Department of Biomedical Engineering and Computational Science

# Representation of auditory space in human cortex

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**Nelli Salminen**

Aalto University

DOCTORAL
DISSERTATIONS

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**DOCTORAL DISSERTATIONS** 20/2011

# Representation of auditory space in human cortex

**Nelli Salminen**

Doctoral dissertation for the degree of Doctor of Philosophy to be presented with due permission of the School of Science for public examination and debate in Auditorium of the Department of Biomedical Engineering and Computational Science at Aalto University School of Science (Espoo, Finland) on the 25th of March 2011 at 12 noon.

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# Abstract

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## Abstract

Auditory space poses a difficult computational challenge to the nervous system. The localization of a sound source is based on the extraction of cues embedded in a neural representation organized according to sound frequency. Single-neuron studies on the neural representation of space and the computations leading to it have been performed on animals. This has given rise to two alternative models of auditory spatial representation: a place code consisting of narrow spatial receptive fields and a hemifield code formed by neurons tuned widely to the left or to the right. The aim of this thesis was to reveal which of these codes explains the representation of auditory space in human cortex.

Predictions based on the place and the hemifield code were tested in a series of magnetoencephalography (MEG) experiments utilizing a stimulus-specific adaptation paradigm. The pattern of location-specific adaptation of brain responses found for realistic spatial sound stimuli closely followed that predicted by the hemifield code. Further, results consistent with the hemifield code were found also with sound containing only the interaural time difference cue for which place coding has long been assumed to apply. The right hemisphere contained more neurons tuned to the left than to the right hemifield whereas such asymmetries did not occur in the left hemisphere. Cortical activity was found in parietal and frontal areas but only after the presentation of a target stimulus requiring an active response. The implications of wide neural tuning for sound discrimination were explored in a neural network model. The best discrimination power of neurons was found to be related to the slopes of the tuning curves which in the hemifield code coincide with frontal sound source directions that are optimally localized by human listeners.

In conclusion, the results support a hemifield code representation of sound source location in human cortex formed by two populations of neurons: one tuned to the left and the other to the right hemifield. Further, the present studies provide an encouraging example on how theories originating from studies of single-neuron tuning properties can be tested with methods available for the study of human brain function at the mass-action level.

**Keywords** spatial hearing, magnetoencephalography, cortex, stimulus-specific adaptation

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**Tiivistelmä**

Äänen tulosuunnan havaitseminen asettaa hermoston toiminnalle haastavan laskennallisen tehtävän. Äänilähteen sijainnin havaitseminen perustuu vihjeisiin, jotka on poimittava äänen taajuuden perusteella jäsentyneestä hermostollisesta edustuksesta. Yksittäisten solujen toimintaan kohdistuvat tutkimukset eläimillä ovat johtaneet kahteen vaihtoehtoiseen malliin äänen tulosuunnan hermostollisesta esityksestä. Paikkakoodauksessa solujen reseptiiviset kentät äänen tulosuunnalle ovat kapeita. Puolikenttäkoodi vuorostaan muodostuu soluista, joiden reseptiiviset kentät ovat leveitä ja kattavat joko vasemman tai oikean puolen kuuloavaruudesta. Tämän väitöskirjan tavoitteena oli selvittää kumpi näistä koodeista vastaa äänilähteen sijainnin edustusta ihmisen aivokuorella.

Mallien perusteella muotoiltujen ennusteiden pätevyyttä arvioitiin sarjassa magnetoenkefalografia-mittauksia, joissa sovellettiin ärsykekohtaisen adaptaation paradigmaa. Kun mittauksissa esitettiin todenmukaisia tilaääniä, aivovasteiden adaptaatio noudatti tarkasti puolikenttäkoodin perusteella tehtyjä ennusteita. Myös silloin kun äänissä esiintyi ainoana sijaintivihjeenä korvien välinen aikaero, tulokset olivat puolikenttäkoodin mukaiset, vaikka tämän vihjeen hermostollisen esityksen on pitkään oletettu olevan paikkakoodi. Oikealla aivopuoliskolla oli enemmän vasemmalle kuin oikealle puolelle virittyneitä soluja, kun taas vasemmalta aivopuoliskolta tällaisia eroja ei löydetty. Kun koehenkilöltä edellytettiin äänten havainnointia, kuuloaivokuoren lisäksi päälaen- ja otsalohkolla havaittiin aktiviteettia, mutta ainoastaan tarkkailun kohteena olleiden äänien esityksen yhteydessä. Leveiden virityskäyrien vaikutuksia äänien erotteluun arvioitiin hermoverkkomallin avulla.

Tämän väitöskirjan tulosten perusteella äänen tulosuunnan edustus ihmisen kuuloaivokuorella näyttää noudattavan puolikenttäkoodia, joka koostuu ääniavaruuden oikealle tai vasemmalle puolelle virittyneistä soluista. Lisäksi tutkimukset ovat kannustava esimerkki siitä, että yksittäisten solujen ominaisuuksien perusteella muodostettuja teorioita on mahdollista arvioida ihmisaivojen tutkimukseen soveltuvilla menetelmillä.

**Avainsanat** suuntakuulo, magnetoenkefalografia, aivokuori, ärsykekohtainen adaptaatio

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# CONTENTS

# List of publications

This thesis is based on the following five publications. They are referred to in the thesis by their roman numerals.

- **I** Salminen NH, May PJC, Alku P, Tiitinen H (2009) A population rate code of auditory space in the human cortex. *PLoS ONE*, 4:e7600 (1-9).
- **II** Salminen NH, Tiitinen H, Yrttiaho S, May PC (2010) The neural code for interaural time difference in human auditory cortex. *Journal of the Acoustical Society of America*, 127:EL60-65.
- **III** Salminen NH, Tiitinen H, Miettinen I, Alku P, May PJC (2010) Asymmetrical representation of auditory space in the human cortex. *Brain Research*, 1306:93-99.
- **IV** Tiitinen H, Salminen NH, Palomäki KJ, Mäkinen VT, Alku P, May PJC (2006) Neuromagnetic recordings reveal the temporal dynamics of auditory spatial processing in the human cortex. *Neuroscience Letters*, 396:17-22.
- **V** Salminen NH, Tiitinen H, May PJC (2009) Modeling the categorical perception of speech sounds: A step toward biological plausibility. *Cognitive, Affective, & Behavioral Neuroscience*, 9:304-313.

### Author's contributions

The studies of this thesis were a collaborative effort. The candidate planned the experiments in Studies I, II, and III. The candidate prepared the stimulus material in Studies II and V and participated in the preparation in Studies I and III. The candidate performed data acquisition for Studies I, II, and III and participated in the recordings in Study IV. All data analyses and modeling work were performed by the candidate. The candidate wrote Publications I, II, III, & V with input from the other authors.

# List of abbreviations

| | |
|---|---|
| EEG | electroencephalography |
| ERF | event-related field |
| ERP | event-related potential |
| fMR | functional magnetic resonance imaging |
| HRTF | head-related transfer function |
| IC | inferior colliculus |
| ILD | interaural level difference |
| ITD | interaural time difference |
| LSO | lateral superior olive |
| MEG | magnetoencephalography |
| MMN | mismatch negativity |
| MSO | medial superior olive |
| PET | positron emission tomography |
| SC | superior colliculus |

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I would like to thank the preliminary examiners Professors Jennifer M. Groh and Jyrki Ahveninen for their thoughtful comments on the thesis.

I wish to express my heartfelt gratitude to my supervisor Professor Mikko Sams for all his encouragement during this work. His enthusiasm and love for science make it a great pleasure to work with him. I also wish to thank all the members of the Mind and Brain Laboratory at the Department of Biomedical Engineering and Computational Science for making it such an inspiring environment.

The experiments described in this thesis were conducted at the BioMag Laboratory. I thank Dr Jyrki Mäkelä for always making me feel welcome there and Dr Juha Montonen for his help with technical issues.

For the opportunity to study spatial hearing, I am grateful to Professor Paavo Alku from the Department of Signal Processing and Acoustics. I also wish to thank Dr Miikka Tikander for his careful work and expertise in constructing sound material.

During this work I have been very fortunate to share the office with Ismo Miettinen and Santeri Yrttiaho. Their company through the best and worst times has been much appreciated. I thank them for inspiring conversations, good humor and compassion, and for all the help at the lab.

This work would not have been possible without the continued support and encouragement from my thesis instructors Docents Patrick May and Hannu Tiitinen. They have shown endless patience and confidence in my abilities as I have tried and failed repeatedly until finally finding the right way. They never lost faith in me and for that I am deeply grateful.

Finally, I would like to thank my family for their unconditional support for whatever I have chosen to do. My deepest gratitude goes to my husband Hugo Gabriel Eyherabide for his love and for reminding me every day on what is really important in life.

Espoo, March 2011
Nelli Salminen

# 1. INTRODUCTION

Hearing has a special role in allowing us to be aware of our environment. Audition provides us with information on objects and events in all directions, in darkness and behind visual obstacles. Compared to audition, other sensory modalities are spatially limited: vision to locations in front and to objects not occluded by others and the somatosensory system to objects very near the body. Hearing allows the detection of potentially harmful or desirable objects in all directions and lets us know where in our environment these objects are. This helps us in choosing the direction to which to move in order to avoid or approach the object and in directing other sensory modalities to the location of interest to gain more information.

Auditory spatial awareness poses a difficult computational challenge to the human brain. Auditory sensors are organized according to sound frequency and the tonotopic organization is maintained throughout the entire auditory pathway from the ears to the auditory cortex. The location of the sound source needs to be computed based on acoustical cues embedded in the tonotopically organized representation of sound. Human behavioral sound source localization relies on the differences in timing and level between the signals arriving to the two ears and on the spectral structure of the sound (Blauert 1997).

Studies on the neural bases of auditory spatial cognition in humans have revealed a network of areas that take part in sound source localization consisting of auditory cortical areas in the temporal cortex as well as posterior parietal and frontal areas (Rauschecker & Tian 2000). The main focus of the research on human auditory spatial processing has been on finding out where in the brain spatial processing takes place. Much less attention has been dedicated to understanding how these brain areas extract and represent spatial information and what their tasks in establishing auditory spatial cognition are.

The question of how auditory space is neurally computed has received much attention in animal studies and computational modeling efforts (Grothe et al. 2010). From this work, two alternative schemes of auditory spatial representation have emerged. In the place coding strategy, spatial receptive fields are narrow and all locations in space are represented by neurons dedicated to coding them (Jeffress 1948, Joris et al. 1998). In the hemifield code, spatial receptive fields are wide and centered to the left or right (van Bergeijk 1962, Grothe 2003). Animal studies have found evidence both in favor and against each of these two models. Their suitability for describing human brain function has not been addressed.

This thesis consists of studies on the representation and processing of auditory space in human cortex. The primary method was magnetoencephalography (MEG) recordings of normal human brain function in response to realistic spatial sound stimuli. The interpretation of the experimental data was facilitated by neural network models. The aim of the studies was to determine which of the alternative models, the place code or the hemifield code, better describes the form of auditory spatial representation in human brain. Further, the implications of the receptive field properties and the participation of various cortical areas to active sound source localization behaviors were explored.

# 2. BACKGROUND

## 2.1 Sound source localization by humans

The perception of sound source location is based on the extraction of acoustical localization cues (Blauert 1997). The sound is altered on its path from the source to the eardrums of the listener. This gives rise to features in the relative timing and level of the sound in the two ears and in the spectral structure. These features are dependent on the location of the sound source with respect to the listener and, therefore, they can be used as cues for perceiving auditory space.

### *2.1.1 Acoustical cues for sound source localization*

A sound from a single source may reach one of the ears slightly before the other depending on the direction in which the source is in the horizontal plane (Fig. 1; Strutt 1907, Hartley & Fry 1921, Firestone 1930, Mills 1958, Kuhn 1977). For instance, when a sound source is to the left of the listener, the sound source is closer to the left than to the right ear and, therefore, the wave front will reach the left ear slightly before the right one (Fig. 2). This difference in arrival times is called the interaural time difference (ITD). In natural listening conditions, ITDs range from 0 ms when the sound source is directly in front or behind the subject (at 0° or 180° of azimuth) to 0.65-0.7 ms for extreme left and right locations (at -90° or 90°; Kuhn 1977). The upper limit of possible ITD values is determined by the size of the human head, i.e. the distance between the two ears.

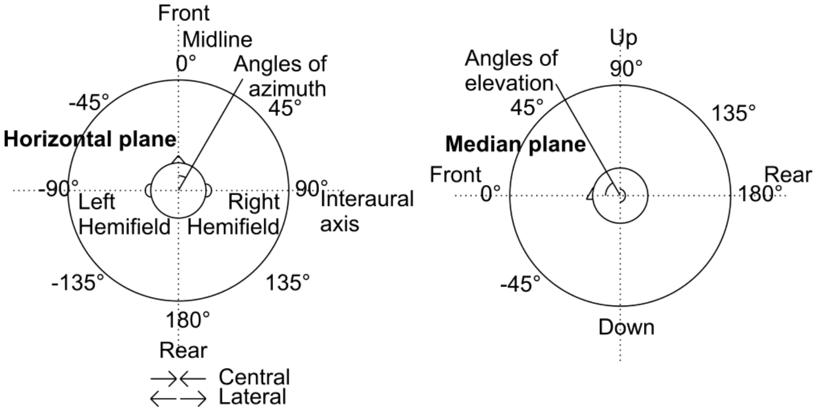

**Figure 1.** A coordinate system of auditory space used in spatial hearing experiments. The direction of a sound source with respect to the listener can be described in angles of azimuth and elevation.

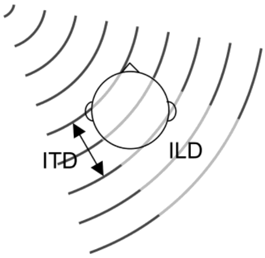

**Figure 2.** The binaural localization cues. An interaural time difference (ITD) occurs when the sound reaches one ear before the other. An interaural level difference (ILD) is created by the head shadow.

The path traveled by the sound from the source to the ears causes alterations also to sound level. The head acts as an acoustical shadow and attenuates the sound traveling to the ear on the side opposite to the sound source (Fig. 2). This results in an interaural level difference (ILD). The magnitude of ILD depends on sound frequency (Hartley & Fry 1921, Firestone 1930, Sivian & White 1933, Shaw 1974). Sounds with long wavelength (low frequency) travel around the head with very little change in level but higher frequencies are attenuated strongly. ILD is minimal when the sound source is on the midline and increases when it moves towards the left or right. This increase is not monotonic but instead maximal ILDs may occur for locations at approximately 50° to 60° from the midline and decline for locations further to the side (Firestone 1930, Shaw 1974). The exact pattern of ILD variation according to horizontal sound source location is dependent on sound frequency.

The binaural ITD and ILD cues provide information on lateralization (location in the left-right axis) of the sound source but are ambiguous about the elevation and on whether the sound source is in front or behind the listener. These ambiguities do not occur in monaural spectral cues which arise from the filtering effects of the pinnae, the head, and the body. These alter the sound spectrum selectively by attenuating and amplifying different frequencies depending on the direction from which the sound arrives (Shaw 1974, Wightman & Kistler 1989a). This leads to a distinct pattern of spectral alterations corresponding to each location in the three dimensional auditory space. Prominent spectral cues mostly occur in high frequencies as the short wavelengths resonate well with the relatively small structures of the human outer ear.

### *2.1.2 Behavioral performance in localization*

Humans can localize sounds presented from speakers in a free auditory field with an accuracy ranging from one to several degrees depending on the location of the sound source (Mills 1958, Wightman & Kistler 1989b, Makous & Middlebrooks 1990). Localization performance in the horizontal plane is at its best for sound sources directly in front. There, subjects can point to the location of a sound source with the accuracy of 2° (Makous & Middlebrooks 1990) and detect changes in location as small as 1° (Mills 1958, Perrott & Pacheco 1989, Perrott & Saberi 1990). For sound sources to the left or to the right of the listener, pointing accuracy drops to about 6-10° (Makous & Middlebrooks 1990) and the smallest change that can be detected is 6° (Mills 1958).

In addition to the sound source direction, localization accuracy depends on the characteristics of the sound itself. Wideband white noise is relatively easy to localize as it contains frequencies needed for carrying all the localization cues: ITD, ILD, and spectral cues. For low frequency sounds, localization relies on ITD as the ILD and spectral cues are weak (Strutt 1907, Stewart 1920ab, Simpson 1920, Mills 1958, Wightman & Kistler 1992). For frequencies higher than about 1.3 kHz, ITD becomes ambiguous as the wavelength of the sound is short relative to the distance between the two ears (Fig. 3; Stewart 1920b, Klumpp & Eady 1956, Zwislocki & Feldman 1956, Yost 1974). For frequencies higher than this, localization relies primarily on ILD (Strutt 1907, Mills 1960) and spectral cues (Gardner & Gardner 1973, Hebrank & Wright 1974, Carlile et al. 1999). However, when the sound contains slow amplitude modulation, ITD can also be detected in high frequency sounds (Klumpp & Eady 1956, David et al. 1959, Henning 1974, Nuetzel & Hafter 1976, McFadden & Pasanen 1976).

Spectral cues are essential for localizing sound sources in elevation and for distinguishing between sound sources in front and in rear directions (Roffler & Butler 1967a, Gardner & Gardner 1973, Hebrank & Wright 1974, Langendijk & Bronkhorst 2002). They also create the impression of sounds originating from locations outside the head (Plenge 1974, Wightman & Kistler 1989a, Hartmann & Wittenberg 1996). When spectral cues are disrupted or made unavailable, localization is possible only in the left-right dimension. The spectral cues are individual for each listener and one way of disrupting them is to present virtual spatial sound stimuli based on the spectral cues of another listener (Butler & Belendiuk 1977, Wenzel et al. 1993). Situations in which the spectral cues are not useful occur also in natural listening conditions. When the sound has no energy in high frequencies, it cannot carry spectral cues (Gardner & Gardner 1973, Hebrank & Wright 1974, Carlile et al. 1999). Also, in the case of sounds with narrow bandwidth (Pratt 1930, Roffler & Butler 1967ab, Butler & Planert 1976, Middlebrooks 1992) or a spectral structure that varies unpredictably (Wightman & Kistler 1997, MacPherson & Middlebrooks 2003), the interpretation of spectral cues becomes erratic whereas binaural cues can still be used effectively.

When listened to in isolation through headphones, ITD and ILD cues produce the impression of a sound source located inside the head in varying positions along the axis between the ears. In head-phone presentation, the perception of ITD and ILD can be tested beyond their naturally occurring limits. ITDs are normally shorter than approximately 0.7 ms but for wide-band sounds interaural delays up to several milliseconds are perceived as sounds originating from the side of the ear with the leading signal (Blodgett et al. 1956, Mossop & Culling 1998). The ability to discriminate between small differences in ITD is however better for ITDs within realistic values suggesting that the human auditory system is specialized in processing physiologically plausible values of ITDs (Mossop & Culling 1998). ILDs occur naturally only for high-frequency signals but when an ILD is imposed on a low-frequency sound it is still perceived lateralized towards the ear with the higher signal level (Feddersen et al. 1957, Small et al. 1959, Mills 1960, Hafter et al. 1977). The discrimination of ILDs is slightly poorer for low than for high frequencies but this difference is very small (Small et al. 1959, Mills 1960, Hafter et al. 1977). That is, the ILD detection system shows only weak specialization to the frequencies in which ILDs occur in natural hearing.

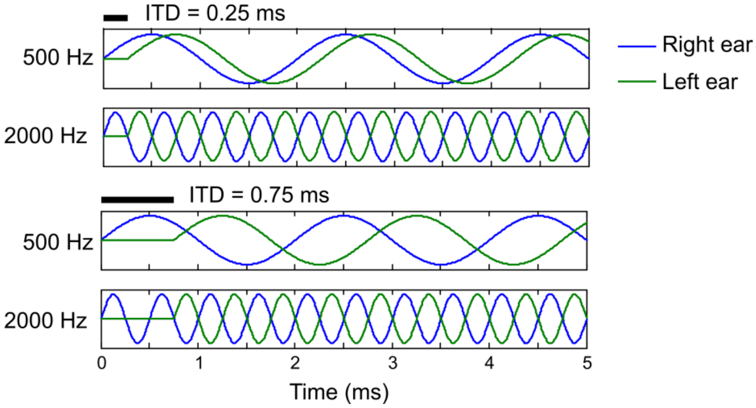

**Figure 3.** Sound waves reaching the ear for a low- and high-frequency tone at two ITDs. For the low-frequency tone, the two ITDs can be distinguished from one another. For the high-frequency tone, the ITD is long compared to the wavelength of the sound and the cue becomes ambiguous.

## 2.2 Processing of auditory space in cortex

The auditory cortex is essential for localization behavior. In the absence of the auditory cortex, animals are not capable of approaching sound sources in their environment (Thompson & Cortez 1983, Heffner 1997) and human patients with auditory cortical lesions show similar deficits (Zatorre & Penhune 2001). The studies of the intact human brain have provided lines of converging evidence on the importance of the cortex in auditory spatial cognition. For the study of normal human brain function, several methods are available and these measure different aspects of neural activity. Electroencephalography (EEG) and magnetoencephalography (MEG) measure the electrical activity of the brain. When a large number of neurons are active concurrently, the combined electrical current and the magnetic field associated to it can be measured non-invasively with EEG and MEG, respectively. The activity related to the presentation of a sound is of small amplitude and occluded in the ongoing brain activity and in the background noise of the recording. To make the sound-related activity detectable, activity following the sound presentation is averaged over several repetitions. These averaged responses are called auditory event-related potentials (ERPs) and fields (ERFs), in EEG and MEG respectively. The ERPs and ERFs found for the presentation of a transient sound have a stereotyped form consisting of several response deflections. The most prominent peak is the N1 or N1m (in ERPs and ERFs, respectively) that occurs at around 100 ms after stimulus onset (Elberling et al. 1980, Hari et al. 1980). Other important methods include functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) that detect changes in metabolism and blood flow that accompany neural activation. All of these methods provide information on neural processing at the level of large neural populations. Recording the activity of single neurons is possible normally only in animal studies.

### *2.2.1 Selectivity to spatial location in the human auditory cortex*

Previous studies suggest that neurons selective to sound source location exist in the human auditory cortex. This evidence comes from studies that utilize the effects of the stimulation context on the responses measured to spatial sounds. The first indication was obtained in an EEG experiment utilizing a stimulus-specific adaptation paradigm (Butler 1972). In this study, sounds were presented from two alternating locations: the probe and the adaptor location (Fig. 4). Stimulus-specific adaptation was measured in the amplitude of the N1 response. The response amplitude for the probe sound varied depending on the spatial separation between the two sound sources: the larger the separation the larger the response amplitude was.

This finding was interpreted to arise from a population of spatially selective neurons. When the probe and the adaptor are in the same spatial location, they activate the same spatially selective neurons. These neurons are then activated repeatedly leading to attenuated activity and small responses. However, when a spatial separation is introduced between the sources, they activate different neurons. Then, each neuron is activated less frequently and this leads to less attenuation and larger response amplitudes. Location-selective adaptation of the N1 response occurs also for ITD (McEvoy et al. 1993) and ILD (Näätänen et al. 1988) cues alone.

The existence of spatially selective neurons in human cortex is further suggested by EEG and MEG studies that utilize ongoing sounds in which an abrupt change in lateralization is introduced in the middle of the sound presentation by the manipulating ITD or ILD (Halliday & Callaway 1978, Ungan et al. 1989, McEvoy et al. 1990, 1991, Jones et al. 1991, Sams et al. 1993, Mäkelä & McEvoy 1996, Krumbholz et al. 2007). The change in perceived lateralization leads to a location-shift potential akin to the N1 response but with a longer latency. Increasing the size of the shift in spatial location leads to an enlargement in response amplitude (Sams et al. 1993). These results can be explained by spatially selective neurons: the change in the location of the sound source activates a new, previously inactive group of neurons selective to the new location of the sound source and the onset of their activity gives rise to an N1 response similar to that found at the onset of a sound.

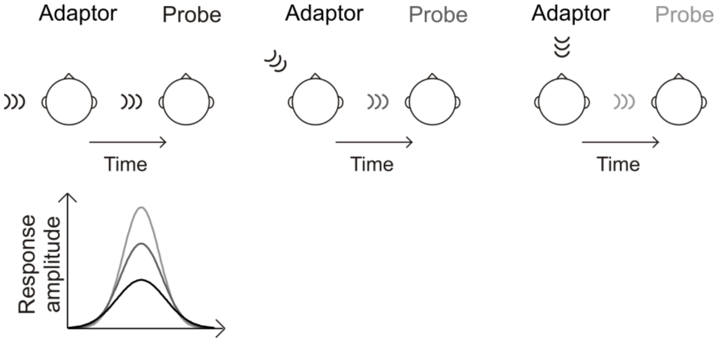

**Figure 4.** Stimulus-specific adaptation of the N1 response. Two alternating sounds, a probe and an adaptor, are presented and responses are measured to the probe. When the adaptor and the probe are presented in the same location, responses are small. When a spatial separation is introduced between the two sources larger responses are observed.

Another line of evidence for spatial selectivity of single neurons in the human auditory cortex comes from PET and fMRI studies. In a PET study looking for auditory cortical areas specialized in spatial processing, a series of sounds was presented either constantly from the same loudspeaker directly in front of the subject or so that the sound presentation was spread to multiple loudspeakers in several locations in front, to the left and to the right of the subject (Zatorre et al. 2002). The hemodynamic response in the planum temporale, a posterior auditory cortical area, was found to increase as the spatial spread of the sound presentation increased. Assuming that the increase in the hemodynamic response reflects the recruitment of an increasing number of neurons, this finding shows that the spatial spread of sound presentation leads to more neurons becoming activated. This implies the existence of spatially selective neurons. These findings have later been replicated in similar settings for sound sequences presented either from one constant location or spread to several locations in the left and right hemifields (Warren & Griffiths 2003, Smith et al. 2004, Brunetti et al. 2005, Barrett & Hall 2006, Deouell et al. 2007). Also, when a sound source is moving from the left to the right hemifield or vice versa, posterior auditory cortex shows stronger activity than for a stationary sound (Baumgart et al. 1999, Smith et al. 2004, Krumbholz et al. 2005a).

### *2.2.2 Spatial selectivity of single neurons in auditory cortex*

The above-described studies of the human cortex demonstrate that location selective neurons exist in the human auditory cortex. For more detailed information at the level of single neurons, invasive animal studies measuring the firing patterns of single units are needed. The primary approach towards understanding how neurons represent spatial locations has been to map the spatial receptive field: the sound source directions to which the neuron is responsive. Also, the tuning curves to isolated spatial cues have been measured.

Relatively large numbers of neurons are selective to sound source location in the auditory cortex of the cat (Eisenman 1974, Sovijärvi & Hyvärinen 1974, Middlebrooks & Pettigrew 1981, Rajan et al. 1990a, Imig et al. 1990, Poirier et al. 1997, Middlebrooks et al. 1998, Jiang et al. 2000, Mickey & Middlebrooks 2003) and of the monkey (Leinonen et al. 1980, Benson et al. 1981, Ahissar et al. 1992, Woods et al. 2006, Werner-Reiss & Groh 2008). These neurons usually have very large receptive fields in the horizontal plane with a width of nearly 180°. The receptive fields are typically centered to left or right locations so that they cover an entire hemifield. Very few neurons have narrow receptive fields or receptive fields centered at a frontal direction. Some studies have looked at organization of the neurons on the cortical surface according to their spatial preferences (Rajan et al. 1990b, Clarey et al. 1994, Werner-Reiss & Groh 2008). These studies have found only weak clustering of the neurons into groups with similar preferences. Instead, neighboring neurons often have clearly distinct spatial receptive fields.

Cortical neurons are selective also to the binaural localization cues presented in isolation through headphones. Sensitivity to ILD is similar to spatial selectivity found in loudspeaker presentation (Brugge et al. 1969, Brugge & Merzenich 1973, Orman & Phillips 1984). Neurons respond selectively to sound stimuli lateralized to one hemifield and are not activated or are inhibited by sounds in the opposite hemifield. For these neurons, firing rate rises with increasing ILD monotonically. Neurons selective to ITD are also found in the auditory cortex. However, ITD tuning is not confined to a single hemifield as in the case of ILD and free-field tuning (Brugge et al. 1969, Brugge & Merzenich 1973, Reale & Brugge 1990). There is a variety of ITD tuning functions to wideband stimuli in the cortex (Fitzpatrick et al. 2000). Peak-type neurons have a well-defined peak at a specific ITD with a low level of activity or even inhibition for other values. For a trough-type neuron, activity is very low for a specific ITD while for other values the neuron remains active. Some neurons are also of intermediate-type so that their ITD tuning functions have both a peak and a trough.

In most studies of spatial sensitivity of auditory cortical neurons, only the number of spikes following each stimulus is considered. Information may, however, be encoded in other forms, especially in the timing of the neural activity (Middlebrooks et al. 1994, Xu et al. 1998, Furukawa et al. 2000, Furukawa & Middlebrooks 2002). For instance, the latency of the first spike of the neurons has been found to be related to horizontal sound source location (Middlebrooks et al. 1998, Reale et al. 2003). Typically, earlier responses are found for sound sources in one hemifield than in the other. Also, the relative timing of spikes within the response and in relation to the activity of other neurons may carry information on sound source location (Furukawa et al. 2000).

### *2.2.3 Interhemispheric differences in sensitivity to sound source location*

The overall level of activity measured from the human auditory cortex varies according to sound source direction differently in the two hemispheres. This is especially evident in the N1m response measured in MEG. Above each cortical hemisphere, maximal responses are measured for contralateral sound sources and minimal for ipsilateral ones (Fig. 5).

For instance, the amplitude of the right-hemispheric N1m response is smallest for sound sources in the right hemifield and largest to those in the left hemifield. This variation occurs for realistic spatial sound (Palomäki et al. 2005) as well as to the binaural cues presented in isolation (Mäkelä & McEvoy 1996, Palomäki et al. 2005, Soeta & Nakagawa 2006). A similar effect has also been found with moving sound sources (Mäkelä & McEvoy 1996, Krumbholz et al. 2007). When an ongoing sound is shifted in location so that it moves from one hemifield to another, the response evoked by the shift is stronger in the hemisphere contralateral to the direction of the motion. Contralateral preference to lateralized sounds can be seen also in the fMRI signals arising from the auditory cortical areas (Krumbholz et al. 2005b, Lehmann et al. 2007).

Single-neuron studies suggest that the increased level of activity to contralateral sound sources seen in the human brain imaging studies could be due to a larger number of single neurons tuned to contralateral than to ipsilateral sound source locations. The majority of spatially selective neurons in cat and monkey auditory cortex have receptive fields centered in the contralateral hemifield (Eisenman 1974, Leinonen et al. 1980, Benson et al. 1981, Rajan et al. 1990a, Imig et al. 1990, Ahissar et al. 1992, Poirier et al. 1997, Middlebrooks et al. 1998, Jiang et al. 2000, Mickey & Middlebrooks 2003, Woods et al. 2006, Werner-Reiss & Groh 2008). This difference occurs also for isolated binaural cues. The preferred hemifield of the ILD-sensitive neurons and the best ITDs of the ITD-selective neurons fall more often to the contralateral than to the ipsilateral side (Reale & Brugge 1990, Fitzpatrick et al. 2000). At the level of a population response such as the N1m this would be reflected as maximal responses to contralateral sound sources.

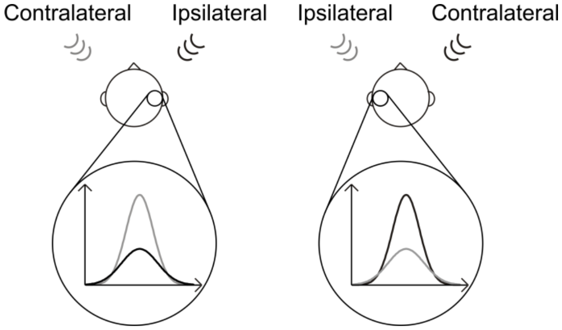

**Figure 5.** Cortical preference of contralateral sound sources. Each cortical hemisphere responds more strongly to sounds presented in the contralateral than to those in the ipsilateral hemifield.

The spatial representations in the two hemispheres differ also in that many of the correlates of auditory spatial processing are more prominent in the right than in the left hemisphere. The preference for contralateral stimulation visible in the amplitude of the N1m response is stronger in the right then in the left hemisphere (Palomäki et al. 2000, 2002, 2005). That is, the amplitude of the right-hemispheric N1m varies more as a function of sound source location. Further, the increase in cortical activity demonstrated in fMRI and PET to sound presentation from multiple source locations as opposed to one is often larger in the right than in the left hemisphere (Baumgart et al. 1999, Griffiths et al. 1998, 2000, Griffiths & Green 1999, Smith et al. 2004, Brunetti et al. 2005). Additionally, increases in cortical activity associated with active performance of a sound source localization task are often more prominent in the right than in the left hemisphere (Weeks et al. 1999, Zatorre et al. 2002, Altmann et al. 2007). Finally, patients suffering from lesions of right-hemispheric cortical areas have more severe impairments in sound source localization tasks than patients with left-hemispheric lesions (Zatorre & Penhune 2001, Spierer et al. 2009).

### *2.2.4 Specialization of posterior auditory cortex to spatial processing*

The auditory cortex comprises several auditory areas that differ in their response properties and functions (Kaas & Hackett 2000). Therefore, attempts have been made to find out whether some of the auditory areas show specialization in auditory spatial processing. In human brain imaging, this question has been approached with experiments in which the activity elicited by spatial sound is contrasted with activity due to sounds without the spatial features. Spatial sounds perceived to originate from a location outside the head activate posterior auditory areas, especially the planum temporale, to a higher level than the presentation of a sound that lacks the spatial cues and is therefore perceived as originating from inside the head (Warren et al. 2002, Hunter et al. 2003). Further, the inclusion of multiple sound source locations in contrast to only one leads to an increase in activity specifically in the planum temporale (Baumgart et al. 1999, Zatorre et al. 2002, Krumbholz et al. 2005a). Stimulus-specific adaptation effects are also stronger in the posterior than in the anterior auditory cortex for changes in sound source location (Ahveninen et al. 2006). Together, these findings could be explained by more neurons being spatially selective in the posterior than in other auditory areas or alternatively by the spatially sensitive neurons being more sharply tuned for location.

At the level of single neurons, selectivity to sound source location has been found in all auditory cortical areas in the monkey and in the cat (monkey: Recanzone 2000, Recanzone et al. 2000, Tian et al. 2001, Woods et al. 2006, cat: Middlebrooks et al. 2002, Stecker et al. 2003, 2005a). The spatial receptive fields in different auditory areas are qualitatively similar being wide and centered at lateral locations. Some quantitative differences have, however, been found. In the cat dorsal zone and posterior auditory field, spatial tuning is sharper, directional modulation deeper, and spatial selectivity more resistant to variations in sound level than in primary auditory cortex (Stecker et al. 2003, 2005a). In the monkey, similar signs of specialization can be found in caudal belt areas when compared to the primary auditory cortex (Recanzone 2000, Recanzone et al. 2000) and the rostral belt (Tian et al. 2001, Woods et al. 2006). Finally, the behavioral consequences of reversibly cooling auditory cortical fields in the cat support posterior specialization to sound source localization (Lomber & Malhotra 2008). The ability of cats to orient to and approach a sound source is disrupted by the cooling of posterior auditory field but remains unaffected by the deactivation of the anterior auditory field.

### *2.2.5 Representation of auditory space in the parietal cortex*

Neural correlates of auditory spatial cognition in human cortex can be found outside the auditory areas in the temporal lobe. Activity in the inferior and superior parietal lobules often appears when the subject is involved in an active task requiring sound source localization (Weeks et al. 1999, Zatorre et al. 1999, 2002, Maeder et al. 2001). Moving sound sources are especially effective in involving these areas (Griffiths et al. 1998, 2000, Pavani et al. 2002, Krumbholz et al. 2005b). Parietal areas activated during auditory spatial tasks have been proposed to form part of an auditory ‘where’ stream that starts from the posterior auditory cortex and is dedicated to processing auditory spatial information (Rauschecker & Tian 2000, Alain et al. 2001, Arnott et al. 2004). The parietal areas responsive during sound source localization tasks have been shown to be involved also in multimodal processing: the areas activated by auditory motion perception overlap those active during the perception of visual motion (Lewis et al. 2000, Bremmer et al. 2001).

Single-unit studies in monkeys have also demonstrated auditory spatial selectivity in parietal neurons (Leinonen et al. 1980, Mazzoni et al. 1996). In posterior parietal cortex, the lateral intraparietal area and the parietal reach region have been identified as multisensory processors that represent spatial locations based on tactile, visual and auditory information and combine it with motor plans and information on the present position of the body and the gaze (Cohen & Andersen 2002). The posterior parietal areas also perform conversions from one spatial frame of reference to another (Stricanne et al. 1996, Cohen & Andersen 2002). The spatial location of a sound source, for instance, is originally head-centered but in posterior parietal cortex it is represented in gaze-centered coordinates (Cohen & Andersen 2000). The auditory spatial sensitivity in the lateral intraparietal area is often dependent on the task the animal is performing and the visual stimuli presented concurrently (Grunewald et al. 1999, Linden et al. 1999, Gifford & Cohen 2004, 2005).

## 2.3 Subcortical origins of spatial selectivity

Information on the spatial locations of sound sources is encoded in the activity of auditory cortical neurons, but the localization cues are presumably extracted already in the nuclei of the lower brainstem (Fig. 6). Therefore, the cortical selectivity to sound source location reflects the results of neural computations taking place at earlier stages of the auditory pathway. Single-unit recordings have been the primary method for exploring the subcortical origins of neural sensitivity to sound source location. In addition to various mammalian species, the owl has been widely used as a model system. Here, the discussion is limited to the studies of mammalian species as the avian auditory brain has been found to differ considerably from the mammalian one especially with respect to spatial representation (Grothe 2003, McAlpine & Grothe 2003, Grothe 2010).

### *2.3.1 Extraction of ITD in the medial superior olive*

The superior olive is the first station along the auditory pathway at which the activity originating from the two ears converges (Fig. 6). The medial division of the superior olive (MSO) is a narrow sheet of bipolar cells that receive excitatory inputs from the cochlear nuclei of both sides (Cant & Casseday 1986, Cant & Hyson 1992, Smith et al. 1993). The neurons in the cochlear nucleus providing the input to the MSO are specialized in preserving or even improving the precision at which the neural activity pattern represents the temporal structure of the sound stimulus (Smith et al. 1993, Joris et al. 1994). Additionally, MSO receives inhibitory projections through the lateral and medial nuclei of the trapezoid body (Cant & Hyson 1992, Grothe & Sanes 1993, 1994, Kapfer et al. 2002). Therefore, the MSO seems to be at an ideal position for integrating binaural timing information.

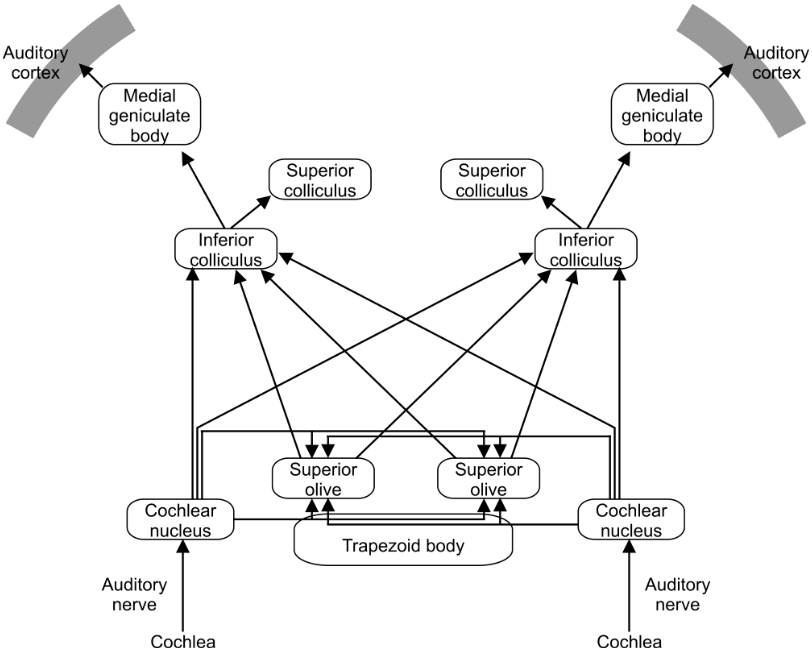

**Figure 6.** A simplified diagram of the ascending mammalian auditory pathway. Signals arriving from the two ears first meet in the superior olive that receives excitatory input from the cochlear nucleus and inhibitory input through the trapezoid body. Thereon the pathway travels through the inferior colliculus and the medial geniculate body of the thalamus to the auditory cortex.

Neurophysiological study of the MSO is technically challenging and therefore very little data is available. Nevertheless, the role of the MSO as an ITD extractor has been established (Hall 1965, Goldberg & Brown 1969). ITD tuning curves in the MSO are cyclic when measured to pure tone stimuli (Yin & Chan 1990). This is due to the cyclic nature of the ITD cue (Figs. 3 & 7). ITD is extracted as the ongoing phase difference between the tones presented to the two ears. When the ITD reaches the length of the tone cycle the phase difference returns to zero. This is also reflected in the shape of the tuning curve of single MSO neurons so that the maximal activity always occurs for the same phase difference. Therefore, the shape of the tuning curves measured for different sound frequencies varies according to the wavelength of the stimulus.

The cyclic ITD tuning curves measured for a single MSO neuron at different stimulus frequencies tend to be aligned so that the same level of activity occurs for every frequency at some specific ITD (Fig. 7). This ITD has been named the characteristic delay of the neuron (Rose et al. 1966). The alignment can occur for the highest or the lowest point of the tuning curve or somewhere in between. When a composite tuning curve is formed by averaging the tuning curves obtained at various tone frequencies, a curve corresponding well to the ITD tuning measured for a wideband noise stimulus is obtained (Yin & Chan 1990). The shape of the composite curve depends on the point at which the tuning curves for tonal stimuli align (Fig. 7). This results in three types of neurons: peak, trough, and intermediate. The neuron classes are not clearly separated groups but rather form a continuum of ITD tuning types. In MSO, most neurons are peak-type (Yin & Chan 1990). Other types of neurons have also been reported but it is not clear whether they fall within the limits of the MSO (Batra et al. 1997).

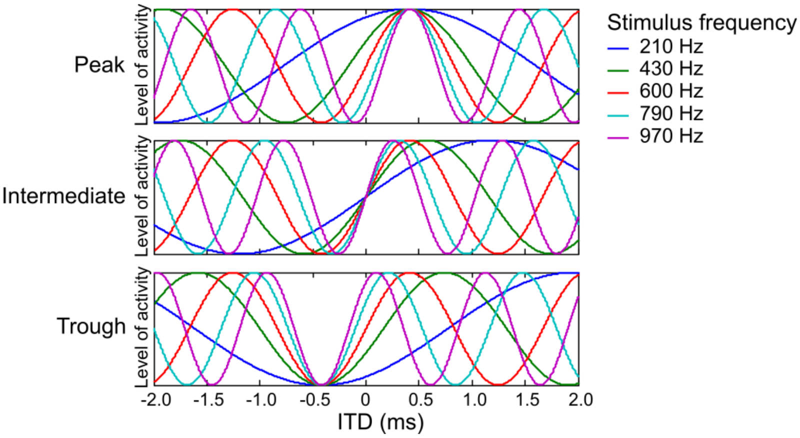

**Figure 7.** Three types of single-neuron tuning to ITD found in the mammalian brainstem. Tuning to the ITD of tones is cyclic with the length of the cycle determined by the tone frequency. The tuning curves measured at different sound frequencies are often aligned at an ITD that is called the characteristic delay of the neuron. The alignment can occur at the peak, the trough, or at an intermediate part of the tuning curve.

The ITD value that maximally activates the neuron is called the best ITD of the neuron. The best ITDs measured for MSO neurons include nearly exclusively delays with the contralateral ear leading (Yin & Chan 1990). Further details of this distribution vary from one study to another. In the cat, best ITDs have been found to fall within values occurring in natural hearing situations (Yin & Chan 1990). Also in the rabbit, the best ITDs fall within the physiological range (Batra et al. 1997). The distribution found in the gerbil, in contrast, favors long ITDs that are well outside the physiological range of the gerbil (Brand et al. 2002, Pecka et al. 2008). Instead, the steepest parts of the slopes of the tuning curves coincide with the physiological ITD values. Further, the best ITD is determined by the best frequency of the neuron in the gerbil (Pecka et al. 2008) but there is no correlation between these measures in the cat (Yin & Chan 1990). The ITD coding found in cat and rabbit MSO, therefore, seems to diverge from that seen in the gerbil. These differences may reflect disparate strategies of ITD extraction in these species. Alternatively, it may be that the distribution of the best ITDs is similar in all species but the same delays that for the cat and the rabbit fall within the physiological range (< 400 microseconds) are well outside the range for the gerbil (< 50 microseconds).

### *2.3.2 ILD extraction in the lateral superior olive*

The lateral superior olive (LSO) is the first station along the auditory pathway where sensitivity to ILD can be found. The LSO neurons receive excitatory input from the cochlear nucleus of the ipsilateral side (Fig. 8; Cant & Casseday 1986, Sanes 1990). The contralateral input received by LSO neurons is inhibitory and originates from the cochlear nucleus via the medial nucleus of the trapezoid body (Spangler et al. 1985, Sanes 1990). The inhibitory-excitatory binaural interaction in LSO neurons leads to sensitivity to ILD (Hall 1965, Boudreau & Tsuchitani 1968, Caird & Klinke 1983, Tollin et al. 2008). When the sound reaching the ipsilateral ear is of a higher intensity than that arriving to the contralateral ear, the neurons are activated. In contrast, when the sound of higher intensity is presented to the contralateral ear, neural activity is inhibited. This leads to ILD tuning curves that monotonically increase with increasing level difference favoring the ipsilateral ear (Fig. 8).

LSO neurons with inhibitory-excitatory interaction may also contribute to high-frequency ITD detection. These neurons are selective to ITDs in the amplitude envelopes of high-frequency sounds (Caird & Klinke 1983, Joris & Yin 1995). When the envelopes are interaurally in phase, activity is maximal. When the envelopes are out of phase minimal activity is found. The sensitivity of ITD is, however, weak compared to the sensitivity to ILD. Relatively large ITDs are needed compared to ILD to change the level of activity in the neurons. Therefore, the functional significance of ITD selectivity in LSO neurons is unclear.

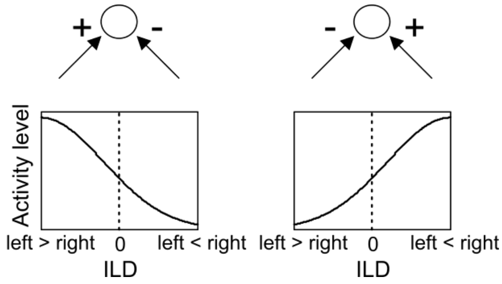

**Figure 8.** Neural tuning to ILD in the mammalian brainstem. Single neurons are excited by the stimulation of one ear and inhibited by the other. This results in monotonic ILD tuning curves.

### *2.3.3 Representation of location information in the inferior colliculus*

The inferior colliculus (IC) forms an obligatory station on the way from the superior olive to the auditory cortex. Therefore, the spatial information represented in the cortex travels through and is possibly modified in IC.

Sensitivity to ITD in IC largely repeats the main properties of ITD tuning found already in MSO. Tuning to pure tone ITD is cyclic with the cycle repeating according to the length of the tone cycle (Rose et al. 1966, Stillman 1971, Kuwada & Yin 1983, Yin et al. 1986, Chan et al. 1987, Kuwada et al. 1987). The peak-, trough-, and intermediate-type ITD tuning curves are found in IC (Rose et al. 1966, Stillman 1971, Yin & Kuwada 1983, Yin et al. 1986, Kuwada et al. 1987, Batra et al. 1993, Fitzpatrick et al. 2002). The majority of ITD-sensitive neurons prefer delays corresponding to locations in the contralateral hemifield (Stillman 1971, Kuwada & Yin 1983, Yin et al. 1986, Kuwada et al. 1987, McAlpine et al. 1996). Discrepancies exist between the IC studies performed on different species. Some studies have found best ITDs to fall within the physiological range (Kuwada & Yin 1983, Kuwada et al. 1987) and others report best ITDs that are clearly longer than those experienced by the animal in natural hearing situations (Stillman 1971, McAlpine et al. 1996, 2001). Further, some studies have found that most neurons are of the peak type (Kuwada et al. 1987) while others report large numbers of intermediate-type neurons with no prevalence of the peak-type tuning pattern (Yin & Kuwada 1983, Fitzpatrick et al. 2002).

Sensitivity to ILD in IC is similar to that found already in LSO. Tuning to ILD is monotonic so that the receptive field spans an entire hemifield and the border is close to the midline (Rose et al. 1966, Moore & Irvine 1981). Most of the ILD-selective neurons in IC prefer ILDs corresponding to contralateral locations (Moore & Irvine 1981). Just as in LSO, the ILD-selectivity in IC reflects the interaction between excitatory input from the ear on the side of the preferred hemifield and inhibitory input from the other (Semple & Aitkin 1979, Moore & Irvine 1981).

In IC, several experiments have been performed with auditory stimuli that correspond well to those experienced by the animals in natural conditions. These have utilized either loudspeakers (Leiman & Hafter 1972, Semple et al. 1983, Moore et al. 1984a, 1984b, Aitkin et al. 1984, 1985, Calford et al. 1986, Aitkin & Martin 1987, Groh et al. 2001, 2003, Zwiers et al. 2004) or virtual spatial sound presented through headphones (Delgutte et al. 1999, Sterbing et al. 2003) to determine the shape of the spatial receptive fields of single IC neurons. These spatial receptive fields typically cover a large part of one hemifield, usually the contralateral one, and the neuron remains unresponsive or is inhibited by sound sources in the opposite hemifield (Leiman & Hafter 1972, Aitkin et al. 1984, 1985, Aitkin & Martin 1987, Groh et al. 2003). Therefore, the tuning to sound source location in free-field resembles largely the sensitivity measured to the ILD cue alone.

Some early studies on the receptive fields in cat IC found large numbers of neurons with very narrow spatial receptive fields centered at frontal locations in the contralateral hemifield (Semple et al. 1983, Moore et al. 1984a, 1984b). These receptive fields were well defined only at very low sound levels and expanded when sound level was increased. They also occurred for high stimulus frequencies only. This narrow tuning at low sound levels can be accounted for by the amplification produced by the cat pinna. The pinna amplifies the level of high-frequency sounds presented at a limited range of frontal locations. When sounds are presented in those locations at a low level, the pinna amplifies them to a level above the activation threshold of the neurons. Therefore, the narrow receptive fields emerge from the combination of frequency selectivity, pinna amplification and a very low sound level. Presumably these receptive fields do not reflect mechanism related to sound source localization as all spatial selectivity is lost at sound levels that are optimal for behavioral sound source localization (Moore et al. 1984b).

### *2.3.4 Multimodal spatial maps in the superior colliculus*

The superior colliculus (SC) does not form a part of the pathway leading from the ears to the auditory cortex but it is interconnected with auditory cortical areas (Wallace et al. 1993, Wallace & Stein 1994). In SC, information from visual, auditory, and somatosensory modalities and from the motor system converges. The surface layers of the nucleus represent visual information and the deep layers contain multimodal neurons, including those responsive to sound (Gordon 1973, Updyke 1974, Palmer & King 1982). The auditory neurons are selective to the location of the sound source (Gordon 1973, Updyke 1974) and they are topographically organized according to their spatial preferences (Gordon 1973, Palmer & King 1982, King & Palmer 1983, Wise & Irvine 1983, King & Hutchings 1987, Campbell 2006). The auditory space map in the deep layers of SC is aligned with the visual map on the surface so that neurons responsive to sounds presented from a specific direction tend to be found close to visual neurons that respond selectively to flashes of light presented in the same direction (Gordon 1973, Harris et al. 1980, Palmer & King 1982, Middlebrooks & Knudsen 1984).

Two approaches have been used in demonstrating the auditory space map in SC. First, the receptive fields have been measured for sounds at very low levels barely above the threshold of the neuron (King & Hutchings 1987). When measured in this way, the receptive fields are very narrow and have a well defined peak. This peak is then taken as the preferred location of the neuron and the neurons are found to be topographically organized according to this preference. Alternatively, the receptive fields can be measured with higher sound levels that correspond to situations in which sound source localization is behaviorally good (Gordon 1973, King & Palmer 1983). In these cases, the receptive fields are much wider and no clearly distinguishable peaks are found. Often, the receptive field covers a large part of the contralateral hemifield and only a medial border can be defined. The preferred location is then determined as the midpoint of the steepest slope of the tuning curve. When defined this way, the preferred locations are organized topographically (Gordon 1973, Wise & Irvine 1983).

### *2.3.5 Binaural processing in the human brainstem*

Activity related to human spatial hearing functions can be detected in the brainstem response measured with electrodes placed on the scalp. A binaural difference potential can be obtained by calculating the difference between the response to a binaurally presented sound stimulus and the sum of the responses to monaural stimuli to each ear (Ito et al. 1988). The V component that reflects the activity in the superior olive, the lateral lemniscus, and the inferior colliculus is usually larger in the sum of the two monaural responses than in the binaural response (Junius et al. 2007). In the binaural difference potential this is then reflected as a prominent deflection at around the latency of the V component. This deflection is called the binaural interaction component and its existence is interpreted as evidence for binaural processing taking place in the human brainstem. The binaural response being smaller than the sum of the monaural responses may reflect inhibitory binaural interactions or possibly saturation in the monaural responses (Gaumond & Psaltikidou 1991). A fMRI experiment has also revealed correlates of binaural processing in the human IC. The binaural interaction component similar to that studied with electrical recordings was calculated based on fMRI signals arising from the IC (Krumbholz et al. 2005a). The activity was found to decrease considerably for binaural presentation compared to monaural presentation. The binaurally induced activity was even lower than that found with the stimulation of one ear alone. This supports an explanation of the binaural interaction component based on binaural inhibitory mechanisms.

## 2.4 Neural models of auditory spatial processing

As described above, neurons at various stages of the auditory pathway are sensitive to sound source location and to auditory spatial cues. To understand the process leading to this sensitivity, various computational models of sound source localization have been proposed. Two of these have been formulated as neural computations: delay line models and count-comparison models. Importantly, the two models predict distinct types of neural representation of horizontal sound source location. The delay-line model predicts a place code and the count-comparison model a hemifield code.

### *2.4.1. Delay lines and the place code*

The delay line model was originally proposed by Jeffress (1948) as a neural mechanism for converting ITD into a neural place code (Fig. 9). In the model, ITD is compensated for by delay lines formed by neural fibers of different lengths. The delay lines arriving from the auditory periphery of each side meet at an auditory nucleus. Here, each neuron receives input from one delay line of each side and acts as a coincidence detector: it activates only when input signals arrive concurrently from both sides. Therefore, each coincidence detector is activated when the sound has an ITD that corresponds to that compensated for by the delay lines arriving to it. The coincidence detector neurons within the nucleus and the delay lines terminating in them are organized topographically. When moving from one end of the nucleus to the other, the ITD that leads to a coincidence and therefore best activates the neuron progressively changes from very short delays to those at the extreme values that can be reached in natural hearing situations.

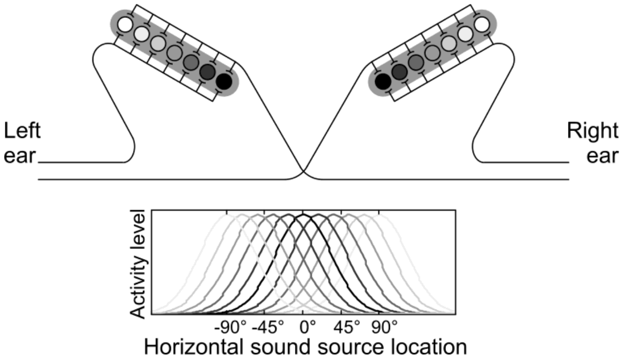

**Figure 9.** The delay line model leading to a place code of horizontal sound source location. Neurons in an auditory nucleus receive excitatory inputs from both ears. The input arrives through orderly delay lines that compensate for the interaural delays occurring in the sound. This results in narrow tuning to ITD.

The delay line model was originally formulated as a model of ITD detection. Later, extensions to ILD detection have been proposed (David et al. 1958, Deatherage & Hirsh 1959). This suggestion stems from the observation that the neural activity occurs at a longer latency when the sound level is progressively lowered. Therefore, the neural activity corresponding to the ear with the lower sound level might travel to the binaural nucleus more slowly. The resulting delay could then the detected and converted to a place code by the system of delay lines and coincidence detectors.

Models based on computations reminiscent of the delay line model are often called crosscorrelation models. An extensive formulation of these computations has been developed by Colburn and others (Colburn 1973, 1977, Colburn & Latimer 1978, Stern & Colburn 1978, Stern & Zeiberg 1988). This work has been guided by attempts to account for various psychophysical findings on binaural hearing. Similar results can be obtained with another binaural framework: the equalization-cancellation model (Durlach 1963). Potential neural implementations of the equalization-cancellation operation have, however, not been developed.

### *2.4.2 Physiological evidence for delay lines and place coding*

First, a crucial prediction made by the delay line model is the existence of a place code of spatial location. That is, the model predicts that auditory spatial receptive fields are relatively narrow and that their peaks cover the range of physiologically possible values of the binaural cues. The receptive fields may also be organized topographically according to the preferred locations. In line with this prediction, relatively narrow tuning to ITD has been found in the cat MSO (Goldberg & Brown 1969, Yin & Chan 1990) and also in other nuclei of the ascending auditory pathway (Rose et al. 1966, Stillman 1971, Kuwada & Yin 1983, Yin et al. 1986, Chan et al. 1987, Kuwada et al. 1987). As predicted, the preferred ITDs of MSO neurons are mostly within the physiologically plausible values (Yin & Chan 1990, Batra et al. 1997). Further, some evidence for topographical organization of ITD selectivity in the MSO has been reported although this finding is based on a very small sample of neurons (Yin & Chan 1990). Findings in smaller mammals seem to contradict those in cats. In gerbil MSO, the best ITDs of the neurons are beyond the physiological range determined by the small head of the animal (Brand et al. 2002, Pecka et al. 2008). Therefore, it seems that evidence both against and in support of the place code can be found in the mammalian MSO, depending on the species and the study.

Second, the delay line model predicts that the narrow spatial receptive fields of single neurons are resistant to alterations in other sound features such as frequency. In the model, the coincidence detectors are activated maximally by particular ITDs and their ITD selectivity is unaffected by other sound features. Neurons of this type are found in the cat MSO (Yin & Chan 1990). The tuning curves measured at different sound frequencies are aligned so that the peak of maximal activity always occurs at the same ITD. Other types of neurons less consistent with the model have, however, often been encountered in IC. The alignment does not necessarily occur at the peak of the ITD tuning curve but can also be at the minimum or somewhere in between the two extremes (Yin & Kuwada 1983, Fitzpatrick et al. 2002). Furthermore, some studies have found that the preferred ITD is dependent on the preferred frequency of the neuron, a feature inconsistent with the place code (Pecka et al. 2008). Together, these findings may indicate that the coincidence detection taking place in MSO is more complex than Jeffress originally proposed.

Third, the model predicts that the fibers arriving at the binaural nucleus detecting ITD should be organized into delay lines of various lengths and that the input they provide should be timed at a precision sufficient for correctly identifying the submillisecond timing differences. Very few studies have described the structure of the projections arriving at the MSO neurons in mammals. One study has shown structures reminiscent of the delay lines in the cat but arriving only from one ear and not the other (Smith et al. 1993). These would, however, be sufficient for establishing the orderly ITD code. The timing of the monaural inputs is very precise as required by the model. The bushy cells in the ventral cochlear nucleus providing the excitatory input to MSO neurons are specialized in faithfully preserving or even enhancing the precision at which neural activity represents the temporal structure of the sound (Smith et al. 1993, Joris et al. 1994). Further, the latencies at which MSO neurons respond to monaural stimulation of each ear predict well the ITD to which the neuron is responsive (Goldberg & Brown 1969, Yin & Chan 1990). When the ITD of a binaural sound matches the difference between the latencies measured to the monaural stimulation of the left and the right ear, the neuron is maximally activated.

Consistent with the delay line model, MSO neurons are bipolar, with each dendritic branch receiving excitatory input from the cochlear nucleus of one side (Cant & Casseday 1986, Cant & Hyson 1992, Smith et al. 1993). This is, however, not the only input that the ITD-selective neurons in MSO receive. There is also ample inhibitory input arising from the cochlear nucleus through the nuclei of the trapezoid body (Cant & Hyson 1992, Grothe & Sanes 1993, 1994, Kapfer et al. 2002). The effects of inhibition are seen in the functional properties of ITD-selective neurons. They are not only excited by sound with their preferred ITD but inhibited to activity levels below their spontaneous firing rates when sounds with non-preferred ITDs are presented (Rose et al. 1966, Kuwada et al. 1984, Carney & Yin 1989). This inhibition has been shown to be crucial for ITD tuning in gerbil MSO. When the inhibition is blocked or otherwise disrupted, ITD tuning is altered (Brand et al. 2002, Pecka et al. 2008). Inhibitory binaural interactions are also seen in human brain stem responses (Krumbholz et al. 2005a). This shows that although coincidence detection of excitatory inputs seems to take place, the process is more complex than originally formulated in the model.

Evidence for place coding emerging from a delay line structure applies only to the coding of ITD. The ILD tuning curves in LSO (Hall 1965, Boudreau & Tsuchitani 1968, Caird & Klinke 1983, Tollin 2003) and elsewhere in the subcortical auditory pathway (Rose et al. 1966, Moore & Irvine 1981) are wide and typically span an entire hemifield. Also, when measured for free-field sounds, spatial receptive fields tend to be wide and centered at lateral locations (Leiman & Hafter 1972, Aitkin et al. 1984, 1985, Aitkin & Martin 1987, Groh et al. 2003). An exception to this are the narrow frontal receptive fields found in cat (Semple et al. 1983, Moore et al. 1984ab). These seem to be a species-specific effect caused by the directional pinna of the cat, and have not been found in primates (Groh et al. 2003). In trying to understand how the human auditory system operates, the findings on ITD code may, however, be more relevant than those on ILD extraction. Human hearing and many relevant sounds such as speech are concentrated at low frequencies in which ITD occurs. ITD is also the dominant cue in behavioral sound source localization (Wightman & Kistler 1992). When ITD is put in contradiction with ILD and the spectral cues, the perceived sound source direction is mainly determined by ITD as long as the sound has any low-frequency content.

### *2.4.3 Count-comparison and the hemifield code*

The count-comparison model was first suggested by von Békésy (1930, 1960). He envisioned a code of horizontal sound source location formed by two sets of neurons: one corresponding to each hemifield of auditory space (Fig. 10). In this model, the activity of the right- and left-tuned neurons is determined by the interaural differences occurring in the sound. If the sound arrives at the right ear first or is louder in the right than in the left ear, the right-tuned neurons are more likely to be activated than the left-tuned ones and vice versa. The resulting spatial receptive fields are very wide, spanning an entire hemifield thereby forming a hemifield code of horizontal sound source location in which the relative activation rates of the two populations together signal the spatial location. The next stage of processing is count-comparison in which the number of the active neurons in the two groups is counted and compared. Van Bergeijk (1962) elaborated on this idea and suggested that the right- and left-tuned neurons could be single neurons in the left and right superior olive. He also proposed that this hemifield preference would arise from the interaction between inhibitory and excitatory inputs from the two ears.

The original suggestions on the count-comparison model did not describe specifically the mechanisms of neural computations leading to the preference of left- or right-lateralized sounds. The count-comparison model has also not been further developed. Therefore, it has not been formulated precisely in computational terms and its power for predicting psychophysical findings remains unknown. This lack of interest has presumably been due to the extensive effort put into the delay line and crosscorrelation models and to their subsequent success in replicating psychophysical findings.

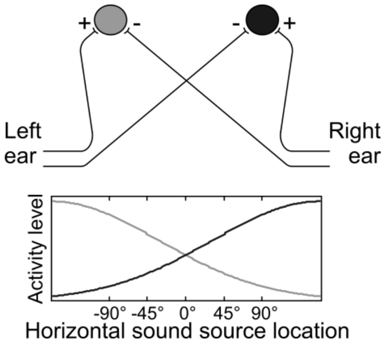

**Figure 10.** The count-comparison model and hemifield tuning to horizontal sound source location. Neurons in an auditory nucleus receive excitatory input from one ear and inhibitory input from the other. This leads to wide spatial tuning with a preference to sound sources on the side of the ear providing excitatory input.

### *2.4.4 Physiological evidence for count-comparison and the hemifield code*

The most important prediction made by the count-comparison model is that there are essentially only two kinds of spatially selective neurons: those tuned to the left and those to the right hemifield. Thus, receptive fields encountered in the auditory nervous system should be wide and centered at lateral locations. Consistent with this, the tuning curves measured to ILD are almost exclusively monotonic functions of ILD with a flat peak at a lateral location and the steepest slope close to the midline (Hall 1965, Rose et al. 1966, Boudreau & Tsuchitani 1968, Moore & Irvine 1981, Caird &

Klinke 1983, Tollin 2003). The studies on ILD selective neurons in LSO have revealed that the selectivity emerges from the neuron receiving excitatory input from the ipsilateral ear and inhibitory input from the contralateral one (Hall 1965, Boudreau & Tsuchitani 1968, Caird & Klinke 1983, Tollin 2003). This leads to a preference for ipsilateral sound sources.

The spatial receptive fields measured in free-field conditions also resemble the hemifield code. Most neurons are activated by a wide range of locations confined to a single hemifield (Leiman & Hafter 1972, Aitkin et al. 1984, 1985, Aitkin & Martin 1987, Groh et al. 2003). It is not clear to what extent the free-field spatial receptive fields reflect the sensitivity to other cues than ILD. If the neurons in the sample are mostly high-frequency neurons, they are likely to repeat the tuning pattern found for ILD also in free-field conditions as it is the dominant localization cue at their frequency range. Therefore, it is possible that the free-field receptive fields measured in many experiments reflect primarily sensitivity to ILD.

The experimental evidence related to a hemifield code of ITD is controversial. The data from different laboratories using different species diverge in crucial ways. A series of studies performed on the gerbil seem to support a neural code of ITD that is in line with the hemifield code. In the gerbil MSO, tuning curves to ITD have maxima at long ITDs outside the physiological range determined by the head size of the animal (Brand et al. 2002, Pecka et al. 2008). Further, the best ITDs are not evenly distributed to all values but instead, they occur only for long delays. The best ITD is determined by the best frequency of the neuron so that longer ITDs are preferred by neurons with lower best frequency. This limited distribution of best ITDs suggests a population rate code of ITD formed by two populations: one tuned to the left and the other to the right. The support for a hemifield code of ITD is, however, based on data from a very small animal, the gerbil. Previous experimental data on cat whose head size is closer to the human head demonstrates a prevalence of shorter best ITDs within the physiological range and no correlation between the best frequency and best ITD (Yin & Chan 1990).

The original formulations of the count-comparison models assumed that at some higher level of processing, the activity levels of the two populations are compared. No such comparators have, however, been reported in the auditory nervous system. This does not necessarily invalidate the count-comparison model. It only requires a re-evaluation of the necessity of a higher level comparison stage. It may well be that the population rate code formed by the two opponent populations is already a desirable form of representation for the higher levels of processing to use. Then, no explicit comparisons are needed.

### *2.4.5 The code of horizontal sound source location in human cortex*

As described above, differences between mammalian species, especially the hearing range and the size of the head, may be relevant to spatial hearing mechanisms. Therefore, the applicability of the results from animal studies to humans may be limited. In the following, an attempt is made to infer from previous experimental results in humans which code of the auditory space, the place code or the hemifield code, best describes the representation of auditory space in the human cortex.

The clearest evidence for spatial selectivity in human auditory cortex can be found in stimulus-specific adaptation studies. In these, a probe sound is presented from a constant location in the left hemifield and the effect of a preceding adaptor sound on the N1 response to the probe is measured (Butler 1972, Näätänen et al. 1988, McEvoy et al. 1993). If the adaptor is presented from locations progressively more distant from the probe, this leads to an increase in the amplitude of the response to the probe. Butler (1972) originally interpreted this finding in terms of the place code. The increase in the separation between the probe and the adaptor sound source locations leads to a decrease in the overlap between the spatially selective neurons that the two sounds activate. In other words, the further the two sound sources are from one another the fewer are the spatial receptive fields spanning both of the locations. This effect can, however, be equally well accounted for by the hemifield code. In previous studies, the probe was always presented in the left hemifield and in the hemifield code it activates primarily the left-tuned population. The effect the adaptor presentation has on the response to the probe depends on how much the adaptor activates and thereby attenuates the left-tuned population. When the adaptor is presented in the left hemifield close to the probe it attenuates the left-tuned population strongly leading to diminished responses to the probe. Adaptor locations more to the right activate the left-tuned population less and thereby the attenuation is weaker. This is then seen as amplified responses to the probe when the adaptor is located increasingly towards the right hemifield.

Another demonstration of cortical selectivity to sound source location is the location-shift potential. This response is observed when the location or the spatial cues of an ongoing sound are switched from one hemifield to the other (Halliday & Callaway 1978, Ungan et al. 1989, McEvoy et al. 1990, 1991, Jones et al. 1991, Sams et al. 1993, Mäkelä & McEvoy 1996, Krumbholz et al. 2007). It is reminiscent to the N1 response measured to transient sounds but occurs at a longer latency. If interpreted as arising from the engagement of a fresh population of previously inactive neurons, the response can be seen as a demonstration of limited spatial receptive fields. In both the place code and the hemifield code, the relatively large shift in spatial location between the left and right hemifield leads to the sound source falling to the receptive fields of a new population of neurons not responsive to the previous location of the sound source. Therefore, the location shift potential is consistent with both the place code and the hemifield code.

In hemodynamic studies, selectivity to sound source location has been demonstrated as an increase in the response strength to the spread of the sound presentation from one to multiple locations (Zatorre et al. 2002, Warren & Griffiths 2003, Smith et al. 2004, Brunetti et al. 2005, Barrett & Hall 2006, Deouell et al. 2007). This experimental setup was designed to find the cortical areas representing spatial location as a place code consisting of restricted and relatively narrow receptive fields (Zatorre et al. 2002). The logic was that when all the sounds are presented from the same, central location, they only activate the neurons having their receptive fields directly in front. When sounds are presented from several locations the number of spatial receptive fields covered by the sound presentation increases. Therefore, a large number of spatially selective neurons activate and, at the population level, the response is stronger. This increase in response strength can also be accounted for by the hemifield code. When all the sounds are presented directly in front, both the left- and the right-tuned populations are engaged but their activity is not maximal. When sound presentation in left- and right-locations are added, the sound presentation falls to higher levels on the tuning curves of both subpopulations and this leads to an increase in the activity seen at the level of the entire population. Therefore, these findings do not distinguish between the two alternative codes.

Finally, studies on psychophysical adaptation aftereffects may provide observations for identifying the neural code of sound source location utilized by humans. In these studies, exposure to an adaptor sound presented from one location for several tens of seconds leads to changes in the perceived locations of subsequent probe sounds. The perceived location of the probe usually shifts away from the location of the adaptor and the outcome can be described as a repelling effect of the adaptor location. This has been described for both free-field stimuli (Carlile et al. 2001) and for sound lateralized by ITD alone (Kashino & Nishida 1998). The repelling effect is best accounted for by a place code of spatial location. The prolonged presentation of the adaptor sound leads to fatigue in the neurons responsive to the adaptor location. Consequently, the activity of these neurons is attenuated during the probe presentation and the neurons corresponding to the neighboring locations dominate in forming the perceived location of the probe sound source. However, other findings on adaptation aftereffects are harder to account for by the place code. Laterally presented adaptors lead to shifts in the perceived locations of sound sources relatively far from the adaptor location (Phillips & Hall 2005, Phillips et al. 2006, Vigneault-MacLean et al. 2007). For instance, adaptors in extreme lateral locations can lead to shifts of sound sources presented in the midline. Such far-reaching effects are hard to account for by the narrow tuning curves required by the place code but are well in line with the widely tuned neurons of the hemifield code. Therefore, the adaptation aftereffect results cannot be fully accounted for by either the place code or the hemifield code.

In sum, the research conducted so far on auditory spatial processing in the human brain does not reveal how the neurons represent horizontal sound source location. Some studies have implicitly assumed a place code (for instance, Butler 1972, Zatorre et al. 2002, Deouell et al. 2007) but as described above, the neural correlates of spatial selectivity found in human cortex can equally well be accounted for by a hemifield code. This leaves unresolved whether the human brain implements a place code or a hemifield code of auditory space.

# 3. AIMS OF THE STUDIES

The aim of this thesis was to find out how neurons in human cortex represent sound source location. Each study addressed a specific question on the neural code of auditory space.

- **I** Two alternative theories have been posed on the representation of space in the mammalian auditory brain: the place code and the hemifield code. The aim of Study I was to determine which of these alternatives best describes the neural code of auditory space in human auditory cortex.
- **II** The main discrepancies in previous studies on the neural representation of auditory space are specific to the coding of ITD. Results both in favor and against the hemifield code have been presented. Therefore, Study II was designed to reveal the neural code of ITD in human cortex.
- **III** In many previous studies, the right hemisphere has appeared to be more sensitive to auditory spatial information than the left one. The aim of Study III was to elucidate the single-neuron tuning properties that give rise to this difference in sensitivity.
- **IV** When a subject is actively engaged in an auditory spatial detection task, brain activity is found in parietal and frontal areas in addition to the auditory cortex. The aim of Study IV was to disambiguate the role of these areas in auditory spatial processing and to describe the time scale of their participation.
- **V** The wide tuning in the hemifield code requires an alternative account for explaining behavioral sound source location discrimination different from those applied to place coding and narrowly tuned neurons. Study V explored the implications of wide tuning to behavioral sound discrimination in a neural network model.

# 4. METHODS

The aims of the present studies pose two major methodological challenges. First, presenting controlled and realistic spatial sound stimuli concurrently with brain recordings is problematic. Second, the models that the studies aim to test involve properties of single neurons but the recording methods available for the study of the human brain reflect the combined activity of very large populations of neurons. This chapter describes the methodological choices made to meet these challenges. The interested reader can find the more detailed descriptions of the methods in the original publications.

## 4.1 Virtual spatial sound for brain imaging purposes

In brain imaging settings, it is often not possible to use loudspeakers for sound presentation. The measurement rooms are small and the equipment limits the possibilities of positioning loudspeakers even further. Even when the use of loudspeakers is possible (e.g. Butler 1972, Zatorre et al. 2002), the acoustical properties of the measurement chamber are hard to control for and to replicate elsewhere. Due to these complications, brain imaging studies usually utilize earphones. In this form of presentation, the sound travels only the distance from the entrance of the ear canal to the eardrum and the alterations normally taking place on the path from the sound source to the ears do not occur. Therefore, the sound contains no spatial cues. The alterations can, however, be simulated in the sound presented through headphones.

Various virtual spatial sound strategies have been adopted in brain imaging studies. The simplest solution has been to simulate sound presentation from the left and right hemifields by stimulating the left or right ear only and possibly a frontal location by presenting the sound to both ears (e.g. Zatorre et al. 1999, Sestieri et al. 2006). These sounds are perceived to originate from the left or the right ear or from the middle of the head. The monaural presentation can be thought of as an infinitely large ILD, but apart from that, it contains no spatial cues. Further, binaural processing is a crucial part in the perception of spatial sound. With the monaural sound stimulus, this processing is not possible. A continuum of perceived lateralizations can be produced by imposing an ITD or an ILD on the sound presented through headphones (used, for instance, in Ungan et al. 1989, Griffiths et al. 1998, Baumgart et al. 1999, Bremmer et al. 2001, Barrett & Hall 2006, Krumbholz et al. 2007). The larger the ITD or ILD, the further the sound is perceived towards the ear of the leading or louder sound. In natural listening conditions, all localization cues normally occur and therefore, using only one of them in isolation leads to a considerable deviation from how the cues would normally occur. A further problem in using ILD or ITD alone is that they lead to a perceived sound source location inside the head in contrast to one in a location outside the head. They can simulate only lateralization, i.e. locations on the left-right axis. For sounds to be perceived as originating from locations outside the head and in different elevations, spectral cues need to be included. Using ITD or ILD in isolation may provide interesting test cases for theories of spatial cue extraction but they cannot be considered adequate for simulating real spatial locations.

The full set of auditory localization cues can be applied to a sound presented through headphones with the use of head-related transfer functions (HRTFs). HRTFs describe how the head changes the sound spectrum, as well as the level and time of arrival of a sound originating from a distant source. HRTFs are acquired by binaural recordings: sounds are presented from loudspeakers in an anechoic or otherwise acoustically controlled environment and recorded with a miniature microphone placed at the ear canal (Fig. 11). Applying HRTFs filters the sound to contain the same localization cues as would occur in the loudspeaker presentation. As preparing HRTFs for each subject individually is laborious and requires access to specialized equipment, often the HRTFs of a single subject or a mannequin head are used for all subjects (for instance, Bushara et al. 1999, Alain et al. 2001, Palomäki et al. 2002, Warren et al. 2002, Ahveninen et al. 2006). As the spatial cues are determined by the shape and size of the head and ears of each individual subject, this leads to virtual spatial sound that does not match perfectly the cues that the subject experiences in real life sound source localization. Spatial sounds created with the non-individualized HRTFs are usually localized well in the horizontal plane but the perception of elevation is less accurate. Further, the impression of externalization of the sound sources is weaker with the non-individualized HRTFs.

Binaural recordings can also be used as virtual spatial sound directly without the extraction and application of HRTFs (Fig. 11). Then, each sound stimulus is presented from the loudspeakers and recorded as it arrives to the ear canal of the subject. These recordings can then be played through headphones during brain imaging. This does not provide the flexibility of the HRTFs that allow the conversion of any sound into a virtual spatial sound. Only the sounds presented during the binaural recordings are available. However, when the number of sounds required is limited and the stimuli are known and available already at the stage of the binaural recordings, a more straightforward solution is provided by using the recordings directly. With binaural recordings performed individually for each subject a very realistic perception of auditory space can be reached. The subjects localize the sound with an accuracy equal to those presented through loudspeakers and they are often unable to detect any differences between the virtual and the real spatial sound.

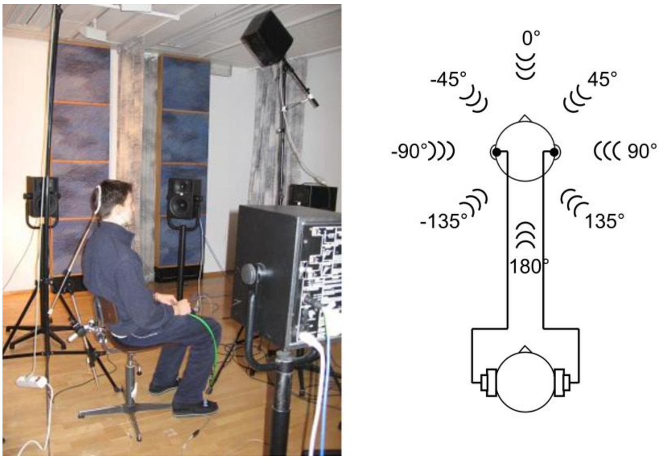

**Figure 11.** Virtual spatial sound produced with binaural recordings. Miniature microphones were placed at the ear canals of the subject and sounds were presented from the surrounding speakers in an acoustically controlled environment. These recordings were then presented through headphones during MEG experiments.

## 4.2 Magnetoencephalography (MEG)

Magnetoencephalography (MEG) provides a method for tracking cortical activity non-invasively with high temporal and spatial precision (Hämäläinen et al. 1993, Lounasmaa et al 1996, Hämäläinen & Hari 2002). The sensitive detectors of the MEG device pick up the weak magnetic fields generated by currents in the brain. For the current and thereby the magnetic field to be detectable, large numbers of neurons need to be simultaneously active. The currents in individual neurons need to flow in parallel for their magnetic fields not to cancel out. Further, the orientation of the current determines whether it gives rise to a magnetic field detectable outside the skull. For these reasons, the MEG signal reflects primarily the simultaneous post-synaptic activity in the apical dendrites of cortical pyramidal cells.

MEG has advantages over other methods available for the study of the human brain that make it especially suitable for the purposes of the present studies. Unlike fMRI or PET, MEG records signals directly arising from neural activity rather than the metabolic changes related to it (Hämäläinen et al. 1993). This makes MEG a temporally precise method. The stimulus-specific adaptation paradigm described below demands that the activity following immediately the presentation of a sound can be distinguished between sounds with a relatively short temporal separation. Such a distinction would be problematic to achieve in fMRI or PET. EEG represents an alternative method for obtaining temporally precise recordings. MEG, however, has the benefit over EEG of being also spatially precise. The sensors of the MEG device detect the magnetic field arising from the cortex directly underneath the sensor position (Hämäläinen et al. 1993). In the present studies this allows a straightforward separation between the activities arising the right and left auditory cortices by selecting data from the sensors above these two areas for the analyses.

The brain recordings described in the present thesis were conducted with a 306-channel magnetoencephalography (MEG) device (Vectorview 4-D, Neuromag, Finland). Event-related fields (ERFs) following from sound stimulation were obtained by presenting the sounds repeatedly and averaging the MEG activity time-locked to the stimulus onset over a minimum of 150 repetitions. The analyses of the ERFs were based on the gradiometer channel pairs showing the largest response amplitudes selected over the left and right cortical hemispheres above the temporal lobe. The peak amplitude of the N1m response was used as a measure of the overall level of activity in the auditory cortex following from the sound presentation. The N1m response reflects the activity of several auditory cortical areas with major contributions from the planum temporale in the posterior and the planum polare in the anterior end of the auditory cortex (Liégeois-Chauvel et al. 1994, Jääskeläinen et al. 2004).

## 4.3 Stimulus-specific adaptation of the N1m response

The models of auditory spatial processing have been formulated at the level of single auditory neurons. Therefore, their testing has so far relied largely on the data from animals. Testing the models in the human brain would require a method capable of revealing the tuning properties of different types of neurons even when they are intermingled within the same cortical area. Such a measure could potentially be provided by the stimulus-specific adaptation paradigm. In this paradigm, the effect of an adaptor sound is measured on the response to a subsequent probe sound. The properties of the probe are kept constant while those of the adaptor are varied. When the probe and the adaptor are identical, maximal adaptation of the N1/N1m response is measured. However, when the probe and the adaptor differ in some of their features, for instance frequency or spatial location, larger response amplitudes are found (Butler 1968, 1972). The more the adaptor differs from the probe, the larger the response amplitude is.

The stimulus-specific adaptation of the N1/N1m response can be interpreted in terms of selectivity of single auditory cortical neurons to the stimulus feature, for instance spatial location, by which the probe and the adaptor differ (Fig. 12). Assuming that the neurons giving rise to the N1/N1m response are selective to sound source location, the probe and the adaptor activate the same neurons when they are presented from the same location and separate populations of neurons when they are presented from different locations. When the probe and the adaptor activate different neurons, each neuron is activated only at every other stimulus presentation. Therefore, the effective interstimulus interval for each neuron is doubled from the interval they experience when they are activated by both the probe and the adaptor. Since the neurons are activated more rarely, their responses become less attenuated. This is then reflected at the population level as a larger N1/N1m amplitude. This interpretation makes an important assumption about the activity of single auditory cortical neurons: that the level of single neuron activity depends on the interstimulus interval. Single-unit recordings in cats and monkeys show that the activity level of single neurons is affected by the time interval between consecutive auditory stimuli so that the longer the interval, the higher the level of activity is (Hocherman & Gilat 1981, Phillips et al. 1989, Bartlett & Wang 2005, Werner-Reiss et al. 2006, Brosch & Scheich 2008). For instance, the activity of single neurons in the primary auditory cortex and lateral belt areas of awake and behaving monkeys is attenuated by previous stimuli presented even 5 seconds before (Werner-Reiss et al. 2006). The fastest recovery from adaptation, however, occurs within 3 seconds after the presentation of the first stimulus.

The stimulus-specific adaptation paradigm seems to bear some resemblance to the widely used mismatch negativity (MMN) paradigm (Nelken & Ulanovsky 2007, May & Tiitinen 2010). For measuring the MMN, two sounds are presented in a sequence so that the presentation of a frequent standard stimulus is occasionally interrupted by a rare deviant. The MMN is then obtained by subtracting the averaged response to the standard from that to the deviant. The stimulus-specific adaptation paradigm has some advantages over the MMN especially in light of the aims of the present studies. When measuring stimulus-specific adaptation of the N1m, the probe and the adaptor are presented equally often. In the MMN paradigm, the deviant is presented considerably less frequently than the standard. For this reason, reaching a sufficient number of repetitions for the probe takes considerably less measurement time than reaching it for the deviant sound in MMN. Further, the MMN requires the subtraction operation in which the noise level of two averaged responses is combined and the signal-to-noise ratio is decreased. Most importantly, the interpretation of the stimulus-specific adaptation paradigm is more straightforward than that of the MMN. Since the interest of the present studies is on neural selectivity, rather than on other hypothetical change detection mechanisms, stimulus-specific adaptation provides a faster and simpler method than the MMN.

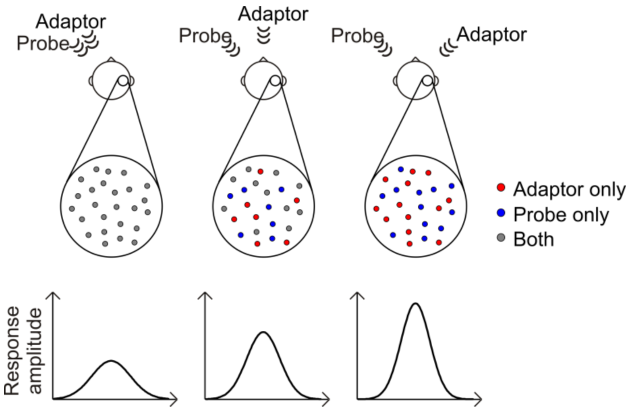

**Figure 12.** Interpretation of the stimulus-specific adaptation of the N1/N1m response in terms of spatially selective single neurons. When the probe and the adaptor sound sources are near one another, the sounds activate mostly the same neurons. This leads to high levels of neuronal adaptation and small N1/N1m responses. When the sounds are presented from different locations, the number of neurons activated by only one of the sound sources increases. These neurons experience a longer interstimulus interval than neurons responding to both sounds and therefore their activity is attenuated less. At the level of the N1/N1m response, this is manifested as larger response amplitudes.

# 5. SUMMARIES OF THE STUDIES

## 5.1 Auditory spatial receptive fields in the human cortex (Study I)

Previous research has established that neurons in the human auditory cortex are selective to sound source location but have left the shape of the spatial receptive fields unexplored. An MEG experiment utilizing the stimulus-specific adaptation paradigm was conducted to test two alternative hypotheses on the spatial tuning properties of human auditory cortical neurons in the horizontal plane: the place code and the hemifield code. Predictions were formulated for the hemifield code and for two versions of the place code: a uniform code with receptive fields of equal widths for all locations and a non-uniform code in which the receptive fields become wider when moving from front to rear. The probe and the adaptor locations were chosen to maximize the difference between the predictions based on the alternative codes. Spatial sound stimuli were prepared for each subject individually.

The amplitude of the N1m response to the probe sounds depended strongly on the location of the adaptor (Fig. 13). When the adaptor was in the same hemifield as the probe, low-amplitude responses were measured independent of the separation between the probe and the adaptor. However, when the adaptor was at the midline or in the opposite hemifield to the probe, larger responses were measured. This result corresponds to the predictions based on the hemifield code of auditory space. These findings are also in line with previous single unit recordings in the monkey auditory cortex that report wide spatial tuning spanning entire hemifields. Therefore, the results show that the human auditory cortex codes horizontal sound source location as a hemifield code similar to that found previously in monkeys.

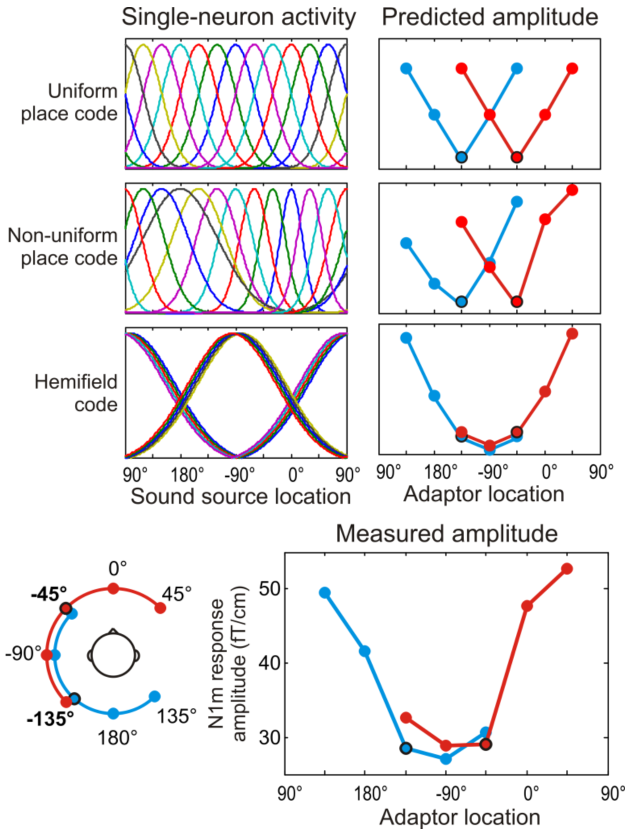

**Figure 13.** Results of Study I. Experimental predictions were formulated based on the place code and the hemifield code and tested in an MEG experiment utilizing the stimulus-specific adaptation paradigm. The amplitude of the N1m response to probe sounds varied depending on the location of the adaptor. The pattern of this variation was consistent with the predictions based on the hemifield code.

## 5.2 The neural code for ITD in the human cortex (Study II)

The hemifield code was demonstrated in Study I for highly realistic spatial sound stimuli that contained all localization cues. Therefore, the results do not allow the distinction between the contributions of different localization cues to the formation of the hemifield code. Single-neuron studies report hemifield tuning to ILD (Tollin 2003) while the findings on ITD coding are more ambiguous (Joris et al. 1998, McAlpine & Grothe 2003). Therefore, it remains possible that the coding found in Study I with realistic spatial sound reflects primarily the coding of ILD while the representation of ITD may be different. An MEG experiment was conducted in which probes and adaptors varied only in their ITD while other sound features were kept constant. The values of the probe and adaptor ITD were chosen so that the predictions based on the place code and the hemifield code were clearly distinct. Further, the ITD has a natural upper limit determined by the size of the human head. To test how this is reflected in the cortical representation, ITD values both within and outside the natural limits were included.

When ITDs within the physiological range were used, the adaptor ITD modulated the amplitude of the N1m response measured to the probe sound (Fig. 14). Responses to the probe sound with an intermediate ITD in the left hemifield was attenuated strongly by an adaptor presented with an ITD further to the left. This attenuation was even stronger than that caused by an adaptor with an identical ITD to the probe. This modulation coincided with the prediction based on the hemifield code. For ITD values larger than those occurring naturally, the N1m response amplitude to the probe did not depend on the adaptor ITD. In conclusion, ITD is represented in the human auditory cortex with a hemifield code and this code is tuned to providing selectivity specifically to ITDs that occur naturally.

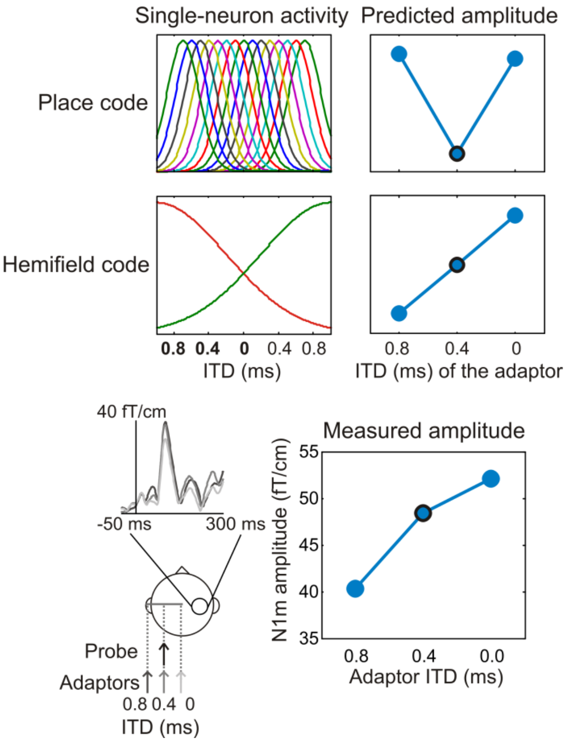

**Figure 14.** Results of Study II. Predictions based on the place code and the hemifield code were tested specifically for ITD. The N1m response amplitude variation was similar to that predicted by the hemifield code.

## 5.3 Interhemispheric differences in auditory spatial representation (Study III)

The two cortical hemispheres have been shown to differ in their representations of auditory space. First, the right hemisphere is more sensitive to spatial sound features (Baumgart et al. 1999, Zatorre et al. 2002). Second, the two hemispheres are activated more by contralateral than by ipsilateral stimulation (Palomäki et al. 2005). The single-neuron tuning properties that give rise to these differences in humans are unknown. An MEG experiment was conducted utilizing the stimulus-specific adaptation paradigm and individually prepared spatial sound stimuli to compare spatial tuning properties in the two hemispheres. To facilitate the interhemispheric comparisons, the probe sound was always situated directly in front of the subject and the adaptors occurred either to the left or to the right.

The attenuation of the right-hemispheric N1m response depended on the location of the adaptor sound source (Fig. 15). The adaptor located to the left of the subject caused stronger attenuation than that located to the right. No such differences were observed in the left-hemispheric N1m response amplitude: the left- and right-located adaptors caused similar attenuation. These results can be accounted for by differences in the sizes of the left- and right-tuned populations. The response to the probe directly in front reflects the combined activity of the right- and left-tuned populations. In the right cortical hemispheres, more neurons are tuned to the left than to the right hemifield. Therefore, the adaptor in the left hemifield affects a larger number of neurons and consequently causes stronger attenuation than that in the right hemifield. In the left hemisphere, the relative sizes of these two populations seem to be more balanced since no differences between the effects of the adaptor to the left and right were found.

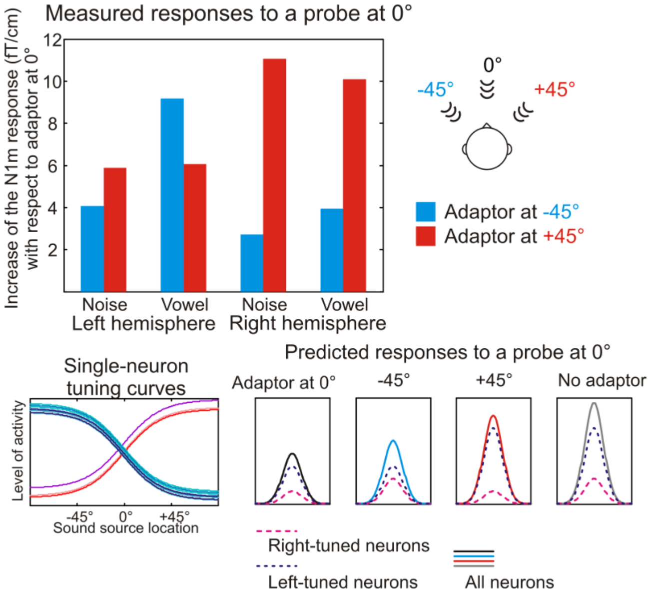

**Figure 15.** Results of Study III. To compare spatial sensitivity in the two hemispheres, N1m response amplitudes were measured to probe sounds directly in front with adaptors to the left or to the right. For the right-hemispheric N1m, the adaptor in the contralateral (left) hemifield caused stronger adaptation than the adaptor in the ipsilateral (right) hemifield. This could be explained by more neurons being tuned to the contralateral than to the ipsilateral hemifield.

## 5.4 The role of parietal and frontal areas in active sound source localization (Study IV)

When subjects are involved in an active sound source localization task, activity can be found in parietal and frontal areas in addition to the auditory areas in the temporal lobe (Rauschecker & Tian 2000, Zatorre et al. 2002, Arnott et al. 2004). The role of these areas in auditory spatial processing and the time course of activation are not known. To explore possibilities for elucidating the time course of parietal and frontal contributions to sound source localization, MEG recordings were performed while the subjects were involved in an active spatial sound detection task. The distribution of brain activities was visualized with minimum-current estimates (MCE, Uutela et al. 1999). The result of the MCE analysis is an estimated current distribution consisting of several local or distributed sources that can in a plausible way account for the recorded MEG signal.

Activities within regions of interest covering large parts of temporal, parietal and frontal cortices were analyzed (Fig. 16). When the activity was averaged and mapped for the target and the non-target presentations separately, it was found that notable activity in parietal and frontal regions of interest occurred only after target presentation while temporal activity was found for all sounds. Further, the level of activity peaked later in the parietal and frontal than in the temporal areas. Given that the parietal and frontal activities in sound source localization occurred only for target sounds that the subject responded to and that the activity took place later than that in the temporal areas, it seems that the parietal and frontal activity reflect the active responding to auditory spatial stimuli, rather than the processing of auditory spatial information itself.

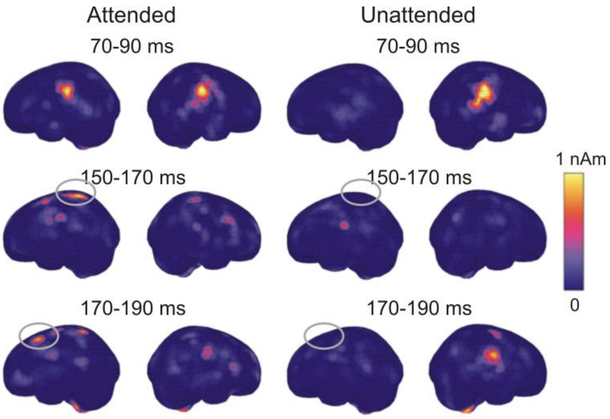

**Figure 16.** Results of Study IV. MEG recordings were performed while the subject was involved in a spatial sound detection task. The activity following the presentation of a target sound was initially found in temporal areas and later extended to parietal and frontal areas. When the sound was not the target, it led to activity confined to temporal areas.

## 5.5 Implications of wide tuning to sound discrimination (Study V)

Often, narrow neural tuning to a stimulus feature is associated with good behavioral discrimination and wide tuning with poor performance. In this light, the wide tuning curves of the hemifield code appear inconsistent with the good behavioral performance in sound source localization by humans. Therefore, another explanation for behavioral discrimination of sound source location is needed. Attempts to apply narrowly tuned neurons in models of speech sound discrimination have also led to inconsistencies. Exposure to a native language phonemic structure early in life leads to discontinuous perception of speech sounds (Liberman et al. 1957, Kuhl 1991). This is manifested as increased discriminability and expansions in the perceptual space at category boundaries and as compression within categories and close to the category prototypes. The category boundaries have been suggested to be represented by large numbers of narrowly tuned neurons (Bauer et al. 1996) but this seems counterintuitive as the neurons would need to specialize in atypical speech sounds instead of the prototypical ones. Alternatively, more neurons could be dedicated to the coding of the prototypes (Guenther & Gjaja 1996) but this model cannot account for the better behavioral discrimination for sounds near the category boundary. A neural network model was constructed in order to explore the possibilities for solving these controversies with wide neural tuning curves.

A neural network was allowed to self-organize while being exposed to speech sound input that simulated the presence of phonetic categories (Fig. 17). After the exposure to speech, the maximal tuning of the neurons of the network occurred for prototypical instances of the categories more often than to other speech sounds. However, the ability of the network to discriminate between speech sounds was best close to the category boundaries. The tuning curves of the model neurons were wide with the maximal activity falling close to the category prototype and the steepest slope coinciding with the category boundaries. The weakest discriminability that fell close to the category prototypes was associated with the flat parts of the tuning curves. This demonstrates that the best discrimination power that a tuning curve provides does not necessarily coincide with the highest level of activity of the neurons. Rather, discriminability is better described as arising from the slopes of the tuning curves.

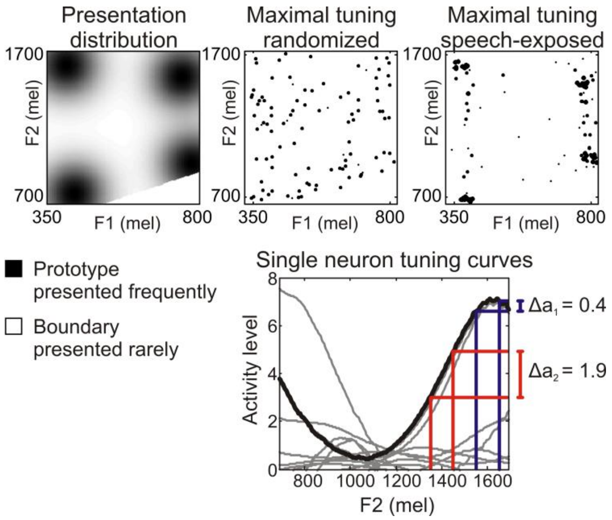

**Figure 17.** Results of Study V. A neural network was exposed to a distribution of speech sounds. In the resulting network, neurons were maximally tuned to prototypical instances and discriminated best between sounds close to the category boundaries. The good discrimination ability was due to the slopes of the tuning curves coinciding with the category boundaries.

# 6. DISCUSSION

Studies of the nervous system in humans and in animals describe the neural activity at different levels. Invasive recordings in animals typically reveal properties of single neurons at various stages of neural processing. In contrast, human brain imaging records the overall level of activity of very large populations of neurons and provides information on the functional specialization of entire brain areas. These differences in the level of description lead to situations in which the human and animal studies on the same topic test different hypotheses and build their own theoretical frameworks independent of one another. For instance, the spatial receptive fields and tuning properties to spatial cues have been mapped for single neurons in the nuclei along the auditory pathway in animal studies (reviewed in Joris et al. 1998, McAlpine & Grothe 2003, Grothe et al. 2010). These findings have inspired the construction of computational theories of sound source localization (Colburn 1973, 1977, Colburn & Latimer 1978, Stern & Colburn 1978, Stern & Zeiberg 1988, Pulkki & Hirvonen 2009). Meanwhile, human brain imaging studies have explored the relative importance of different cortical areas and the two hemispheres in spatial hearing (for instance, Baumgart et al. 1999, Weeks et al. 1999, Rauschecker & Tian 2000, Alain et al. 2001, Zatorre et al. 2002, Warren et al. 2002, Arnott et al. 2004, Ahveninen et al. 2006). Here, the aim was to bridge this gap between single neuron and population-level measures and to test the hypotheses and theories of the single neuron framework utilizing measures available in human brain imaging.

The present results characterize the spatial receptive fields in human auditory cortex. In Study I, these were found to be wide and laterally centered consistent with the hemifield code of horizontal sound source location suggested by previous animal studies. In Study II, hemifield coding was demonstrated for the ITD cue in isolation, for which place coding has long been assumed to apply. According to the results of Study III, the two populations of the hemifield code appear to be of unequal sizes in each cortical hemisphere, so that the population responding to contralateral sound sources is the larger one and that this imbalance is much larger in the right than in the left hemisphere. An active spatial listening task in Study IV led to parietal and frontal areas to activate but their participation occurred only after the presentation of a target sound for which a response was required. Finally, a neural network model implemented in Study V explored the implications of wide tuning curves to behavioral sound discrimination.

## 6.1 Hemifield coding of auditory space in human cortex

### *6.1.1 Converging evidence for the hemifield code*

Studies I and II provide strong support for a hemifield code of auditory space in human cortex. Although previous studies have not addressed the shape of the receptive fields in humans, such measures are available for the monkey auditory cortex. Most of these studies have not explicitly targeted the distinction between a place code and a hemifield code but their descriptions on the receptive field properties are well in line with a hemifield code. The spatial receptive fields are wide and the maximal activity occurs for lateral sound locations in the vast majority of the neurons (Leinonen et al. 1980, Benson et al. 1981, Ahissar et al. 1992, Woods et al. 2006, Werner-Reiss & Groh 2008). One explicit analysis comparing the place and the hemifield code hypotheses has been conducted on the spatial tuning of neurons in the monkey auditory cortex (Werner-Reiss & Groh 2008). This analysis was clearly in favor of the hemifield code.

Another indirect line of evidence for the hemifield code in the human auditory brain comes from psychophysical adaptation studies (Phillips & Hall 2005, Phillips et al. 2006, Vigneault-MacLean et al. 2007). In these studies, the subject is first exposed to a prolonged adaptor sound presented at some location or lateralization and is then asked to localize test sounds. The presentation of the adaptor causes a bias on the localization of the test sound source. For instance after an adaptor has been presented in the right hemifield, subsequent test sounds are perceived to originate from locations towards the left from their actual locations. A test sound presented directly in front appears to originate from a location leftwards from the midline. Interestingly, this effect reaches sound sources far apart from the adaptor location. These biases cannot then be described as local repelling effects of the adaptor location as would be expected in the case of a place code of auditory space. Instead, they are consistent with a hemifield code. When the adaptor is presented in the right hemifield, the activity of the neurons tuned to the right becomes attenuated. Then, during the presentation of the subsequent test sounds, the activity of the right-tuned neurons is at a lower level than normal causing an imbalance between the two populations favoring the left-tuned neurons. Due to this imbalance, all perceived sound source locations, including those far apart from the adaptor, are biased towards the left.

### 6.1.2 *Further experiments for testing the hemifield code*

Here, hemifield tuning was demonstrated with one experimental paradigm, the stimulus-specific adaptation applied in MEG. The experimental paradigms utilized by studies demonstrating spatial selectivity described in Section 2.2.1 could be useful in seeking further evidence for hemifield tuning. For instance, the evoked potential arising in response to a change in the location of an ongoing sound (Halliday & Callaway 1978, Ungan et al. 1989, McEvoy et al. 1990, 1991, Jones et al. 1991, Sams et al. 1993, Mäkelä & McEvoy 1996, Krumbholz et al. 2007) could be used for testing the hemifield code in EEG. A comparison between a shift from one hemifield to the other and a shift within one hemifield could provide an interesting comparison. The hemifield code predicts that even a large shift within one hemifield would produce only a small response or no response at all. In contrast, even a small shift crossing from one hemifield to another would cause a large response.

The validity of the hemifield code hypothesis in the human cortex could be tested in fMRI by utilizing the effects of spatial spread of sound presentation. Previously, it was found that the activity in auditory cortex increases when sounds are presented from several locations as opposed to only one location (Baumgart et al. 1999, Zatorre et al. 2002, Warren & Griffiths 2003, Smith et al. 2004, Krumbholz et al. 2005b, Brunetti et al. 2005, Barrett & Hall 2006, Deouell et al. 2007). This type of an experiment could be modified to test for the validity of the hemifield code in fMRI. The hemifield code predicts that when all sounds are presented from locations confined to one hemifield, a smaller increase in activity occurs than when locations from both hemifields are included. This is because the spatial spread across hemifields activates both the left- and right-tuned populations but the spread within one hemifield leaves one of the populations relatively inactive.

### 6.1.3 *Implications of the hemifield code to localization accuracy*

Often areas of space with better perceptual resolution, for instance the tips of the fingers or the central visual field, are represented by large numbers of neurons maximally activated by stimuli in these locations. From this perspective, the hemifield code of auditory space may seem counterintuitive. Maximal activity is elicited by lateral locations and not by the frontal locations for which behavioral localization is more accurate. A related discrepancy was identified and resolved for the neural representation of speech sounds in Study V. This solution was based on the observation that in a wide tuning curve the best discrimination power of the neuron can be far apart from the location causing maximal activity (Kim &

Bao 2008). The top of the tuning curve is relatively flat and, therefore, two nearby stimuli cause very similar levels of activity. However, when two stimuli with a separation of the same magnitude between them fall onto the slope of the tuning curve, the level of activity they cause in the neuron can be very different. In the hemifield tuned neurons, the steepest slopes of the tuning curves fall to spatial locations near the midline (Leiman & Hafter 1972, Eisenman 1974, Aitkin & Martin 1987, McAlpine et al. 2001, Stecker et al. 2005b). This is well in line with behavioral localization accuracy being at its best for frontal locations.

The requirements for sound source localization accuracy may vary from one task to another. The nervous system may adapt to such situation by dynamically modulating the properties of spatial receptive fields. Studies on frequency tuning provide evidence for task-related changes in receptive fields (Fritz et al. 2003). In the human auditory cortex, this process seems to operate through two mechanisms: sharpening of the tuning curves and increasing gain for the neurons representing the relevant frequency region (Kauramäki et al. 2007). Frequency is coded in the brain with a narrowly tuned place code and consequently these mechanisms are not suitable for improving the hemifield code for a specific area in space. As tuning is wide and maximal activity occurs only for lateral locations, there is no obvious way of sharpening the receptive fields in order to enhance the coding. Also, adding gain does not seem to provide any obvious benefit. Understanding the neural mechanisms that make these improvements possible will require new ideas on how neural representations can be modulated to provide temporary enhancements in coding specific to a single location. One such mechanism could be a temporary shift in the location of the slope of the tuning curve. This would direct the best discrimination power provided by the slope towards the sound source direction of interest.

### *6.1.4 Subcortical neural computations leading to the hemifield code*

The auditory cortical activity indicating the existence of a hemifield code in human auditory cortex presumably reflects the results of neural computations taking place in brainstem auditory nuclei. Animal studies show that the ITD and ILD cues are extracted in the superior olive in the lower brainstem (Joris et al. 1998, Tollin 2003). The computations through which ILD is extracted in LSO are well in line with the hemifield code. LSO neurons receive inhibitory input from one ear and excitatory input from the other (Hall 1965, Boudreau & Tsuchitani 1968, Caird & Klinke 1983, Tollin et al. 2008). This leads to monotonic ILD tuning in LSO neurons so that activity is maximal for sound sources in one hemifield and minimal for those in the opposite hemifield. Further, the slope of the tuning curve coincides with the midline.

The case of ITD extraction is more problematic. Much of the research involving ITD extraction in the brainstem has been conducted to verify the delay-line model (reviewed in Joris et al. 1998) giving rise to a place code representation of auditory space. Recently, an alternative model of neural ITD extraction has emerged from experimental work on small mammals such as gerbil and guinea pig (McAlpine et al. 2001, Brand et al. 2002, Grothe 2003, McAlpine & Grothe 2003, Pecka et al. 2008). According to this view, ITD selectivity emerges from the detailed interplay of bilateral inhibitory and excitatory inputs arriving to the MSO neurons. This leads to ITD tuning curves that are maximal for ITDs corresponding to the quarter of a cycle of the neuron's preferred frequency and have their maximal slope at the midline. That is, maximal activity occurs for ITDs corresponding to lateral locations and the steepest slope of the tuning curve coincides with locations in front. This is consistent with the hemifield code found in Studies I and II in human auditory cortex.

The new theory of ITD extraction consistent with the hemifield code arises from studies of very small mammals with a head size far smaller than that of humans (Grothe 2003, McAlpine & Grothe 2003). Therefore, it cannot be taken for granted that such computations take place also in the human brainstem. The delay line models and thereby place coding are strongly supported by behavioral studies as they have been successful in accounting for many aspects of psychophysically measured binaural processing (Colburn 1973, 1977, Colburn & Latimer 1978, Stern & Colburn 1978, Stern & Zeiberg 1988). It remains, however, possible that equal success could be achieved with alternative computational strategies if they were to be explored. Some attempts have recently been made to create computational binaural models that follow principles consistent with the recent small mammal data and hemifield coding (Pulkki & Hirvonen 2009). These models seem to be able to account for some psychophysical findings traditionally accounted for by the delay-line models.

### *6.1.5 Other codes for auditory space*

The present findings demonstrate that hemifield tuned neurons can be found in the human auditory cortex and presumably in large numbers. They do not, however, exclude the possibility of other types of additional codes of auditory space in the cortex. In addition to the hemifield tuned majority, there may, for instance, be neurons tuned to locations directly in front. In animal studies, these have been reported to coexist with hemifield-tuned neurons (Semple et al. 1983, Moore et al. 1984ab). They may, however, be a side product of frequency tuning and pinna effects that occurs only for very low sound levels as explained in Section 2.3.3 (Moore et al. 1984b). Recent psychophysical adaptation studies suggest that neurons tuned to locations directly in front may operate in the human auditory nervous system (Dingle et al. 2010). Such neurons, if they exist, may serve functions beyond the localization of a sound source. They may provide selectivity to interaural correlation as the correlation is highest for sounds presented directly in front. Such neurons may be very useful, for instance, in hearing in reverberant or noisy environments. It would be interesting to test their existence more directly by the measurement of brain activity. Establishing an experimental setting that brings out the effects of the frontally tuned neurons over the hemifield tuned majority will, however, be challenging.

The hemifield code is capable of representing sound source locations only in the left-right dimension. Humans are, however, fairly good at detecting also sound source elevation (Makous & Middlebrooks 1990, Perrott & Saberi 1990, Carlile et al. 1997, Grantham et al. 2003). Still, almost nothing is known about the neural bases of this ability. Evidence for selectivity to spectral cues corresponding to sound source elevation has been found in the cochlear nucleus (Imig et al. 2000, Davis et al. 2003) and auditory cortical neurons may also carry information on elevation in the timing and level of their activity (Xu et al. 1998). Still, no clear picture of the representation has emerged. The failure to find the code for sound source elevation may have several reasons. First, presenting sounds with reliable elevation cues is challenging in brain research conditions. This should, however, be solvable with individualized virtual spatial sound stimuli and good quality sound reproduction. Second, in experiments of elevation perception, sounds are often presented in the median plane. However, elevation perception is much better for sound sources away from the median plane than to those close to it (Makous & Middlebrooks 1990). Thus, by placing the sound sources appropriately, more neural sensitivity to elevation might be found. Finally, the experimental work on sound source lateralization perception has greatly benefited from the theoretical work in the same area. For elevation perception, no such theoretical frameworks have been proposed yet.

Another spatial dimension missing from the hemifield code is sound source distance. The perception of absolute distance is unreliable and can be altered by variations in sound level (Gardner 1969, Litovsky & Clifton 1992). Its neural bases have also received very little attention. For the distinction between sound sources very near (within grasp) or far from the body, neural correlates have been identified in monkey premotor cortex. These neurons become activated selectively by sounds presented from sources very near to the head (Graziano et al. 1999). These neurons respond also to tactile stimulation from the same direction. Studies of brain damaged patients suggest that such neurons may operate also in the human brain (Farnè & Làdavas 2002).

## 6.2 Interhemispheric differences in auditory spatial processing

The right hemisphere is more sensitive to spatial sound stimulation and takes more actively part in spatial tasks than the left hemisphere (Weeks et al. 1999, Baumgart et al. 1999, Griffiths et al. 1998, 2000, Zatorre et al. 2002, Smith et al. 2004, Brunetti et al. 2005, Palomäki et al. 2005, Altmann et al. 2007). The results of Study III suggest how some of these interhemispheric differences may be accounted for in terms of hemifield-tuned neurons. The two cortical hemispheres were found to differ in the sizes of the left- and right-tuned neural populations. In the right hemisphere, the left-tuned neurons were in a clear majority whereas in the left hemisphere, no differences were found between the sizes of the two populations. This interhemispheric asymmetry probably underlies the previous findings that the right-hemispheric brain responses vary more in their amplitude than the left hemispheric ones depending on sound source location. The N1m response measured over the right hemisphere shows large variation in its amplitude as the sound source is moved from the left to the right hemifield (Palomäki et al. 2005). This variation is consistent with the left-tuned population being larger than the right-tuned one. In contrast, the N1m measured over the left hemisphere varies much less depending on the location of the sound source. This is presumably because in the left hemisphere, the right- and left-tuned populations are of approximately the same size. Therefore, variation in their activities cancels out at the level of the activity of the entire population. In light of these findings, it seems that the neurons in the left and right auditory cortices are equally sensitive to spatial location and the apparent superior sensitivity of the right hemisphere arises from an imbalance between left- and right-tuned populations. Whether there is any functional benefit in a larger asymmetry in the sizes of the two populations remains to be established.

Other findings on the superior sensitivity of the right auditory cortex to spatial stimulation are harder to account for by the asymmetries in spatial representation. The spread of spatial sound presentation to multiple locations instead of only one leads to a larger increase in the activity of the right than the left auditory cortex (Baumgart et al. 1999, Griffiths et al. 1998, 2000, Smith et al. 2004, Brunetti et al. 2005). There is no apparent way in which the asymmetry could account for this interhemispheric difference. When the sound presentation is spread to include several lateral locations in both hemifields in addition to a single frontal source, the activity of both left- and right-tuned neurons should increase equally. Therefore, differences in the sizes of the two populations should have no effect on the increase of the activity. Instead, the increase in the right hemispheric activity may reflect a larger overall number of spatially selective neurons. A larger number of spatially selective neurons in the right than in the left hemisphere is also consistent with the present studies. The N1m response amplitudes measured in Studies I, II, and III for spatial sound and the variation of the amplitude according to the spatial locations of the probe and the adaptor sounds were both larger in the right- than in the left-hemispheric responses.

## 6.3 Parietal areas and the auditory "where" stream

Auditory cortical processing has been suggested to be organized into two processing streams: a ventral "what" stream and a dorsal "where" stream (Rauschecker & Tian 2000, Alain et al. 2001, Arnott et al. 2004). The dorsal stream specialized in spatial processing starts from the posterior auditory cortex and extends from there to parietal and frontal areas. These ideas are based on a similar framework proposed previously for the visual system (Mishkin et al. 1983, Haxby et al. 1991).

The measures of spatial selectivity obtained in Studies I, II, and III may well be dominated by the activity of the posterior auditory cortical neurons serving as the starting point for the dorsal "where" stream. The posterior auditory areas contribute strongly to the N1m response (Liégeois-Chauvel et al. 1994, Jääskeläinen et al. 2004). Both animal and human studies show a higher degree of spatial selectivity in the posterior than in the anterior parts of the auditory cortex (Tian et al. 2001, Woods et al. 2006, Ahveninen et al. 2006). The N1m response has, however, also an anterior component whose contribution to the present findings cannot be excluded. The anterior neurons are selective to spatial location and their receptive fields are of the same shape as those in posterior locations (Tian et al. 2001, Woods et al. 2006, Ahveninen et al. 2006). Therefore, the present studies do not differentiate between the functions of dorsal and ventral streams but rather describe the neural strategy of representing auditory spatial locations that probably is shared by all auditory cortical areas.

Previous work on the dorsal stream has focused primarily on delineating the "where" stream areas from the ventral "what" stream (Rauschecker & Tian 2000, Alain et al. 2001, Arnott et al. 2004). Less effort has been put into understanding what the functions of the various dorsal stream areas are in auditory spatial cognition. In previous studies, parietal and frontal activity has been found in experimental conditions that require active responding to spatial sound stimulation but not during passive listening to the same sounds (Zatorre et al. 2002). Study IV suggests that the parietal and frontal activity is specific to the experimental trials in which a target sound requiring a response is presented and that parietal and frontal areas are activated later than the auditory cortex. Studies on monkey parietal neurons also suggest a role involved in processes related to active utilization of auditory spatial information. Single neurons in posterior parietal cortex often respond to auditory and visual or haptic stimulation and are related to motor plans (Leinonen et al. 1980, Cohen & Andersen 2000). The spatial receptive fields of these neurons are aligned so that they respond, for instance, to flashes of light and sound bursts presented in the same direction (Mazzoni et al. 1996). Further, the responses of the spatially selective neurons in the parietal areas are modulated by task demands (Grunewald et al. 1999, Linden et al. 1999). Based on these findings it seems that the function of parietal areas in spatial hearing is to integrate the multimodal information and to relate it to motor plans and responses.

# 7. CONCLUSIONS

The present findings support a hemifield code representation of sound source location in human cortex. This representation was found even for the ITD cue to which the place code has long been assumed to apply. The delay-line model leading to the place code representation is the prevalent theory on the neural basis of sound source localization presented in textbooks of hearing and neuroscience (for instance, Gazzanica et al. 2002, Møller 2006). The place code is also the foundation of most computational models of spatial hearing (Blauert 1997). In light of the present findings, the relevance of the delay line model and the place code of auditory space to understanding human hearing need to be re-evaluated.

This thesis provides an encouraging example of the plausibility of testing theories inspired by single-neuron tuning properties with methods available for the study of the human brain. This was made possible by the stimulus-specific adaptation paradigm that capitalizes on the sensitivity of cortical activity to stimulation history. Such methods could be applied also to other sound features than source location to reveal the auditory cortical representation of sounds.

# References

Ahissar MV, Ahissar E, Bergman H, Vaadia E (1992) Encoding of sound-source location and movement: Activity of single neurons and interactions between adjacent neurons in the monkey auditory cortex. *J Neurophysiol*, 67:203-215.

Ahveninen J, Jääskeläinen IP, Raij T, Bonmassar G, Devore S, Hämäläinen M, Levänen S, Lin FS, Sams M, Shinn-Cunningham BG, Witzel T, Belliveau JW (2006) Task-modulated "what" and "where" pathways in human auditory cortex. *Proc Natl Acad Sci U S A*, 103:14608-14613.

Aitkin LM, Gates GR, Phillips SC (1984) Responses of neurons in inferior colliculus to variations in sound-source azimuth. *J Neurophysiol*, 52:1-17.

Aitkin LM, Martin RL (1987) The representation of stimulus azimuth by high best-frequency azimuth-selective neurons in the central nucleus of the inferior colliculus of the cat. *J Neurophysiol*, 57:1185-1200.

Aitkin LM, Pettigrew JD, Calford MB, Phillips SC, Wise LZ (1985) Representation of stimulus azimuth by low-frequency neurons in inferior colliculus of the cat. *J Neurophysiol*, 53:43-59.

Alain C, Arnott SR, Hevenor S, Graham S, Grady CL (2001) "What" and "where" in the human auditory system. *Proc Natl Acad Sci U S A*, 98:12301-12306.

Altmann CF, Bledowski C, Wibral M, Kaiser J (2007) Processing of location and pattern changes of natural sounds in the human auditory cortex. *NeuroImage*, 35:1192-1200.

Arnott SR, Binns MA, Grady CL, Alain C (2004) Assessing the auditory dual-pathway model in humans. *NeuroImage*, 22:401-408.

Barrett DJK, Hall DA (2006) Response preferences for "what" and "where" in human non-primary auditory cortex. *NeuroImage*, 32:968-977.

Bartlett EL, Wang X (2005) Long-lasting modulation by stimulus context in primate auditory cortex. *J Neurophysiol*, 94:83-104.

Batra R, Kuwada S, Fitzpatrick DC (1997) Sensitivity to interaural time disparities of low- and high-frequency neurons in the superior olivary complex. I. Heterogeneity of responses. *J Neurophysiol*, 78:1222-1236.

Batra R, Kuwada S, Stanford TR (1993) High-frequency neurons in the inferior colliculus that are sensitive to interaural delays of amplitude-modulated tones: Evidence for dual binaural influences. *J Neurophysiol*, 70:64-80.

Bauer HU, Der R, Herrman M (1996) Controlling the magnification factor in of self-organizing feature maps. *Neural Comput*, 8:757-771.

Baumgart F, Gaschler-Markefski B, Woldorff MG, Heinze HJ, Scheich H (1999) A movement-sensitive area in the auditory cortex. *Nature*, 400:724-726.

Benson DA, Hienz RD, Goldstein MH (1981) Single-unit activity in the auditory cortex of monkeys actively localizing sound sources: spatial tuning and behavioral dependency. *Brain Res*, 219:249-267.

Blauert J (1997) Spatial hearing: the psychophysics of human sound localization. Cambridge: MIT Press, Revised edition.

Blodgett H, Wilbanks WA, Jeffress LA (1956) Effect of large interaural time differences upon judgment of sidedness. *J Acoust Soc Am*, 28:639-643.

Boudreau JC, Tsuchitani C (1968) Binaural interaction in the cat superior olive S segment. *J Neurophysiol*, 31:442-454.

Brand A, Behrend O, Marquardt T, McAlpine D, Grothe B (2002) Precise inhibition is essential for microsecond interaural time difference coding. *Nature*, 417:543-547.

Bremmer F, Schlack A, Shah NJ, Zafiris O, Kubischik M, Hoffmann K-P, Zilles K, Fink GR (2001) Polymodal motion processing in posterior parietal and premotor cortex: A human fMRI study strongly implies equivalencies between humans and monkeys. *Neuron*, 29:287-296.

Brosch M, Scheich H (2008) Tone-sequence analysis in the auditory cortex of awake macaque monkeys. *Exp Brain Res*, 184:349-361.

Brugge JF, Dubrovsky NA, Aitkin LM, Anderson DJ (1969) Sensitivity of single neurons in auditory cortex of cat to binaural tonal stimulation: effects of varying interaural time and intensity. *J Neurophysiol*, 32:1005-1024.

Brugge JF, Merzenich MM (1973) Responses of neurons in auditory cortex of the macaque monkey to monaural and binaural stimulation. *J Neurophysiol*, 36:1138-1158.

Brunetti M, Belardinelli P, Caulo M, Del Gratta C, Della Penna S, Ferretti A, Lucci G, Moretti A, Pizzella V, Tartaro A, Torquati K, Olivetti Belardinelli M, Romani GL (2005) Human brain activation during passive listening to sounds from different locations: an fMRI and MEG study. *Hum Brain Mapp*, 26:251-261.

Bushara KO, Weeks RA, Ishii K, Catalan MJ, Tian B, Rauschecker JP, Hallett M (1999) Modality-specific frontal and parietal areas for auditory and visual localization in humans. *Nat Neurosci*, 2:759-766.

Butler RA (1968) Effect of changes in stimulus frequency and intensity on habituation of the human vertex potential. *J Acoust Soc Am*, 44:945-950.

Butler RA (1972) The influence of spatial separation of sound sources on the auditory evoked response. *Neuropsychologia*, 10:219-225.

Butler RA, Belendiuk K (1977) Spectral cues utilized in the localization of sound in the medial sagital plane. *J Acoust Soc Am*, 61:1264-1269.

Butler RA, Planert N (1976) The influence of stimulus bandwidth on localization of sound in space. *Percept Psychophys*, 19:103-108.

Caird D, Klinke R (1983) Processing of binaural stimuli by cat superior olivary complex neurons. *Exp Brain Res*, 52:385-399.

Calford MB, Moore DR, Hutchings ME (1986) Central and peripheral contributions to coding of acoustic space by neurons in inferior colliculus of cat. *J Neurophysiol*, 55:587-603.

Campbell RAA, Doubell TP, Nodal FR, Schnupp JWH, King AJ (2006) Interaural timing cues do not contribute to the map of space in the ferret superior colliculus: A virtual acoustic space study. *J Neurophysiol*, 95:242-254.

Cant NB, Casseday JH (1986) Projections from the anteroventral cochlear nucleus to the lateral and medial superior olivary nuclei. *J Comp Neurol*, 247:457-476.

Cant NB, Hyson RL (1992) Projections from the lateral nucleus of the trapezoid body to the medial superior olivary nucleus in the gerbil. *Hear Res*, 58:26-34.

Carlile S, Delaney S, Corderoy A (1999) The localisation of spectrally restricted sounds by human listeners. *Hear Res*, 128:175-189.

Carlile S, Hyams S, Delaney S (2001) Systematic distortions of auditory space perception following prolonged exposure to broadband noise. *J Acoust Soc Am*, 110:416-424.

Carlile S, Leong P, Hyams S (1997) The nature and distribution of errors in sound localization by human listeners. *Hear Res*, 114:179-196.

Carney LH, Yin TCT (1989) Responses of low-frequency cells in the inferior colliculus to interaural time differences of clicks: Excitatory and inhibitory components. *J Neurophysiol*, 62:144-161.

Chan JCK, Yin TCT, Musicant AD (1987) Effects of interaural time delays of noise stimuli on low-frequency cells in the cat's inferior colliculus II. Responses to band-pass filtered noises. *J Neurophysiol*, 58:543-561.

Clarey JC, Barone P, Imig TJ (1994) Functional organization of sound direction and sound pressure level in primary auditory cortex of the cat. *J Neurophysiol*, 72:2383-2405.

Cohen YE, Andersen RA (2002) A common reference frame for movement plans in the posterior parietal cortex. *Nat Rev Neurosci*, 3:553-562.

Cohen YE, Andersen RA (2000) Reaches to sounds encoded in eye-centered reference frame. *Neuron*, 27:647-652.

Colburn HS (1973) Theory of binaural interaction based on auditory-nerve data. I. General strategy and preliminary results on interaural discrimination. *J Acoust Soc Am*, 54:1458-1470.

Colburn HS (1977) Theory of binaural interaction based on auditory-nerve data. II. Detection of tones in noise. *J Acoust Soc Am*, 61:525-533.

Colburn HS, Latimer JS (1978) Theory of binaural interaction based on auditory-nerve data. III. Joint dependence on interaural time and amplitude differences in discrimination and detection. *J Acoust Soc Am*, 64:95-106.

David EE, Guttman N, van Bergeijk WA (1958) On the mechanisms of binaural fusion. *J Acoust Soc Am*, 30:801-802.

David EE, Guttman N, van Bergeijk WA (1959) Binaural interaction of high-frequency complex stimuli. *J Acoust Soc Am*, 31:774-782.

Davis KA, Ramachandran R, May BJ (2003) Auditory processing of spectral cues for sound localization in the inferior colliculus. *J Assoc Res Otolangyngol*, 4:148-163.

Deatherage BH, Hirsh IJ (1959) Auditory localization of clicks. *J Acoust Soc Am*, 31:486-492.

Delgutte B, Joris PX, Litovsky RY, Yin TCT (1999) Receptive fields and binaural interactions for virtual-space stimuli in the cat inferior colliculus. *J Neurophysiol*, 81:2833-2851.

Deouell LY, Heller AS, Malach R, D'Esposito M, Knight RT (2007) Cerebral responses to change in spatial location of unatteneded sounds. *Neuron*, 55:985-996.

Dingle RN, Hall SE, Phillips DP (2010) A midline azimuthal channel in human spatial hearing. *Hear Res*, 268:67-74.

Durlach NI (1963) Equalization and cancellation theory of binaural masking-level differences. *J Acoust Soc Am*, 35:1206-1218.

Eisenman LM (1974) Neural encoding of sound location: an electrophysiological study in auditory cortex (AI) of the cat using free field stimuli. *Brain Res*, 75:203-215.

Elberling C, Bak C, Kofoed B, Lebech J, Saermark K (1980) Magnetic auditory responses from the human brain. *Scan Audiol*, 9:185-190.

Farnè A, Ladavas E (2002) Auditory peripersonal space in humans. *J Cogn Neurosci*, 14:1030-1043.

Feddersen WE, Sandel TT, Teas DC, Jeffress LA (1957) Localization of high-frequency tones. *J Acoust Soc Am*, 29:988-991.

Firestone FA (1930) The phase difference and amplitude ratio at the ears due to a source of pure tone. *J Acoust Soc Am*, 2:260-270.

Fitzpatrick DC, Kuwada S, Batra R (2000) Neural sensitivity to interaural time differences: beyond the Jeffress model. *J Neurosci*, 20:1605-1615.

Fitzpatrick DC, Kuwada S, Batra R (2002) Transformations in processing interaural time differences between the superior olivary complex and inferior colliculus: beyond the Jeffress model. *Hear Res*, 168:79-89.

Fritz J, Shamma S, Elhilali M, Klein D (2003) Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex. *Nat Neurosci*, 6:1216–1223.

Furukawa S, Middlebrooks JC (2002) Cortical representation of auditory space: Information-bearing features of spike patterns. *J Neurophysiol*, 87:1749-1762.

Furukawa S, Xu L, Middlebrooks JC (2000) Coding of sound-source location by ensembles of cortical neurons. *J Neurosci*, 20:1216-1228.

Gardner MB (1969) Distance estimation of 0 and apparent 0-oriented speech signals in anechoic space. *J Acoust Soc Am*, 45:47-53.

Gardner MB, Gardner RS (1973) Problem of localization in the median plane: Effect of pinnae cavity occlusion. *J Acoust Soc Am*, 53:400-408.

Gaumond RP, Psaltikidou M (1991) Models for the generation of the binaural difference response. *J Acoust Soc Am*, 89:454-456.

Gazzaniga MS, Ivry RB, Mangun GR (2002) *Cognitive neuroscience: the biology of the mind*. New York: Norton, Second edition.

Gifford GW, Cohen YE (2004) Effect of central fixation light on auditory spatial responses in area LIP. *J Neurophysiol*, 91:2929-2933.

Gifford GW, Cohen YE (2005) Spatial and non-spatial auditory processing in the lateral intraparietal area. *Exp Brain Res*, 162:509-512.

Goldberg JM, Brown PB (1969) Response of binaural neurons of dog superior olivary complex to dichotic tonal stimuli: Some physiological mechanisms of sound localization. *J Neurophysiol*, 32:613-636.

Gordon B (1973) Receptive fields in deep layers of cat superior colliculus. *J Neurophysiol*, 36:157-178.

Grantham DW, Hornsby BWY, Erpenbeck EA (2003) Auditory spatial resolution in horizontal, vertical, and diagonal planes. *J Acoust Soc Am*, 114:1009-1022.

Graziano SA, Reiss LAJ, Gross CG (1999) A neuronal representation of the location of nearby sounds. *Nature*, 397:428-430.

Griffiths TD, Green GGR (1999) Cortical activation during perception of a rotating wide-field acoustic stimulus. *NeuroImage*, 10:84-90.

Griffiths TD, Green GGR, Rees A, Rees G (2000) Human brain areas involved in the analysis of auditory movement. *Human Brain Mapping*, 9:72-80.

Griffiths TD, Rees G, Rees A, Green GGR, Witton C, Rowe D, Büchel C, Turner R, Frackowiak RSJ (1998) Right parietal cortex is involved in the perception of sound movement in humans. *Nat Neurosci*, 1:74-79.

Groh JM, Kelly KA, Underhill AM (2003) A monotonic code for sound azimuth in primate inferior colliculus. *J Cogn Neurosci*, 15:1217-1231.

Groh JM, Trause AS, Underhill AM, Clark KR, Inati S (2001) Eye position influences auditory responses in primate inferior colliculus. *Neuron*, 29:509-518.

Grothe B (2003) New roles for synaptic inhibition in sound localization. *Nat Rev Neurosci*, 4:1-11.

Grothe B, Pecka M, McAlpine D (2010) Mechanisms of sound localization in mammals. *Physiol Rev*, 90:983-1012.

Grothe B, Sanes DH (1993) Bilateral inhibition by glycinergic afferents in the medial superior olive. *J Neurophysiol*, 69:1192-1196.

Grothe B, Sanes DH (1994) Synaptic inhibition influences the temporal coding properties of medial superior olivary neurons: An in vitro study. *J Neurosci*, 14:1701-1709.

Grunewald A, Linden JF, Andersen RA (1999) Responses to auditory stimuli in macaque lateral intraparietal area I. Effects of training. *J Neurophysiol*, 82:330-342.

Guenther FH, Gjaja M (1996) The perceptual magnet effect as an emergent property of neural map formation. *J Acoust Soc Am*, 100:1111-1121.

Hafter ER, Dye RH, Nuetzel JM, Aronow H (1977) Difference thresholds for interaural intensity. *J Acoust Soc Am*, 61:829-834.

Hall JL (1965) Binaural interaction in the accessory superior-olivary nucleus of the cat. *J Acoust Soc Am*, 37:814-823.

Halliday R, Callaway E (1978) Time shift evoked potentials (TSEPs): Method and basic results. *Electroenc Clin Neurophys*, 45:118-121.

Hari R, Aittoniemi K, Järvinen ML, Katila T, Varpula T (1980) Auditory evoked transients and sustained magnetic fields of the human brain. *Exp Brain Res*, 40:237-240.

Harris LR, Blakemore C, Donaghy M (1980) Integration of visual and auditory space in the mammalian superior colliculus. *Nature*, 288:56-59.

Hartley RVL, Fry TC (1921) The binaural location of pure tones. *Phys Rev*, 18:431-442.

Hartmann WM, Wittenberg A (1996) On the externalization of sound images. *J Acoust Soc Am*, 99:3678-3688.

Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, Herscovitch P, Schapiro MB, Rapoport SI (1991) Dissociation of object and spatial visual processing pathways in human extrastriate cortex. *Proc Natl Acad Sci U S A*, 88:16211625.

Hebrank J, Wright D (1974) Spectral cues used in the localization of sound sources on the median plane. *J Acoust Soc Am*, 56:1829-1834.

Heffner HE (1997) The role of macaque auditory cortex in sound localization. *Acta Oto-Lanryng Supp*, 532:22-27.

Henning GB (1974) Detectability of interaural delay in high-frequency complex waveforms. *J Acoust Soc Am*, 55:84-90.

Hocherman S, Gilat E (1981) Dependence of auditory cortex evoked unit activity on interstimulus interval in the cat. *J Neurophysiol*, 45:987-997.

Hunter MD, Griffiths TD, Farrow TFD, Zheng Y, Wilkinson ID, Hegde N, Woods W, Spence SA, Woodruff PWR (2003) A neural basis of the perception of voices in external auditory space. *Brain*, 126:161-169.

Hämäläinen M, Hari R, Ilmoniemi RJ, Knuutila J, Lounasmaa OV (1993) Magnetoencephalography- theory, instrumentation, and applications to noninvasive studies of the working human brain. *Rev Mod Phys*, 65:413-497.

Hämäläinen M, Hari R (2002) Magnetoencephalographic characterization of dynamic brain activation: basic principles and methods of data collection and source analysis. In *Brain mapping: the methods*, edited by A Toga and JC Mazziotta, Amsterdam: Academic Press, second edition.

Imig TJ, Bibikov NG, Poirier P, Samson FK (2000) Directionality derived from pinna-cue spectral notches in cat dorsal cochlear nucleus. *J Neurophysiol*, 83:907-925.

Imig TJ, Irons A, Samson FR (1990) Single-unit selectivity to azimuthal direction and sound pressure level of noise bursts in cat high-frequency primary auditory cortex. *J Neurophysiol*, 63:1448-1466.

Ito S, Hoke M, Pantev C, Lütkenhöner B (1988) Binaural interaction in brainstem auditory evoked potentials elicited by frequency-specific stimuli. *Hear Res*, 35:9-20.

Jeffress LA (1948) A place theory of sound localization. *J Comp Psysiol Psychol*, 41:35-39.

Jiang H, Lepore F, Poirier P, Guillemot JP (2000) Responses of cells to stationary and moving sound stimuli in the anterior ectosylvian cortex of cats. *Hear Res*, 139:69-85.

Jones SJ, Pitman JR, Halliday AM (1991) Scalp potentials following sudden coherence and discoherence of binaural noise and change in the inter-aural time difference: a specific binaural evoked potential or a "missmatch" response? *Electroenc Clin Neurophys*, 80:146-154.

Joris PX, Carney LH, Smith PH, Yin TC (1994) Enhancement of neural synchronization in the anteroventral cochlear nucleus. I. Responses to tones at the characteristic frequency. *J Neurophysiol*, 94:1022–1036.

Joris PX, Smith PH, Yin TCT (1998) Coincidence detection in the auditory system: 50 years after Jeffress. *Neuron*, 21:1235-1238.

Joris PX, Yin TCT (1995) Envelope coding in the lateral superior olive. I. Sensitivity to interaural time differences. *J Neurophysiol*, 73:1043-1062.

Junius D, Riedel H, Kollmeier B (2007) The influence of externalization and spatial cues on the generation of auditory brainstem responses and middle latency responses. *Hear Res*, 225:91-104.

Jääskeläinen IP, Ahveninen J, Bonmassar G, Dale AM, Ilmoniemi RJ, Levänen S, Lin FH, May P, Melcher J, Stufflebeam S, Tiitinen H, Belliveau JW (2004) Human posterior auditory cortex gates novel sounds to consciousness. *Proc Natl Acad Sci U S A*, 101:6809-6814.

Kaas JH, Hackett TA (2000) Subdivisions of auditory cortex and processing streams in primates. *Proc Natl Acad Sci U S A*, 97:11793-11799.

Kapfer C, Seidl AH, Schweizer H, Grothe B (2002) Experience-dependent refinement of inhibitory inputs to auditory coincidence-detector neurons. *Nat Neurosci*, 5:247-253.

Kashino M, Nishida S (1998) Adaptation in the processing of interaural time differences revealed by the auditory localization aftereffect. *J Acoust Soc Am*, 103:3597-3604.

Kauramäki J, Jääskeläinen IP, Sams M (2007) Selective attention increases both gain and feature selectivity of the human auditory cortex. *PLoS ONE*, 2:e909.

Kim H, Bao S (2008) Distributed representation of perceptual categories in the auditory cortex. *J Comput Neurosci*, 24:277-290.

King AJ, Hutchings ME (1987) Spatial response properties of acoustically responsive neurons in the superior colliculus of the ferret: A map of auditory space. *J Neurophysiol*, 57:596-624.

King AJ, Palmer AR (1983) Cells responsive to free-field auditory stimuli in guinea-pig superior colliculus: Distribution and response properties. *J Physiol*, 342:361-381.

Klumpp RG, Eady HR (1956) Some measurements of interaural time difference thresholds. *J Acoust Soc Am*, 28:859-860.

Krumbholz K, Hewson-Stoate N, Schönwiesner M (2007) Cortical responses to auditory motion suggests an asymmetry in the reliance on inter-hemispheric connections between the left and right auditory cortices. *J Neurophysiol*, 97:1649-1655.

Krumbholz K, Schönwiesner M, Rübsamen R, Zilles K, Fink GR, Yves von Cramon D (2005a) Hierarchical processing of sound location and motion in the human brainstem and planum temporale. *Eur J Neurosci*, 21:230-238.

Krumbholz K, Schönwiesner M, von Cramon DY, Rübsamen R, Shah NJ, Zilles K, Fink GR (2005b) Representation of interaural temporal information from left and right auditory space in the human planum temporale and inferior parietal lobule. *Cereb Cortex*, 15:317-324.

Kuhl PK (1991) Human adults and human infants show a “perceptual magnet effect” for the prototypes of speech categories, monkeys do not. *Percept Psychophys*, 50:93-107.

Kuhn GF (1977) Model for the interaural time differences in the azimuthal plane. *J Acoust Soc Am*, 62:157-167.

Kuwada S, Stanford TR, Batra R (1987) Interaural phase-sensitivity units in the inferior colliculus of the unanesthetized rabbit: Effects of changing frequency. *J Neurophysiol*, 57:1338-1360.

Kuwada S, Yin TCT (1983) Binaural interaction in low-frequency neurons in inferior colliculus of the cat I. Effects of long interaural delays, intensity, and repetition rate on interaural delay function. *J Neurophysiol*, 50:981-999.

Kuwada S, Yin TCT, Sykea J, Buunen TJF, Wickesberg RE (1984) Binaural interaction in low-frequency neurons in inferior colliculus of the cat. IV. Comparison of monaural and binaural response properties. *J Neurophysiol*, 51:1306-1325.

Langendijk EHA, Bronkhorst AW (2002) Contribution of spectral cues to human sound localization. *J Acoust Soc Am*, 112:1583-1596.

Lehmann C, Herdener M, Schneider P, Federspiel A, Bach DR, Esposito F, di Salle F, Scheffler K, Kretz R, Dierks T, Seifritz E (2007) Dissociated lateralization of transient and sustained blood oxygen level-dependent signal components in human primary auditory cortex. *NeuroImage*, 34:1637-1642.

Leiman AL, Hafter ER (1972) Responses of inferior colliculus neurons to free field auditory stimuli. *Exp Neurol*, 35:431-449.

Leinonen L, Hyvärinen J, Sovijärvi ARA (1980) Functional properties of neurons in the temporal-parietal association cortex of awake monkey. *Exp Brain Res*, 39:203-215.

Lewis JW, Beauchamp MS, DeYoe EA (2000) A comparison of visual and auditory motion processing in human cerebral cortex. *Cereb Cortex*, 10:873-888.

Liberman AM, Safford Harris K, Hoffman HS, Griffith BC (1957) The discrimination of speech sounds within and across phoneme boundaries. *J Exp Psychol*, 54:358-368.

Liégeois-Chauvel C, Musolino A, Badier JM, Marquis P, Chauvel P (1994) Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroenc Clin Neurophys*, 92:204-214.

Linden JF, Grunewald A, Andersen RA (1999) Responses to auditory stimuli in macaque lateral intraparietal area II. Behavioral modulation. *J Neurophysiol*, 82:343-358.

Litovsky RY, Clifton RK (1992) Use of sound-pressure level in auditory distance discrimination by 6-month old infants and adults. *J Acoust Soc Am*, 92:794-802.

Lomber SG, Malhotra S (2008) Double dissociation of “what” and “where” processing in auditory cortex. *Nat Neurosci*, 11:609-616.

Lounasmaa OV, Hämäläinen M, Hari R, Salmelin R (1996) Information processing in the human brain: magnetoencephalographic approach. *Proc Natl Acad Sci U S A*, 92:8809-8815.

Macpherson EA, Middlebrooks JC (2003) Vertical-plane sound localization probed with ripple-spectrum noise. *J Acoust Soc Am*, 114:430-445.

Maeder PP, Meuli RA, Adriani M, Bellmann A, Fornari E, Thiran JP, Pittet A, Clarke S (2001) Distinct pathways involved in sound recognition and localization: a human fMRI study. *NeuroImage*, 14:802-816.

Makous JC, Middlebrooks JC (1990) Two-dimensional sound localization by human listeners. *J Acoust Soc Am*, 86:2188-2220.

May PJC, Tiitinen H (2010) Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. *Psychophysiology*, 47:66-122.

Mazzoni P, Bracewell RM, Barash S, Andersen RA (1996) Spatially tuned auditory responses in area LIP of macaques performing delayed memory saccades to acoustic targets. *J Neurophysiol*, 75:1233-1241.

McAlpine D, Grothe B (2003) Sound localization and delay lines - do mammals fit the model? *Trends Neurosci*, 26:347-350.

McAlpine D, Jiang D, Palmer AR (1996) Interaural delay sensitivity and the classification of low best-frequency binaural responses in the inferior colliculus of the guinea pig. *Hear Res*, 97:136-152.

McAlpine D, Jiang D, Palmer AR (2001) A neural code for low-frequency sound localization in mammals. *Nat Neurosci*, 4:396-401.

McEvoy L, Hari R, Imada T, Sams M (1993) Human auditory cortical mechanisms of sound lateralization: II. Interaural time differences at sounds onset. *Hear Res*, 67:98-109.

McEvoy LK, Picton TW, Champagne SC, Kellett AJC, Kelly JB (1990) Human evoked potentials to shifts in the lateralization of a noise. *Audiology*, 29:163-180.

McEvoy LK, Picton TW, Champagne SC (1991) Effects of stimulus parameters on human evoked potentials to shifts in the lateralization of a noise. *Audiology*, 30:286-302.

McFadden D, Pasanen EG (1976) Lateralization at high frequencies based on interaural time differences. *J Acoust Soc Am*, 59:634-639.

Mickey BJ, Middlebrooks JC (2003) Representation of auditory space by cortical neurons in awake cats. *J Neurosci*, 23:8649-8663.

Middlebrooks (1992) Narrow-band sound localization related to external ear acoustics. *J Acoust Soc Am*, 92:2607-2624.

Middlebrooks JC, Clock AE, Xu L, Green DM (1994) A panoramic code for sound location by cortical neurons. *Science*, 264:842-844.

Middlebrooks JC, Knudsen EI (1984) A neural code for auditory space in the cat's superior colliculus. *J Neurosci*, 4:2621-2634.

Middlebrooks JC, Pettigrew JD (1981) Functional classes of neurons in primary auditory cortex of the cat distinguished by sensitivity to sound location. *J Neurosci*, 1:107-120.

Middlebrooks JC, Xu L, Clock Eddins A, Green DM (1998) Codes for sound-source location in nontonotopic auditory cortex. *J Neurophysiol*, 80:863-881.

Middlebrooks JC, Xu L, Furukawa S, Macpherson EA (2002) Cortical neurons that localize sounds. *Neuroscientist*, 8:73-83.

Mills AW (1958) On the minimum audible angle. *J Acoust Soc Am*, 30:237-246.

Mills AW (1960) Lateralization of high-frequency tones. *J Acoust Soc Am*, 32:132-134.

Mishkin M, Ungerleider LG, Macko KA (1983) Object vision and spatial vision: two cortical pathways. *Trends Neurosci*, 6:414-417.

Moore DR, Irvine DRF (1981) Development of responses to acoustic interaural intensity differences in the cat inferior colliculus. *Exp Brain Res*, 41:301-309.

Moore DR, Semple MN, Addison PD, Aitkin LM (1984a) Properties of spatial receptive fields in the central nucleus of the cat inferior colliculus I. Responses to tones of low intensity. *Hear Res*, 13:159-174.

Moore DR, Hutchings ME, Addison PD, Semple MN, Aitkin LM (1984b) Properties of spatial receptive fields in the central nucleus of the cat inferior colliculus II. Stimulus intensity effects. *Hear Res*, 13:175-188.

Mossop JE, Culling JF (1998) Lateralization of large interaural delays. *J Acoust Soc Am*, 104:1574-1579.

Mäkelä JP, McEvoy L (1996) Auditory evoked fields to illusory sound source movements. *Exp Brain Res*, 110:446-454.

Møller AR (2006) Hearing: anatomy, physiology, and disorders of the auditory system. Boston: Academic Press.

Nelken I, Ulanovsky N (2007) Mismatch negativity and stimulus-specific adaptation in animal models. *J Psychophysiol*, 21:214-223.

Nuetzel JM, Hafter ER (1976) Lateralization of complex waveforms: Effects of fine structure, amplitude, and duration. *J Acoust Soc Am*, 60:1339-1346.

Näätänen R, Sams M, Alho K, Paavilainen P, Reinikainen K, Sokolov EN (1988) Frequency and location specificity of the human vertex N1 wave. *Electroenc Clin Neurophys*, 69:523-531.

Orman SS, Phillips DP (1984) Binaural interactions of single neurons in posterior field of cat auditory cortex. *J Neurophysiol*, 51:1028-1039.

Palmer AR, King AJ (1982) The representation of auditory space in the mammalian superior colliculus. *Nature*, 299:248-249.

Palomäki KJ, Alku P, Mäkinen V, May PJC, Tiitinen H (2000) Sound localization in the human brain: neuromagnetic observations. *Neuroreport*, 11:1535-1538.

Palomäki KJ, Tiitinen H, Mäkinen V, May PJC, Alku P (2002) Cortical processing of speech sounds and their analogues in a spatial auditory environment. *Brain Res Cogn Brain Res*, 14:294-299.

Palomäki KJ, Tiitinen H, Mäkinen V, May PJC, Alku P (2005) Spatial processing in human auditory cortex: The effects of 3D, ITD, and ILD stimulation techniques. *Brain Res Cogn Brain Res*, 24:364-379.

Pavani F, Macaluso E, Warren JD, Driver J, Griffiths TD (2002) A common cortical substrate activated by horizontal and vertical sound movement in the human brain. *Curr Biol*, 12:1584-1590.

Pecka M, Brand A, Behrend O, Grothe B (2008) Interaural time difference processing in the mammalian medial superior olive: the role of glycinergic inhibition. *J Neurosci*, 28:6914-6925.

Perrott DR, Pacheco S (1989) Minimum audible angle thresholds for broadband noise as a function of the delay between the onset of the lead and lag signals. *J Acoust Soc Am*, 85:2669-2672.

Perrott DR, Saberi K (1990) Minimum audible angle thresholds for sources varying in both elevation and azimuth. *J Acoust Soc Am*, 87:1728-1731.

Phillips DP, Carmichael ME, Hall SE (2006) Interactions in the perceptual processing of interaural time and level differences. *Hear Res*, 211:96-102.

Phillips DP, Hall SE (2005) Psychophysical evidence for adaptation of central auditory processors for interaural differences in time and level. *Hear Res*, 202:188-199.

Phillips DP, Hall SE, Hollett JL (1989) Repetition rate and signal level effects on neuronal responses to brief tone pulses in cat auditory cortex. *J Acoust Soc Am*, 85:2537-2549.

Plenge G (1974) On the differences between localization and lateralization. *J Acoust Soc Am*, 56:944-951.

Poirier P, Jian H, Lepore F, Guillemot JP (1997) Positional, directional and speed selectivities in the primary auditory cortex of the cat. *Hear Res*, 113:1-13.

Pratt CC (1930) The spatial character of high and low tones. *J Exp Psychol*, 13:278-285.

Pulkki V, Hirvonen T (2009) Functional count-comparison model for binaural decoding. *Acta Acustica*, 95:883-900.

Rajan R, Aitkin LM, Irvine DRF, McKay J (1990a) Azimuthal sensitivity of neurons in primary auditory cortex of cats I. Types of sensitivity and the effects of variations of stimulus parameters. *J Neurophysiol*, 64:872-887.

Rajan R, Aitkin LM, Irvine DRF, McKay J (1990b) Azimuthal sensitivity of neurons in primary auditory cortex of cats II. Organization along frequency-band strips. *J Neurophysiol*, 64:888-902.

Rauschecker JP, Tian B (2000) Mechanisms and streams for processing of "what" and "where" in auditory cortex. *Proc Natl Acad Sci U S A*, 97:11800-11806.

Reale RA, Brugge JF (1990) Auditory cortical neurons are sensitive to static and continuously changing interaural phase cues. *J Neurophysiol*, 64:1247-1260.

Reale RA, Jenison RL, Brugge JF (2003) Directional sensitivity of neurons in the primary auditory (AI) cortex: Effects of sound-source intensity level. *J Neurophysiol*, 89:1024-1038.

Recanzone GH (2000) Spatial processing in the auditory cortex of the macaque monkey. *Proc Natl Acad Sci U S A*, 97:11829-11835.

Recanzone GH, Guard DC, Phan ML, Su TIK (2000) Correlation between the activity of single auditory cortical neurons and sound-localization behaviour in the macaque monkey. *J Neurophysiol*, 83:2723-2737.

Roffler SK, Butler RA (1967a) Factors that influence the localization of sound in the vertical plane. *J Acoust Soc Am*, 43:1255-1259.

Roffler SK, Butler RA (1967b) Localization of tonal stimuli in the vertical plane. *J Acoust Soc Am*, 43:1260-1266.

Rose JE, Gross NB, Geisler D, Hind JE (1966) Some neural mechanisms in the inferior colliculus of the cat which may be relevant to localization of a sound source. *J Neurophysiol*, 29:288-314.

Sams M, Hämäläinen M, Hari R, McEvoy L (1993) Human auditory cortical mechanisms of sound lateralization. I. Interaural time differences within sound. *Hear Res*, 67:89-97.

Sanes DH (1990) An in vitro analysis of sound localization mechanisms in the gerbil lateral superior olive. *J Neurosci*, 10:3494–3506.

Semple MN, Aitkin LM (1979) Representation of sound frequency and laterality by units in central nucleus of cat inferior colliculus. *J Neurophysiol*, 42:1626-1639.

Semple MN, Aitkin LM, Calford MB, Pettigrew JD, Phillips DP (1983) Spatial receptive fields in the cat inferior colliculus. *Hear Res*, 10:203-215.

Sestieri C, Di Matteo R, Ferretti A, Del Gratta C, Caulo M, Tartaro A, Olivetti Belardinelli M, Romani GL (2006) "What" versus "where" in the audiovisual domain: An fMRI study. *NeuroImage*, 33:672-680.

Shaw EAG (1974) Transformation of sound pressure level from the free field to the eardrum in the horizontal plane. *J Acoust Soc Am*, 56:1848-1861.

Simpson M (1920) Experiments in binaural phase difference effect with pure tones. *Phys Rev*, 15:421-424.

Sivian LJ, White SD (1933) On minimum audible fields. *J Acoust Soc Am*, 4:288-321.

Small AM, Bacon WE, Fozard JL (1959) Intensive differential thresholds for octave-band noise. *J Acoust Soc Am*, 31:508-510.

Smith KR, Okada K, Saberi K, Hickok G (2004) Human cortical auditory motion areas are not motion selective. *Neuroreport*, 15:1523-1526.

Smith PH, Joris PX, Yin TCT (1993) Projections of physiologically characterized spherical bushy cell axons from the cochlear nucleus of the cat: evidence for delay lines to medial superior olive. *J Comp Neurol*, 331:245-260.

Soeta Y, Nakagawa S (2006) Effects of the frequency of interaural time difference in the human brain. *Neuroreport*, 17:505-509.

Sovijärvi ARA, Hyvärinen J (1974) Auditory cortical neurons in the cat sensitive to the direction of sound source movement. *Brain Res*, 73:455-471.

Spangler KM, Warr WB, Henkel CK (1985) The projections of principal cells of the medial nucleus of the trapezoid body in the cat. *J Comp Neurol*, 238:249-262.

Spierer L, Bellmann-Thiran A, Maeder P, Murray MM, Clarke S (2009) Hemispheric competence for auditory spatial representation. *Brain*, 132:1953-1966.

Stecker GC, Harrington IA, Macpherson EA, Middlebrooks JC (2005) Spatial sensitivity in the dorsal zone (area DZ) of cat auditory cortex. *J Neurophysiol*, 94:1267-1280.

Stecker GC, Harrington IA, Middlebrooks JC (2005) Location coding by opponent neural populations in the auditory cortex. *PLoS Biol*, 3:e78.

Stecker GC, Mickey BJ, Macpherson EA, Middlebrooks JC (2003) Spatial sensitivity in field PAF of cat auditory cortex. *J Neurophysiol*, 89:2889-2903.

Sterbing SJ, Hartung K, Hoffmann K-P (2003) Spatial tuning to virtual sounds in the inferior colliculus of the guinea pig. *J Neurophysiol*, 90:2648-2659.

Stern RM, Colburn HS (1978) Theory of binaural interaction based on auditory-nerve data. IV. A model for subjective lateral position. *J Acoust Soc Am*, 64:127-140.

Stern RM, Zeiberg AS (1988) Lateralization of complex binaural stimuli: A weighted-image model. *J Acoust Soc Am*, 84:156-165.

Stewart GW (1920a) The function of intensity and phase in the binaural location of pure tones. Part I. Intensity. *Phys Rev*, 15:425-431.

Stewart GW (1920b) The function of intensity and phase in the binaural location of pure tones. Part II. Phase. *Phys Rev*, 15:432-445.

Stillman RD (1971) Characteristic delay neurons in the inferior colliculus of the kangaroo rat. *Exp Neurol*, 32:404-412.

Stricanne B, Andersen RA, Mazzoni P (1996) Eye-centered, head-centered, and intermediate coding of remembered sound locations in area LIP. *J Neurophysiol*, 76:2071-2075.

Strutt JW (Lord Rayleigh) (1907) On our perception of sound direction. *Phil Mag*, 6:214-232.

Thompson GC, Cortez AM (1983) The inability of squirrel monkeys to localize sound after unilateral ablation of auditory cortex. *Behav Brain Res*, 8:211-216.

Tian B, Reser D, Durham A, Kustov A, Rauschecker JP (2001) Functional specialization in rhesus monkey auditory cortex. *Science*, 292:290-293.

Tollin DJ (2003) The lateral superior olive: A functional role in sound source localization. *Neuroscientist*, 9:127-143.

Tollin DJ, Koka K, Tsai JJ (2008) Interaural level difference discrimination thresholds for single neurons in the lateral superior olive. *J Neurosci*, 28:4848-4860.

Ungan P, Sahinoglu B, Utkucal R (1989) Human laterality reversal auditory evoked potentials: stimulation by reversing the interaural delay of dichotically presented continuous click trains. *Electroenc Clin Neurophys*, 73:306-321.

Uutela K, Hämäläinen M, Somersalo E (1999) Visualization of magnetoencephalographic data using minimum current estimates. *NeuroImage*, 10:173-180.

Updyke BV (1974) Characteristics of unit responses in superior colliculus of the Cebus monkey. *J Neurophysiol*, 49:896-909.

Wallace MT, Meredith MA, Stein BE (1993) Converging influences from visual, auditory, and somatosensory cortices onto output neurons of the superior colliculus. *J Neurophysiol*, 69:1797-1809.

Wallace MT, Stein BE (1994) Cross-modal synthesis in the midbrain depends on input from cortex. *J Neurophysiol*, 71:429-432.

van Bergeijk WA (1962) Variation to a theme of Békésy: a model of binaural interaction. *J Acoust Soc Am*, 34:1431-1437.

Warren JD, Griffiths TD (2003) Distinct mechanisms for processing spatial sequences and pitch sequence in the human auditory brain. *J Neurosci*, 23:5799-5804.

Warren JD, Zielinski BA, Green GGR, Rauschecker JP, Griffiths TD (2002) Perception of sound-source motion by the human brain. *Neuron*, 34:139-148.

Weeks RA, Aziz-Sulta A, Bushara KO, Tian B, Wessinger CM, Dang N, Rauschecker JP, Hallett M (1999) A PET study of human auditory spatial processing. *Neurosci Lett*, 262:155-158.

Wenzel EM, Arruda M, Kistler DJ, Wightman F (1993) Localization using non-individualized head-related transfer functions. *J Acoust Soc Am*, 94:111-123.

Werner-Reiss U, Groh JM (2008) A rate code for sound azimuth in monkey auditory cortex: Implications for human neuroimaging studies. *J Neurosci*, 28:3747-3758.

Werner-Reiss U, Porter KK, Underhill AM, Groh JM (2006) Long lasting attenuation by prior sounds in auditory cortex of awake primates. *Exp Brain Res*, 168:272-276.

Wightman FL, Kistler DJ (1989a) Headphone simulation of free-field listening I: Stimulus synthesis. *J Acoust Soc Am*, 85:858-866.

Wightman FL, Kistler DJ (1989b) Headphone simulation of free-field listening II: Psychophysical validation. *J Acoust Soc Am*, 85:868-878.

Wightman FL, Kistler DJ (1992) The dominant role of low-frequency interaural time differences in sound localization. *J Acoust Soc Am*, 91:1648-1661.

Wightman FL, Kistler DJ (1997) Monaural sound localization revisited. *J Acoust Soc Am*, 101:1050-1063.

Vigneault-MacLean B, Hall SE, Phillips DP (2007) The effects of lateralized adaptors on lateral position judgments of tones within and across frequency channels. *Hear Res*, 224:93-100.

Wise LZ, Irvine DRF (1983) Auditory response properties of neurons in deep layers of cat superior colliculus. *J Neurophysiol*, 49:674-685.

von Békésy G (1930) Zur Theorie des Hörens. Über das Richtungshören bei einer Zeitdifferenz oder Lautstörkenungleichheit der beiderseitigen Schalleinwirkunger. *Physik Z*, 31:824-935.

von Békésy G (1960) *Experiments in hearing*. New York: McGraw-Hill.

Woods TM, Lopez SE, Long JH, Rahman JE, Recanzone GH (2006) Effects of stimulus azimuth and intensity on the single-neuron activity in the auditory cortex of the alert macaque monkey. *J Neurophysiol*, 96:3323-3337.

Xu L, Furukawa S, Middlebrooks JC (1998) Sensitivity to sound-source elevation in nontonotopic auditory cortex. *J Neurophysiol*, 80:882-894.

Yin TCT, Chan JCK (1990) Interaural time sensitivity in medial superior olive of cat. *J Neurophysiol*, 64:465-488.

Yin TCT, Chan JCK, Irvine DRF (1986) Effects of interaural time delays of noise stimuli on low-frequency cells in the cat's inferior colliculus I: Responses to wideband noise. *J Neurophysiol*, 55:280-300.

Yin TCT, Kuwada S (1983) Binaural interaction in low-frequency neurons in inferior colliculus of the cat III. Effects of changing frequency. *J Neurophysiol*, 50:1020-1042.

Yost WA (1974) Discrimination of interaural phase differences. *J Acoust Soc Am*, 55:1299-1303.

Zatorre RJ, Bouffard M, Ahad P, Belin P (2002) Where is "where" in the human auditory cortex? *Nat Neurosci*, 5:905-909.

Zatorre RJ, Mondor TA, Evans AC (1999) Auditory attention to space and frequency activates similar cerebral systems. *NeuroImage*, 10:544-554.

Zatorre RJ, Penhune VB (2001) Spatial localization after excision of human auditory cortex. *J Neurosci*, 21:6321-6328.

Zwiers MP, Versner H, Van Opstal AJ (2004) Involvement of monkey inferior colliculus in spatial hearing. *J Neurosci*, 24:4145-4156.

Zwislocki J, Feldman RS (1956) Just noticeable differences in dichotic phase. *J Acoust Soc Am*, 28:860-864.

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