanced activity in frontal and parietal areas, even when stimuli are not physically presented (Smith et al. 2010). This suggests that incoming sensory input is indeed processed within a broader temporal context in both human and non-human animals.

3.2.2 Parietal Cortex

Within parietal cortex, LIP neurons are responsive to sound and encode information about a sound source's location (Mazzoni et al. 1996;Stricanne et al. 1996). Spatially sensitive auditory neurons have also been reported in VIP, where many cells are sensitive to both sounds and visual stimuli, and auditory and visual receptive fields overlap (Schlack et al. 2005). Like non-human primates, rodents also have neurons in posterior parietal cortex that encode sound location (Nakamura 1999).

In parietal cortex, active behavioral performance is not required to observe spatially informative LIP responses; however, auditory responses of LIP neurons are behaviorally dependent (Linden et al. 1999). Specifically, auditory responses are stronger when performing behavioral tasks such as memory-guided saccades than during fixation of static locations. The encoding of spatial information about sound locations by LIP neurons was previously thought to depend upon training animals in auditory saccade tasks, as LIP neurons recoded in naïve subjects were uninformative about sound location (Grunewald et al. 1999). Subsequent analysis of the visual context in which sounds were presented revealed that auditory responses in LIP can arise in the absence of visual cues, in animals performing fixation tasks (Gifford and Cohen 2004). Such responses do not require specific training with sounds or execution of saccades, indicating that spatial processing is a natural part of LIP function.

Human parietal cortex also engages in auditory spatial processing in a task dependent manner. For example, Michalka et al. (2016) showed that regions within the superior parietal lobule (SPL) are recruited when subjects engaged spatial but not temporal short-term memory. Here, subjects listened

to two consecutive sequences of four complex tones and were asked to report whether the sequences matched. In all trials, the tones came from four distinct locations (determined by ITD cues) and were presented with variable inter-tone intervals. Both the locations and/or timing could vary between the first (probe) and second (target) sequence. In the spatial task, subjects were asked whether the sequence of locations in the probe and target sequence matched, and in the temporal task subjects reported whether the timing sequence was the same or different. In both task conditions, lateral and anterior regions of the intraparietal sulcus were activated; however only when attending to sound location was SPL activated. In another study, Alain and colleagues (2010) found that inferior parietal lobule (IPL) activation was associated with demand for memory of sound locations; specifically, activity increased as subjects were required to remember sound locations across longer sequences. Together these results suggest that memory for sound location involves neural processing in human parietal cortex.

3.3 Beyond 'What vs. Where'

As the theory that sound location and sound identity were analyzed in parallel pathways across the central auditory system (Rauschecker and Tian 2000; Rauschecker and Scott 2009) became more widely accepted, evidence emerged suggesting that a strictly binary interpretation of this view was oversimplified. For example, neurophysiological studies in animals demonstrated spatial modulation of neurons in ventrolateral prefrontal cortex – a part of the putative "what" pathway (Cohen et al. 2004). Neurons in vlPFC are more spatially selective than neurons in the anterolateral belt region of auditory cortex from which it receives input, suggesting that vlPFC receives spatial information from regions other than rostral auditory cortex. Such areas may include regions within the "where" pathway such as the dorsolateral PFC, to which vlPFC is interconnected (Petrides and Pandya 2001). Furthermore, vlPFC neurons have spatial tuning comparable with LIP neurons associated with the "where" pathway, further suggesting parallel pathways may interact and

potentially converge. Thus, models of spatial tuning have evolved to emphasize the interaction between dorsal and ventral pathways (Rauschecker and Scott 2009).

Performing a meta-analysis across fMRI studies, Arnott et al. (2004) found that areas such as IPL and superior frontal cortex are more often active in tasks where subjects were asked to make spatial judgements about sounds. However non-spatial tasks still activate areas such as IPL in 41% (11 / 27) of the examined studies and, in rare cases, spatial processing engaged regions of the ventral identification pathway such as inferior frontal cortex. Neural recordings have indicated that LIP is not exclusively specialized for the processing of sound location, and LIP neurons can encode non-spatial spectrotemporal features relevant for identifying sounds (Gifford and Cohen 2005). In humans, sound recognition produces greater bilateral activation in precuneus within the SPL than sound localization (Maeder et al. 2001), again bringing into question how strongly spatial and non-spatial functions are separated. Thus, spatial processing beyond auditory cortex is not exclusively limited to the dorsal pathway, nor non-spatial processing to the ventral pathway.

Even within non-primary auditory cortex, the division of labor into discrete processing streams might not be as simple as first proposed. For example, in ferrets (*Mustela putorius furo*), neurons in primary and secondary areas are sensitive to both spatial and non-spatial sound attributes (Bizley et al. 2009; Town et al. 2018). In humans, EEG studies also reveal position-linked object identity information in the ventral processing stream ("what" pathway) (Bourquin et al. 2013). Finally in cats, inactivation of caudal region AES leads to sound localization deficits, while inactivation of rostral region A2 does not (Malhotra et al. 2004). Neurons in both areas show comparable spatial tuning (Middlebrooks et al. 1998) indicating that information about sound location available in neural responses may not always be causally relevant for behavior.

3.3.1 Using Binaural Cues in Auditory Scene Analysis

If spatial information is isolated from the neural pathways responsible for non-spatial processing that underlies sound identification, why then do spatially tuned neural responses exist in

the ventral processing stream (e.g., ventrolateral PFC and anterior regions of secondary auditory cortex)? One possibility is that spatial information allows sound sources to be unmixed during the analysis of auditory scenes. The organization of incoming sound mixtures into perceptual 'objects' is thought to be a key role of the auditory cortex (Bizley and Cohen 2013). Consistent with this idea, similar neural populations are activated in early auditory cortex (HG and PT) when listeners separate a sound mixture into distinct perceptual streams using either pitch or binaural cues (Schadwinkel and Gutschalk, 2010). Neuropsychological studies following patients with stroke damage also show that listeners with complete loss of sound localization abilities can still use spatial information to segregate sound mixtures into distinct objects (Spierer et al. 2007). Finally, there appears to be specialization within the right planum temporale for sound localization in complex acoustic environments with multiple distracters (Zundorf et al. 2014). Lesions to this area impair only localization of sound sources within a mixture and not of a single source by itself, suggesting that this area is critical for segregating sounds based on space and their subsequent localization. Thus, encoding of spatial information may be important for behaviors that do not require subjects to explicitly report sound location.

A common limitation of many spatial coding studies is the use of isolated sound bursts presented in otherwise silent environments. This contrasts starkly with one's daily acoustic experience, where multiple sound sources compete for our attention. Studies employing competing sound sources have revealed that the spatial tuning of neurons in auditory cortex can be much sharper than previously observed with single sources: When cells in field L, an analogue of mammalian primary auditory cortex in the zebra finch (*Taeniopygia guttata*), are tested with single tokens of birdsong, spiking activity locks to the temporal modulations of the song irrespective of its spatial location. When competing tokens are introduced at a second location, cells become spatially selective in their responses (Maddox et al. 2012). Similar findings have also been observed in ferret primary auditory cortex: When competing sound sources are introduced, spatial receptive fields sharpen, becoming both narrower and more strongly modulated by sound location (Wood et al. 2019).

In another study, Middlebrooks and Osnan (2012) presented sequences of sound bursts from multiple sound sources that could be perceived as either a single regular stream of sound when bursts were co-located or two streams with distinct rhythms when sources were separated by only a few degrees. Neural responses in auditory cortex to the same stimuli showed broad spatial tuning when stimuli were co-located. However, for separated sources, neurons selectively responded to the source closest to their preferred location (Middlebrooks and Bremen 2013). These effects were only weakly present at earlier stages of the auditory pathway, arguing in favor of an origin within auditory cortex (Yao et al. 2015). Together these studies illustrate the importance of stimulus competition in measuring spatial tuning properties that might otherwise be missed with single supra-threshold stimuli presented in isolation, and the broader role of binaural processing in auditory scene analysis.

3.3.2 Perception-Action Pathway

In vision, the theoretical separation between spatial and identity processing (Ungerleider and Mishkin 1982) has evolved into a distinction between perception and action (Milner and Goodale 2006). This view emphasizes the importance of behavioral output, with the ventral and dorsal visual streams responsible for perceiving stimuli (e.g., the mosquito flying nearby) and taking action (e.g., swatting it away with one's hand) respectively.

In hearing, the perception-action distinction has also gained prominence (Belin and Zatorre 2000; Rauschecker and Scott 2009), where areas such as parietal cortex are thought to integrate predicted changes in auditory input caused by the subject's actions, with signals sampled from the environment containing information about the actual consequence. For example, if a listener facing a static sound source rotates their head to the right, the source should move to the left of the head. Auditory input allows us track the actual position of the source and can be compared with such predicted changes to detect unexpected events and update predictive models. These "forward models" may originate within premotor cortex, where inverse models (the actions needed to reach a certain goal) and expectations from frontal areas are integrated with information about sounds from parietal and auditory cortex (Rauschecker and Scott 2009).

3.3.3 Descending Connections

The central auditory system has been described as a hierarchical structure in which auditory input is transduced in the cochlea and conveyed via the auditory nerve, through brainstem and midbrain, to thalamic and finally cortical circuits that include both primary and non-primary fields (Kaas and Hackett, 2000; Hackett, 2015). This hierarchical perspective could be expanded to large-scale cortical networks extending from auditory to parietal and frontal cortices. However, the view that the auditory system (and thus central processing of binaural cues) is hierarchically organized overlooks the many descending connections from higher areas back to lower stages (Ryugo et al. 2011). These descending connections are critical for shaping sensory processing and determining how binaural cues sampled at the periphery are represented in the central auditory system.

In addition to many ascending connections from auditory to prefrontal cortex, PFC also sends dense reciprocal connections back to auditory cortex (Hackett et al. 1999; Romanski et al. 1999). Similarly, auditory cortical neurons send cortico-thalamic projections back to the medial geniculate body (Hackett et al. 1998) and cortico-collicular projections to the inferior colliculus (IC) (Bajo et al. 2007). Thalamus and IC also send their own projections to brainstem nuclei such as the Superior Olivary Complex (SOC) where binaural cues are initially extracted (Stecker, Brown and Bernstein, Chap. 5). IC and SOC neurons project directly to the cochlea, to innervate the inner hair cells through which initial transduction occurs (Schofield and Cant 1999). Thus, the auditory system is structured as a highly interconnected cortical and subcortical network through which information can travel in multiple directions.

At a computational level, the auditory system is therefore actually a heterarchy – a form of network organization in which nodes (e.g., brain regions) are widely interconnected and multiple, complex, and potentially cyclical chains of command exist. In the auditory system, the range of descending connections offers multiple pathways for areas such as prefrontal and parietal cortex to sculpt the neural processing of incoming signals. This may serve the ongoing behavioral goals of the

organism such as selectively attending to a particular sound source or spatial location (Ryugo et al. 2011).

Attention provides an example of descending modulation of sensory function, where neural responses in auditory cortex (Fritz et al. 2003) are shaped by the features of sounds that subjects attend. In auditory cortex, attentional modulation is thought to originate from descending connections from frontal cortex (Fritz et al. 2010). Neurons in frontal cortex are highly selective for behaviorally relevant sounds, and measures of functional connectivity such as coherence between frontal and auditory cortex are enhanced when animals actively discriminate sounds. Similar effects have been observed in spatial working memory tasks, in which human subjects are required to detect whether a target sound differed in location from a reference (Lutzenberger et al. 2002). Here, activity in the gamma frequency range of EEG signals (30 – 80 Hz) was enhanced during the delay period of the task when subjects were required to remember the reference location. Interestingly, gamma-band coherence between left parietal and right frontal regions was also enhanced during this phase, indicating a possible coupling between frontal and parietal cortices to preserve spatial information about binaural cues after sound presentation has ended. One of the limitations of measuring interactions between brain regions using functional connectivity metrics is that connectivity is only implied rather than causally demonstrated. However, by optogenetically stimulating neurons in mice, it has been shown that orbitofrontal cortex directly excites neurons in primary auditory cortex and shapes sound-evoked responses (Winkowski et al. 2018).

An example of descending control of spatial processing comes from the study of gaze direction circuits in barn owls (*Tyto alba*). In the Owl, neurons in the arcopallial gaze fields (AGF) and optic tectum (OT) are necessary for orienting to sound sources (Knudsen and Knudsen 1996). AGF is analogous to the frontal eye fields (FEF) in mammals, and AGF neurons show tuning to localization cues such as ITD and ILD (Cohen and Knudsen 1995). However, unlike other structures such as OT, in which ITD and ILD tuning is organized to create a spatial map, the receptive fields across AGF are not topographically arranged (Cohen and Knudsen 1995). Micro-stimulation of AGF sharpens the spatial selectivity and enhances the responses of neurons in the optic tectum (Winkowski

and Knudsen 2006; Winkowski and Knudsen 2007). Enhanced selectivity is specific for those OT neurons that share similar spatial tuning to the site of stimulation in AGF, while the responses of OT neurons tuned to distant sound locations are suppressed. Enhanced selectivity is achieved by specific improvements in tuning consistency and spatial resolution, whereas suppression is driven by global modulations in neural gain within OT (Winkowski and Knudsen 2008). Together this work offers a potential mechanism by which frontal areas like AGF may shape spatial tuning elsewhere in the auditory system.

Use of mouse models has also allowed detailed dissection of the neural circuits through which spatial attention may route binaural signals towards or away from decision making in mammals (Schmitt et al. 2017). This work suggests that the drive for prefrontal cortex to select a particular rule (i.e., prioritize or ignore binaural cues) is sustained by inputs from mediodorsal thalamus. This study highlights that subcortical processing is critical for coordinating cognitive function in cortical circuits as well as providing ascending auditory input to auditory cortex. Thus, the use of binaural information in auditory behaviors requires large networks including multiple brain structures that undermine strong functional divisions between cortical and subcortical processing of auditory space.

4 Plasticity: Adaptive Encoding of Auditory Space

Attention and behavioral goals shape neural processing of binaural cues on very short timescales, but the use of binaural cues in spatial perception changes over longer timescales. Such plasticity is critical for dealing with changes in head size that occur through development, and adapting to changes in the balance of inputs between the two ears occurring with unilateral hearing loss (Keating and King 2013).

One common approach to studying binaural plasticity is to reversibly alter the relationship between binaural cues and sound location by inserting an ear-plug into one ear to delay and attenuate monaural input. When juvenile owls (Knudsen et al. 1984) or ferrets (Keating et al. 2015) are raised with a unilateral ear-plug, they adapt to altered binaural cues to maintain accurate sound localization.

Correspondingly, neurons in primary auditory cortex show a parallel ability to maintain normal spatial receptive fields by 'remapping' altered binaural cues to sound source location (Fig 3A-B). The ability to relearn sound localization following ear-plugging is not restricted to juvenile animals and can be elicited (and accelerated via training) in adult animals (Kacelnik et al. 2006), including humans (Bauer et al. 1966).

PLACE FIGURE 3 ABOUT HERE

Remapping is the process of relearning the relationship between sensory cues and their values in the world. Remapping is complemented by *reweighting*, where an altered or unreliable cue is given less influence on perceptual judgments while an increased emphasis is placed on other unaltered cues (Fig 3C). Reweighting is particularly relevant for sound localization, where redundant information is potentially provided by ILDs, ITDs and spectral cues (Keating et al. 2015). When relearning to localize sounds after unilateral hearing loss, mammalian listeners reweight sounds to reduce the influence of altered binaural cues and give greater importance to monaural spectral cues received by the unaffected ear (Hofman and Van Opstal, 2002; Keating et al. 2016).

Auditory cortex is implicated as a key site for plasticity for both binaural cues and for restoring the perception of sound elevation after the alteration of spectral cues via ear molds (Trapeau and Schonwiesner 2018). Animals with auditory cortical lesions or inactivation are unable to relearn to localize sounds after the introduction of an ear plug (Nodal et al. 2010; Bajo et al. 2019). However, a complex network of brain areas interacts with auditory cortex to adapt sensory processing. In particular, the cholinergic system is a key driver of plasticity, as lesioning the cholinergic basal forebrain also prevents animals from adapting to an ear plug (Leach et al. 2013). Descending pathways are also critical for implementing plasticity, as selectively ablating the descending connections from layer V in auditory cortex to inferior colliculus also prevents the recalibration of auditory space (Bajo et al. 2010). This suggests that adaptation of binaural processing requires adjustments in subcortical processing by top-down cortical control signals.

5 Unanswered Questions

5.1 Does Auditory Cortex Represent Space or Acoustic Localization Cues?

An open question is to what extent spatial tuning in auditory cortex reflects the encoding of acoustic cues for localization (i.e., ITDs, ILDs, and spectral cues), or the actual location of the sound source in the world. While sound location is tightly linked with the values of acoustic cues, our perception of a location of space does not depend on any one cue. A cue- based representation indicates a neuron is tuned to specific physical variables calculated from sounds arriving at the ears; whereas representations of actual location reflect the computation of an abstract property of a sound source across multiple acoustic cues. Dedicated brainstem nuclei are thought to compute ITDs and ILDs and thus encode specific acoustic cues (see Tolin, Chap. 4 and Stecker, Brown and Bernstein, Chap. 5), however the nature of cortical representations remains unclear.

The Duplex theory (Rayleigh 1907; see Hartmann, Chap. 2) posits that the use of ITDs and ILDs is frequency dependent, with locations of high (>2.5 kHz) and low frequency (<1.5 k Hz) sounds determined primarily by ITDs or ILDs respectively (Wightman and Kistler, 1992; MacPherson and Middlebrooks, 2002). In contrast, representations of actual location should integrate across cues to represent sound position consistently across frequencies. Few studies have explicitly tested whether cortical neurons encode acoustic cues or actual sound location, as stimuli in such experiments tend to be presented over headphones or with broadband energy (and thus multiple acoustic cues available).

One exception is a study of primary auditory cortex in ferrets performing a relative localization task, where subjects reported whether sounds moved left or right in space (Wood et al. 2019). During behavior, spatial tuning of neurons was mapped in response to free-field noise that was filtered below 1 kHz or above 3 kHz, so that ITDs or ILDs (but not both) were primarily available as acoustic cues. The authors hypothesized that neurons encoding actual sound location should have similar tuning curves when tested with either stimulus; whereas neurons tuned to specific acoustic cues should only be spatially tuned when tested with one stimulus type. Consistent with the encoding

of actual sound location, a subset of neurons was found to be tuned to the same locations across stimulus types, indicating that primary auditory cortex encodes abstract information about sound location across acoustic cues.

The representation of actual location rather than acoustic cues in auditory cortex parallels findings in humans. For example, using an adaptor-probe design in MEG studies, Salminen et al. (2015) showed that auditory cortex is highly sensitive to changes in sound location, regardless of whether those changes are conveyed by ITD or ILD. However, the limited spatial resolution of MEG makes it difficult to determine whether the same neuronal population responded to both binaural cue types. Using multivoxel pattern analysis of fMRI data, Higgins and colleagues showed that varying ILDs or ITDs to position sounds in VAS activated overlapping regions of caudal auditory cortex (Higgins et al. 2017b). Furthermore, support vector machine classifiers that were trained to decode ILDs from voxel responses to stimuli containing primarily ILDs could also spontaneously (i.e., without further training) decode ITDs from voxel responses to stimuli containing primarily ITDs. The same was true in the opposite direction for decoders trained to extract ITDs and asked to decode ILDs. Both results support the suggestion that auditory cortex represents location rather than acoustic cues.

5.2 Representing Sound Location in Multiple Coordinate Frames

Given the evidence that auditory cortex represents space, as well as spatial cues, a yet to be addressed question is to what extent the representation in space is tied to head-centered coordinates or to another reference frame (also see Takahashi, Chap. 3). Because the cues to sound localization are inherently head-centered, a head-centered or *craniocentric*, representation of auditory space has (with little verification) been long assumed. However, it is difficult to reconcile head-centered representations with properties of spatial sound perception. For example, when a subject rotates their head in the presence of a static sound source, they perceive a stable sound location despite different populations of neurons firing over time in response to changes in sound position relative to the head.

This perceptual stability may be explained by transformation of sound location into other coordinate systems: In animals that make significant eye movements such as primates, spatial tuning could reflect neural selectivity for sound location relative to the position of the eyes (an eye centered or *occulo-centric* reference frame). Alternatively, spatial sensitivity could reflect tuning to a particular location in the world, independent of the subject's head position or direction (a world-centered or *allocentric* representation).

To illustrate why coordinates of space are important, consider a scenario in which a listener wants to check the caller on their phone while working on the computer (Fig. 4A). Initially, they may orient their eyes towards the phone while keeping their head stationary. In this case, the relevant coordinate frame for action (should they answer the call?) is defined by the eyes rather than the head (Fig. 4B-C) and so the brain must therefore transform head-centered representations of sound location into occulo-centric coordinates.

PLACE FIGURE 4 ABOUT HERE

Aligning our perception of sound location with visual input is a critical step in multisensory integration and requires conversion between craniocentric and occulo-centric coordinates. This computation is thought to be achieved by the level of lateral intraparietal cortex, where LIP neurons have similar spatial tuning to auditory and visual stimuli (Mazzoni et al. 1996; Mullette-Gillman et al. 2005). The coordinate frames of auditory representations in LIP have been studied in delayed-saccade tasks, in which monkeys are presented with a sound and required to make eye movements after a short time interval (Stricanne et al. 1996). In the interval between sound offset and eye movement, LIP neurons show activity that is selective for sound location in either head-centered (33%; 14/43 units) or eye-centered coordinates (44%; 19/43 units), with the remainder of neurons (23%; 10/43 units) showing an intermediate representation. Coordinate frame shifts have also been demonstrated in sound-evoked responses, where neurons throughout PPC (including lateral, medial, and ventral intra-parietal areas) represent sounds in head-centered, eye-centered, and intermediate coordinate frames (Mullette-Gillman et al. 2005; Schlack et al. 2005). Together these results indicate that information

about sound location measured relative to the head through binaural cues is converted within the central auditory system into new spaces. Furthermore, they may explain how gaze direction affects sound localization and spatial stream segregation in human hearing (Maddox et al. 2014; Pomper and Chait 2017;).

While parietal cortex may be critical for converting between reference frames, neural activity at earlier processing stages is also influenced by visual information. Effects of eye position are observed in the inferior colliculus (Groh et al. 2001), and visual stimuli can impact on auditory spatial receptive fields; in some cases, sharpening tuning for auditory-visual stimuli relative to auditory only conditions (Bizley and King 2008). Indeed, as many as 80% of recording sites in auditory cortex show an impact of eye position, with a bias for matching eye position and sound source location (Fu et al. 2004). The effects of gaze are strongest in the superficial / supra-granular layers and occur on a relatively slow timescale, suggesting that these signals are likely to be feedback signals, possibly originating in parietal or prefrontal cortex.

Returning to the example of the ringing phone, if the listener is working on something important, they may simply want to silence the call without shifting our gaze – they might therefore reach for the phone and press the relevant button without looking at all. To do this, head-centered sound location must be related to the motor system and specifically the coordinate systems of the hand, arm, and body (Fig. 4D). Cohen and Andersen (2000) extended the study of coordinate frame representations to similar circumstances by asking monkeys to (1) press buttons depending on sound location while fixating gaze on a constant point, or (2) make saccades to sound locations while maintaining a constant hand position. During task performance, neurons were recorded from the parietal reach region (PRR) – an area of posterior parietal cortex in which cells are active when planning reaches (Andersen and Buneo 2002). Within PRR, neurons were found to be sensitive to sound location and this spatial sensitivity was modulated by both hand and eye position (although more neurons were modulated by eye than hand position). Thus, binaural cues sampled at the ear are transformed into a range of spatial coordinate frames that are relevant for the motor system and behavioral output.

Finally, if the example listener is fortunate enough to have a helpful colleague willing to answer the phone, they could ask their colleague to take the call. If the listener wants to describe the phone's location to this other person, however, it is unhelpful to refer the sound's location in a coordinate system defined by the listener's own head, eyes, or other body part as the colleague does not share the listener's egocentric reference frames. Instead, it is more useful to describe the sound's location in a shared reference frame, such as that defined by the outside world (i.e., an allocentric representation, Fig. 4E). Thus, one person might ask another to pick up the phone "from my coat pocket" rather than the phone "to my right, slightly above my head." Such descriptions indicate that listeners can represent sound location in their environment, and have motivated investigations of corresponding neural correlates: Using EEG, several groups have studied the coordinate frames underlying spatial mismatch negativity (MSN)- an amplified neural response to changes in location of a repeated sound. Subjects were presented with a sequence of standard sounds (noise bursts) from a constant location, before being tested with a deviant stimulus that changed position in either head or world coordinate systems. Changes in both world-centered and head-centered sound location elicited MSN responses indicating that human auditory cortex encoded the location of standard sounds in both craniocentric and allocentric space (Altmann et al. 2009; Schechtman et al. 2012).

EEG studies are limited in their ability to localize the sources of neural activity within cortex; however, the co-existence of world-centered and head-centered representations has been confirmed using single neuron recordings within auditory cortex (Town et al. 2017). By recording neurons in freely moving subjects, sound location was varied in both head and world coordinate systems. This allowed spatial tuning of neurons to be contrasted in the two spaces, with most units (80%) tuned to head-centered location, while a smaller population (20%) represented sound position in the world across changes in animals' head direction.

Across the central auditory system then, binaural cues sampled relative to the head are used to represent sound location in a variety of coordinate frames. Coordinate frame transformations allow listeners to organize behavioral responses using their body and to infer the spatial organization of an auditory scene in the environment beyond themselves. However, many open questions remain about

how neural circuits within the brain perform these transformations and integrate signals from other sensory systems into auditory processing.

6 Chapter Summary

The work summarized in this chapter emphasizes that central processing of binaural cues involves large-scale cortical networks including many brain regions. The flow of information within these networks appears to be complex, as the neural processing of stimuli arriving at the ear occurs within the context of ongoing neural activity that is shaped by the subject's attentional state prior to sound onset. Thus, binaural cue processing does not simply proceed serially through the ascending auditory system, but rather involves the integration of incoming sounds with simultaneous multidirectional signaling up ascending and down descending pathways. Disentangling these processes to understand the neural mechanisms of spatial sound perception is thus a significant challenge, but one that is critical for treating sound localization deficits following impairment of hearing or cognitive function.

To understand how neural circuits function, we need as many tools from neuroscience as possible. One of the challenges for spatial hearing is that most advanced techniques for studying brain activity (optogenetics, calcium-imaging, etc.) have been developed in mice. However, it is not clear how binaural processing in mice, in which ILDs are the dominant localization cue, can be related to humans, other primates, or carnivores in which both ITDs and ILDs are combined for spatial perception. Thus, to understand our own spatial hearing, it may be that cutting edge approaches developed for mice must be expanded to other species – particularly those that share our sensitivity to low frequencies and our ability to localize sounds with high acuity.

As principles of spatial auditory processing continue to evolve, it will be important to understand their implications for neuroplasticity and therapeutic strategies addressing hearing loss. For example, plastic changes in brain function following hearing impairment (e.g., ear plugging) occur within the context of existing spatial processing. The implications (and therapeutic

opportunities) of phenomena such as remapping and reweighting therefore must be considered within the context of binaural cue integration, when ILDs and ITDs are integrated into a representation of space across cues. Cue integration may enable more reliable estimates of sound location, but it also provides a specific locus for which reweighting of each cue would be possible following unilateral hearing loss. Thus, if the integrated signal of space is the output from auditory cortex (rather than both binaural cues), then the opportunity to reweight cues later on in the network might be limited, and we would expect remapping to become the dominant form of plasticity in regions such as prefrontal and parietal cortex. Such hypotheses remain to be tested, when the effects of hearing loss on neural processing are studied beyond auditory cortex.

Overall, decades of research have shown that the processing of binaural cues and sound location are significant components of auditory function across cortex. However, we have only scratched the surface of how neural circuits operate, and future developments will likely require integration of knowledge across multiple cortical fields, between cortical and subcortical brain areas, and from fields as diverse as cellular physiology, computational neuroscience, and clinical audiology to understand healthy and impaired spatial hearing. Furthermore, to understand how the central auditory system turns binaural cues into sound perception, it will be critical to study neural processing during active listening, in behaving subjects where processes such as attention and dynamic decision-making can be observed.

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Compliance with Ethics Requirements

Stephen Town declares that he has no conflict of interest.

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Tables

Table 1 List of Abbreviations

A2	Secondary Auditory Cortex
AAF	Anterior Auditory Field
AES	Anterior Ectosylvian Sulcus
AGF	Anterior Gaze Fields
dlPFC	Dorsolateral Prefrontal Cortex
DZ	Dorsal Zone
EEG	Electroencephalography
FEF	Frontal Eye Fields
fMRI	Functional Magnetic Resonance Imaging
GABA	Gamma-Aminobutyric Acid
HG	Heschl's Gyrus
IC	Inferior Colliculus
ILD	Interaural Level Difference
IPD	Interaural Phase Difference
IPL	Inferior Parietal Lobule
ITD	Interaural Time Difference
LIP	Lateral Intraparietal Cortex
MEG	Magenetoencephalography
MGB	Medial Geniculate Body
mPFC	Medial Prefrontal Cortex
OT	Optic Tectum
PAF	Posterior Auditory Field
PET	Positron Emission Tomography
PFC	Prefrontal Cortex

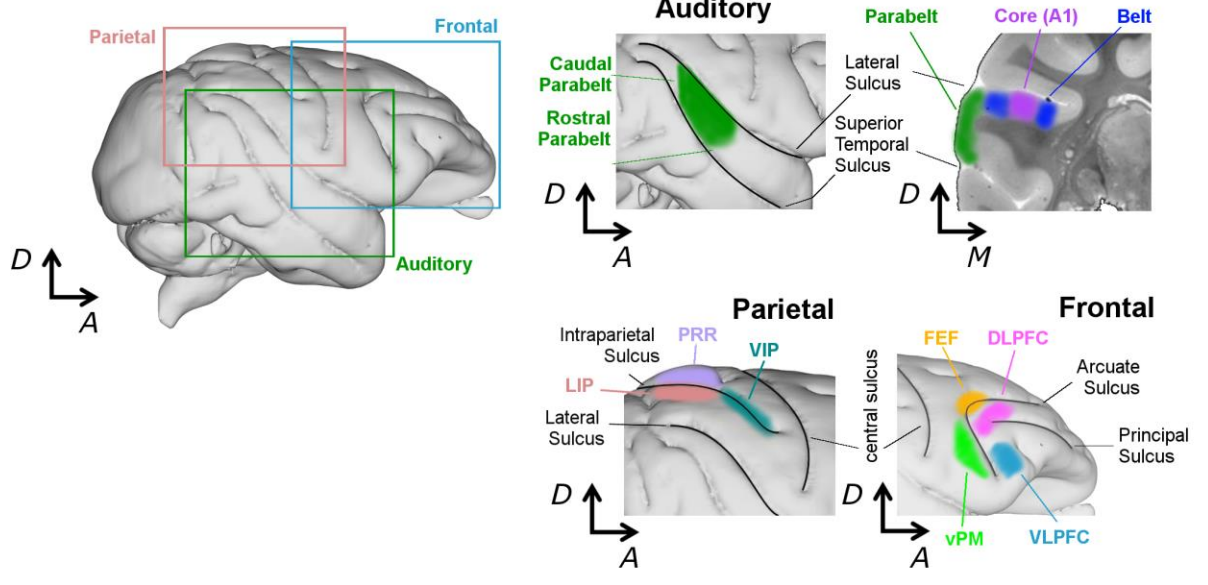|	
PPC	Posterior Parietal Cortex
PRR	Parietal Reach Region
PT	Planum Temporale
SOC	Superior Olivary Complex
SPL	Superior Parietal Lobule
SRF	Spatial Receptive Field
STG	Superior Temporal Gyrus
VAS	Virtual Acoustic Space
VIP	Ventral Intraparietal Cortex
vlPFC	Ventrolateral Prefrontal Cortex
vPM	Ventral Premotor Area

Figure Captions

Figure 1 Anatomical Organization of Binaural Cue Processing in Cortex

A, Human and B, macaque brains (left) with insets depicting auditory cortical (lateral, transverse and coronal views in A, lateral and coronal views in B), parietal, and frontal cortical areas (lateral views) associated with sound localization and binaural cue processing. Specific cortical areas are highlighted in color. Orientation arrows indicate D; dorsal, A; anterior, M; medial, L; lateral. A1 indicates primary auditory cortex. Note that the precise boundaries for human auditory cortex are unclear and the example shown represents one potential organization. Human brain images are modified from (Society for Neuroscience (2017). Macaque data from (Rohlfing et al. 2012).

A Human

Auditory

Superior Temporal Gyrus
(Superior Temporal Suclus)

Transverse

Planum Temporale

Heschl's Gyrus
(A1)

Coronal

Parietal

Frontal

Parietal

Superior Parietal Lobule

Supramarginal Gyrus

Frontal

Inferior Frontal Gyrus

B Macaque

Parietal

Frontal

Auditory

Auditory

Caudal Parabelt

Rostral Parabelt

Lateral Sulcus

Superior Temporal Sulcus

Parabelt

Core (A1)

Belt

Parietal

Intraparietal Sulcus

PRR

VIP

LIP

Lateral Sulcus

Frontal

FEF

DLPFC

Arcuate Sulcus

Principal Sulcus

central sulcus

vPM

VLPFC

Figure 2 Attentional Modulation of Cortical Processing

(**A**) A sound source at 30° generates ITDs, ILDs, and monaural spectral cues. Within the brain, neurons may be sensitive to specific cues (e.g. ITD or ILD) that covary with spatial position (top), or may 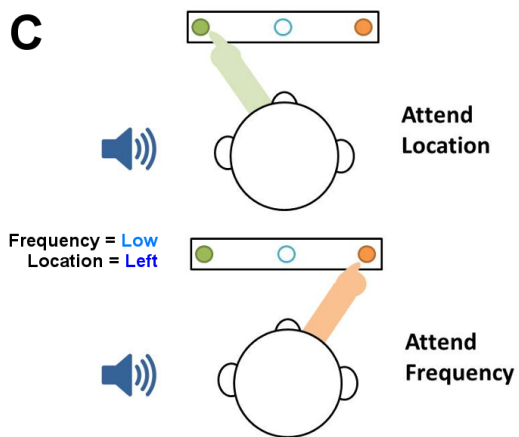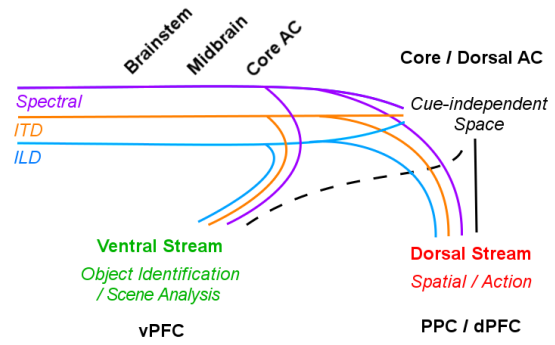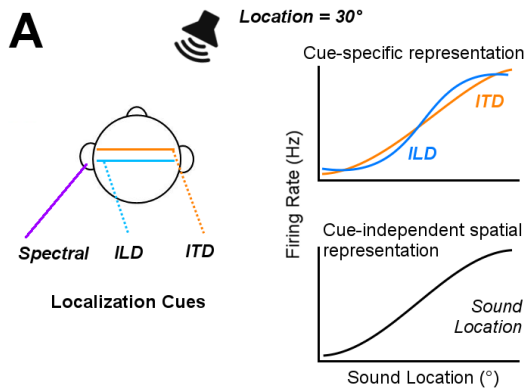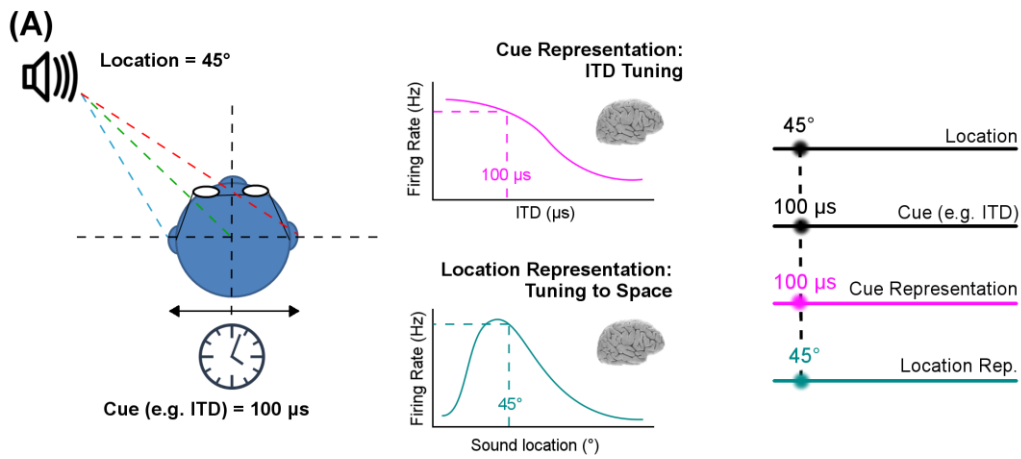integrate these cues into a cue-independent representation of sound location (bottom). Schematic showing the flow of localization cue information through the central auditory system and into dorsal and ventral processing streams. Within auditory cortex, some neurons encode a cue-independent representation of space. (**B-D**) Studying attentional modulation using task-switching. (**B**) An example experimental design in which subjects are presented with high or low frequency sounds from either left or right. On different trials, subjects are instructed to report either the location or frequency of the sound (**C**) and so respond differently to the same stimulus, depending on attentional condition (**D**). The highlighted cell (yellow) indicates the example stimulus shown in C. (**E**) Attention modulates neural activity across the central auditory system during, and before, sound onset. Shown are hypothetical responses of two neurons recorded from auditory cortex and medial prefrontal cortex to the same sounds, depending on whether the animal is required to report the sound's location or frequency.

A

Location = 30°

Cue-specific representation

Firing Rate (Hz)

ITD

ILD

Spectral ILD ITD

Localization Cues

Cue-independent spatial representation

Sound Location

Sound Location (°)

Brainstem Midbrain Core AC

Core / Dorsal AC

Spectral

ITD

ILD

Cue-independent Space

Ventral Stream

Object Identification / Scene Analysis

vPFC

Dorsal Stream

Spatial / Action

PPC / dPFC

B

Response Options

Left Location Low Frequency

Frequency

High

Low

Left

Right

Location

C

Attend Location

Frequency = Low
Location = Left

Attend Frequency

D

Attend Location

		Location	
		Left	**Right**
Freq.	**High**	●	○
	Low	●	○

Attend Frequency

		Location	
		Left	**Right**
Freq.	**High**	○	○
	Low	●	●

E

Auditory Cortex

Attend Location
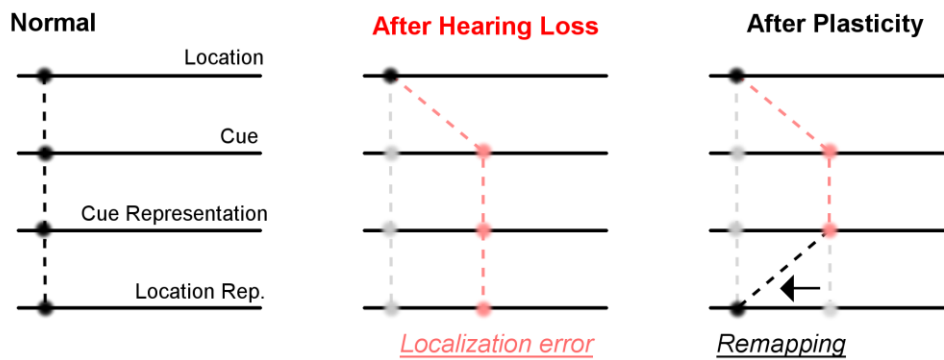
Attend Frequency

mPFC

Time

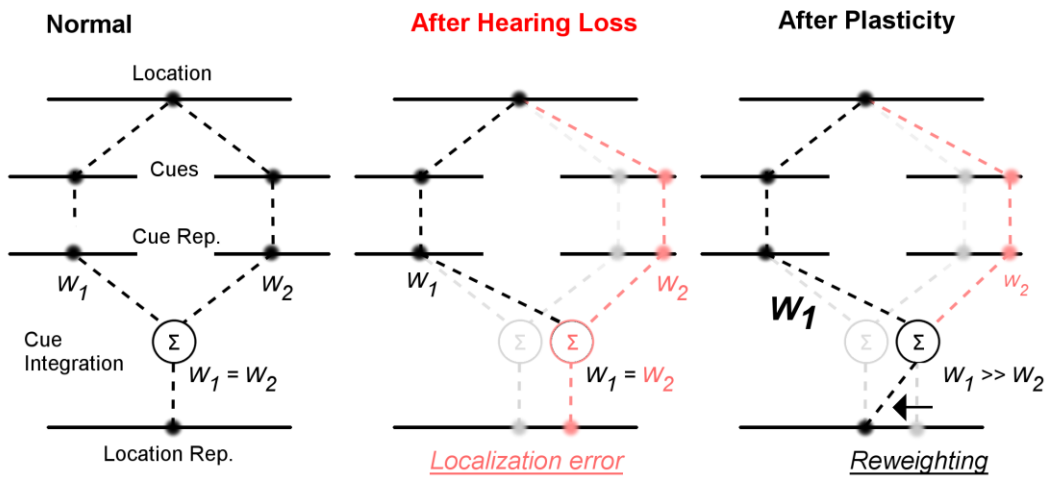**Figure 3 Remapping and Reweighting Cues in Cortical Processing**

(**A**) Cartoon illustrating how a sound source at a particular location generates acoustic cues, such as ITDs. In the brain neurons are tuned to particular ITDs (top) such that the firing rate of a given neuron can indicate the ITD that was presented. Other neurons (bottom) represent the spatial position itself, which is presumably computed from cue-sensitive neurons. At each step, the localization cue and firing rates of neurons can be schematically represented as values on a scale, with the relationship between values indicated by their relative position (right). (**B**) In remapping, hearing loss produces distorted acoustic cues, which initially affects the representation of the sound's location within the brain, leading to errors in localization. Plasticity allows the brain to compensate for the altered cues by altering the relationship between neural representations of acoustic cues and sound location (arrow). (C) Multiple cues (e.g., ITDs and ILDs) are represented in the brain and will be integrated using specific weights for each cue (W_1 and W_2) to localize sounds. If hearing loss distorts one cue (e.g., ILD) this will lead to localization errors. However, if other cues remain reliable, the brain will learn to rely more heavily on the intact cues by changing the size of W_1 and W_2. Reweighting therefore reduces the contribution of distorted cues, so that localization accuracy recovers following plasticity.

(A)

Location = 45°

Cue (e.g. ITD) = 100 µs

Cue Representation: ITD Tuning

Firing Rate (Hz)

100 µs

ITD (µs)

Location Representation: Tuning to Space

Firing Rate (Hz)

45°

Sound location (°)

45°   Location

100 µs   Cue (e.g. ITD)

100 µs   Cue Representation

45°   Location Rep.

(B) Remapping

Normal

After Hearing Loss

After Plasticity

Location

Cue

Cue Representation

Location Rep.

Localization error

Remapping

(C) Reweighting

Normal

After Hearing Loss

After Plasticity

Location

Cues

Cue Rep.

W_1 W_2

Cue Integration

Σ $W_1 = W_2$

Location Rep.

W_1 W_2

$W_1 = W_2$

Localization error

W_1 W_2

$W_1 \gg W_2$

Reweighting

Figure 4 Representing sound location in multiple coordinate frames

Cartoons show a scenario where a listener, seated at a desk, hears a ringing phone. (**A**) In such a situation the sound can be represented in multiple coordinate systems relative to, or independently from, an observer. (**B-E**) For each system the coordinates are depicted by axis, and the angle of the position of the phone is depicted by the orange arrow (**B**) Head-centered sound location, which has been traditionally associated with binaural cue processing. (**C**) Eye-centered location that has been studied in inferior colliculus, auditory cortex, and parietal cortex. (**D**) Arm-centered/hand-centered location that is relevant for neurons in the parietal reach region. (**E**) World-centered coordinate frames which have been observed in auditory cortex.