Functional magnetic resonance imaging of human auditory cortical tuning to interaural level and time differences

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Abstract

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Interaural level and time differences (ILD and ITD) are important cues for localizing sound and segregating signal from noise. Evidence indicates that auditory cortex (AC) plays a critical role in mammalian sound localization, but models of AC binaural processing remain underspecified. A series of experiments was conducted to systematically characterize fMRI tuning to binaural stimulation in human AC. To investigate processing of ILD versus monaural sound, Experiment 1 collected responses to narrowband-filtered Gabor click impulses varying in ILD, average binaural level, monotic level, and presentation rate. Response to monotic sound was greater contralateral to ear of presentation and binaural responses grew with increasingly contralateral ILD values. Contralateral bias was more modest for ILD than for monotic stimulation, and the relationship in bias across the stimulus types was weak, suggesting that ILD tuning is partially independent of monaural level sensitivity. Binaural suppression was observed for diotic and dichotic ILD sound and may actively shape ILD sensitivity.

Experiments 2 and 3 presented parametrically modulated ILD and ITD cues carried by Gabor click trains (ILD_{GCT} and ITD_{GCT}). Consistent with Exp. 1, results showed contralateral tuning to ILD_{GCT}, but little tuning to ITD_{GCT} . Additional experiments manipulated ITD in broadband noise-burst trains (ITD_{NBT}; Experiment

4) and in low-frequency noise (ITD$_{LPN}$; Experiment 5). Modest contralateral tuning to ITD$_{NBT}$ was observed, but only in left hemisphere, consistent with previous neuroimaging and clinical lesion data. Further analysis revealed a similar asymmetry in response to ILD$_{GCT}$. Analyses of stimulus history effects showed that contralateral tuning to ILD$_{GCT}$ and ITD$_{NBT}$ was enhanced by exposure to prior ipsilateral sound, particularly in right hemisphere responses to ITD, potentially serving to minimize the left hemisphere asymmetry observed. Stimulus history analyses also showed greater sensitivity to "outward" (probe sound more lateralized than adaptor) versus "inward" (adaptor more lateralized than probe) sound location change for both ILD and ITD, consistent with opponent-channel models of binaural processing. Differences in the degree of contralateral bias and hemispheric asymmetry across cue types may be due to reduced BOLD sensitivity to ITD, rather than reflecting distinct AC processing mechanisms for ILD and ITD.

DEDICATION

In memory of my father and mother, John and Billie.

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Chapter 1

INTRODUCTION

1.1 Overview: binaural processing in the auditory cortex

For humans, as for many species, the ability to localize sound sources is important not only for environmental awareness, but also for disentangling the multitude of acoustic signals generated in complex listening environments (termed “auditory stream segregation” by Bregman and Campbell 1971), thereby allowing for selective attention to salient sounds. Sound localization in the horizontal plane relative to the head and ears (the “azimuth”) relies largely on the neural coding of disparities between the acoustic signal arriving at a listener’s two ears. These binaural spatial cues result from the location-dependent relationship between a sound source and the route the signal must travel to reach each ear; interaural level differences (ILD) arise from the attenuation of the signal due to absorption by and reflection around the listener’s head, and interaural time differences (ITD) derive from the unequal distance the signal must travel to reach the near and far ears. For humans, the presence of such cues has been shown to improve the detection of speech in noise (Licklider 1948), an effect known as “binaural unmasking.” The phenomenon of binaural unmasking highlights the importance of spatial hearing in detecting speech in noise, an important function often impaired in a number of populations — including the elderly, hearing impaired, and cochlear implant users. It is therefore crucial to understand how binaural cues are processed, both at the level of the periphery and the CNS.

Unlike the coding of visual and somatosensory space, which are represented throughout the CNS by visio- and somatotopic neural maps inherited directly from topographical encoding of the incoming signal by the sensory receptors, auditory spatial processing must instead rely on active computational processing to extract information about sound source location. This is due to the fact that the cochlea codes sound frequency rather than sound source location in a topographically organized manner.

To date, the bulk of our knowledge about the computational processing of binaural cues involves mechanisms at the level of the superior olivary complex (SOC) in the midbrain, which is the first major site of interaction between the neural signals generated in each ear and is the locus of important fundamental processing of the binaural signal (reviewed in Schnupp *et al.* 2011). Relatively little is known, however, about how the more central nuclei comprising the ascending auditory system — the inferior colliculus (IC), the medial geniculate body of the thalamus (MGB), and the auditory cortex (AC) — contribute to further processing of auditory spatial cues, sound localization, and auditory stream segregation, or about the role that impaired processing in these higher-level auditory centers may play in diminished spatial listening abilities.

Additionally, a great majority of the physiological evidence related to CNS processing of auditory space has been collected in non-human animals,[1] and it has proven challenging to extrapolate these findings to humans. This is partly because the research tools employed differ greatly across species. Experimentally manipulated lesions, direct neurophysiological recordings, and the use of *in vivo* anatomical tracers are not ethically feasible in humans; investigations of auditory spatial processing in human CNS instead typically rely on observations of clinical lesion patients and data collected with neuroimaging tools or in postmortem anatomical studies. Moreover, the difficulty in extending binaural processing models based on animal data to humans may also derive from true non-equivalancies across species with respect to AC function and structure, presumably due in some part to the the influence that the

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[1] Although taxonomic classification of species would suggest that it is more precise to distinguish between non-human and human animals, the remainder of this document will for the sake of brevity simply use the terms "animals" (or "mammals" as all the animal studies reviewed herein are mammalian) and "humans."

neural processing demands dictated by such a rich and complex auditory behavior as human language likely exert on the function and structure of human AC.

Based on lesion and cortical cooling studies, it is evident that the AC participates in mammalian auditory spatial processing (Jenkins and Masterton 1982; Malhotra *et al.* 2004); however, the mechanisms of binaural processing in the AC are not well-specified, particularly in humans. Although neurophysiological data from animals demonstrate that there are AC neurons exhibiting binaural tuning — most broadly observed in the form of greater responsiveness to sound coming from contralateral than ipsilateral auditory hemispace ("contralateral bias") — the human neuroimaging evidence is mixed, for (Krumbholz *et al.* 2005a; von Kriegstein *et al.* 2008; Stecker and McLaughlin 2011) and against (Woldorff *et al.* 1999; Zimmer *et al.* 2006) such contralateral bias in the fMRI BOLD response to ITD and ILD cues. Additional hypotheses derived from neurophysiological and/or anatomical studies in animals regarding AC coding of binaural cues — including the influence of potential hemispheric processing asymmetries, the role of "opponent-channel" codes (McAlpine *et al.* 2001; Stecker *et al.* 2005b), the role of stimulus history (e.g., stimulus-specific adaptation) (Ulanovsky *et al.* 2004), the existence of separate or joint representations of ILD and ITD, and the presence of a posterior/anterior axis of areal specialization for spatial versus object coding (Rauschecker 1998) — are supported to varying degrees by human neuroimaging results. The data, however, are limited.

The goal of the present study was therefore to systematically characterize tuning to binaural cues in human AC. To this end, two different lines of investigation were carried out. In the first, we measured BOLD fMRI sensitivity to parametric modulation of ILD and to monaural level differences. The aim was to assess whether — according to the accepted metric of contralateral bias — the BOLD signal is tuned to ILD, and to determine how closely that tuning is related to monaural level sensitivity. In the second set of investigations, the BOLD response to parametrically-modulated ILD and ITD values was measured across stimulus history conditions to test for contralateral tuning to ILD and to ITD, and to explore whether binaural sensitivity differed according to cue type, hemisphere, cortical region, and/or stimulus history condition. The aim was to gather data to help resolve a number of questions surrounding human processing of auditory spatial cues: whether ILD and ITD are represented primarily in contralateral AC, whether there is specialization for binaural processing in particular AC regions or in one versus the other cerebral hemispheres, what types of coding strategies are used to represent auditory space in the AC, what role stimulus history plays in binaural processing, and whether ITD and ILD are represented jointly or separately in the AC. The remainder of this chapter will review some of the animal and human evidence germane to these questions, and briefly describe the rationale underlying the present investigation.

1.2 Evidence from lesion studies

Humans can reliably detect interaural level and time differences as small as 0.5 dB and $10\mu s$, based on disparity values computed in the brainstem and conveyed to the cortex via the ascending auditory system (reviewed in Stecker and Gallun 2012). The precise role of the AC in localizing sound remains unclear, but it is evident from lesion and neurophysiology studies that the AC is involved in binaural processing.

1.2.1 Lesion data: Non-human mammal

Early experimental lesion studies in animals showed that while sound localization and discrimination of left versus right hemifield sound sources are disrupted by ablation of the AC, performance often recovers to pre-morbid levels (reviewed in Jenkins & Masterton 1982). However, subsequent investigations of *within-hemifield* sound localization/discrimination performance revealed that unilateral AC lesions consistently result in lasting and relatively severe deficits for sound sources in the contralesional hemifield (Jenkins and Masterton 1982; Thompson and Cortez 1983; Kavanagh and Kelly 1987; Heffner 1997). More recent reversible cooling experiments (Malhotra *et al.*

2004; Lomber *et al.* 2007), which temporarily disable localized areas of cortex and allow for immediate behavioral testing before any long-term plastic reorganization of the auditory system can occur, have further confirmed that unilateral deactivation in core and posterior regions of cat AC (specifically posterior auditory field/PAF, dorsal zone/DZ, primary auditory cortex/A1, and anterior ectosylvian sulcus/AES) results in acute and profound deficits in sound localization in the contralateral hemifield.

A majority of the experimental lesion studies investigating auditory spatial performance employ sound stimuli presented in free-field conditions, carrying a combination of ITD, ILD, and monaural spatial cues.[2] A few studies, however, have explored the consequences of AC lesions on ILD and ITD processing separately (reviewed in Harrington 2001. Boester (1994) found that unilateral AC lesions in macaques result in elevated thresholds for discriminating sounds in the contralesional hemifield on the basis of ITD cues (with higher thresholds associated with left hemisphere/LH than with right hemisphere/RH lesions, though Harrington (2001) suggests this asymmetry may have been an artifact of stimulus presentation order), but observed no change in ILD discrimination thresholds. Alternatively, bilateral AC lesions result in impaired lateralization performance in response to both ITD and to ILD cues (Heffner and Masterton 1978).

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[2] A free-field is a space in which sound stimuli are presented to listeners as free as possible of interacting sources or reflections. Anechoic chambers are constructed to simulate free-field conditions. Sound location in the free-field is manipulated by physically placing sound sources at different positions relative to the listener's head, which naturally results in acoustic signals carrying a combination of ITD, ILD, and monaural spatial cues. Manipulation of ILD or ITD cues in isolation require the sound stimulus to be presented over headphones, and level or timing differences introduced in each ear between otherwise identical sound signals, resulting in a virtual, intracranial percept of auditory spatial location. Throughout this document, however, for the sake of simplicity, the percept of sound location generated by manipulating ILD and ITD over headphones will be referred to *as if* it exists in relation to sound sources physically located in external space.

1.2.2 Lesion data: Human

Clinical cortical lesions in human patients similarly confirm the involvement of human cortex (likely AC, but locations of clinical lesions are highly variable) in auditory spatial processing. Similar to Boester's (1994) data collected in non-human primates, Spierer *et al.* (2009) find that unilateral cortical lesions in humans result in more severe sound localization deficits in response to ITD than ILD cues. For left hemisphere damaged (LHD) patients, those localization deficits for ITD processing are restricted to the right contralesional hemifield, while for right hemisphere damaged (RHD) patients, deficits are seen for sound sources in both hemifields (though there is a greater deficit for sounds in the contralesional left hemifield)[3]. These results appear consistent with other lesion data in humans showing that while RH damage/disruption is associated with localization deficits for sound sources in both left and right hemispace, LH damage/disruption is associated with generally more mild localization deficits (Altman *et al.* 1979; Ruff *et al.* 1981; Bisiach *et al.* 1984; Zatorre and Penhune 2001), and/or with deficits restricted to contralesional right hemifield sounds (Clarke *et al.* 2000).

All of the above human lesion studies employ only ITD or freefield stimuli, except for Spierer et al. (2009) and Bisiach et al. (1984). Bisiach and colleagues did observe lateralization deficits in response to ILD stimuli, but *only* for RHD patients with comorbid visual field defects, not for RHD patients without visual field defects or for any LHD patients. Spierer et al. (2009) interpret this body of data to suggest that, for humans at least, RH is more strongly associated with coding binaural cues and generating the percept of sound location in both hemifields, while LH plays a role only in encoding sound location in contralateral space. The possibility exists that this hemispheric asymmetry is specifically related to post-morbid "reorganized" auditory spatial processing mechanisms; however, a similarly asymmetrical pattern

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[3] Note that in Boester's (1994) macaque lesion data, ITD discrimination thresholds were higher in macaques with LH lesions than those with RH lesions.

of localization deficits was observed by Altman et al. (1979) immediately following electroshock seizures induced in depressive patients with presumably intact auditory spatial processing systems, thereby eliminating the opportunity for any significant post-insult neural reorganization to occur.[4]

In summary, both the data derived from experimental lesions in animals and from clinical lesions in humans suggest that AC is involved in sound localization, with each hemisphere more strongly associated with auditory spatial behaviors related to sound sources in the contralateral hemifield — though potentially to differing degrees across hemispheres (LH possibly more contralaterally biased, at least for ITD processing, than RH), across binaural cue types (ITD possibly having a more contralateralized representation than ILD), and across AC regions (core and posterior areas more strongly linked to auditory spatial performance). A hemispheric asymmetry in degree of contralateral bias — such that RH is more strongly associated with sound location yet is less contralaterally biased than LH — is observed primarily in humans (due potentially to the fact that testing for hemispheric asymmetries has not been a focus of investigation in animal lesion studies). It is possible however that — should such a functional asymmetry exist — it may involve neural mechanisms outside of fundamental AC sound processing, given that nearly all of the patients in the above human lesion studies sustained damage extending to cortex and underlying white matter beyond canonical AC.

1.3 Neurophysiological and anatomical evidence: non-human mammal

1.3.1 Degree of contralateral bias: mammalian data

Consistent with the evidence from lesion studies suggesting the importance of the AC in sound localization, neurophysiological recordings in mammals confirm that

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[4] NB: the performance measure employed by Altman et al. required verbal report of sound location. This involvement of the spoken language system introduces a significant confound with respect to assessment of hemispheric involvement.

there are AC neurons sensitive to binaural cues, with approximately 67% of neurons recorded in non-human primate AC core regions tuned to auditory spatial cues generated by freefield stimuli (Werner-Reiss and Groh 2008). Phillips and Irvine (1981) report that 67% of neurons recorded in cat A1 are sensitive specifically to ILD cues, while Zhang *et al.* (2004) estimate the number to be more than 90%. There are far fewer neurophysiological studies investigating cortical response to ITD in isolation (low-frequency ITD-responsive neurons are more difficult to access in many mammals), but neurons tuned to ITD have been recorded in rabbit A1 (Fitzpatrick *et al.* 2000), cat A1(Reale and Brugge 1990), and core AC regions in the macaque (Brugge and Merzenich 1973).

A consistent finding across the above studies, in addition to numerous other neurophysiological recordings of AC sensitivity to sound source location, is that the majority of binaural neurons recorded respond maximally to sounds coming from locations in contralateral space, though tuning is typically quite broad, with neurons responding to sounds spanning up to 60-180° of the contralateral hemifield (Middlebrooks and Pettigrew 1981; Rajan *et al.* 1990; Brugge *et al.* 1996; Stecker and Middlebrooks 2003; Mickey and Middlebrooks 2003). Additionally, another smaller population of ipsilaterally-tuned neurons has been observed (reviewed in Stecker *et al.* 2005b). In non-human primates, however, the degree to which contralateral tuning predominates over ipsilateral has been shown to actually be quite modest, with only $\sim 8\%$ more neural activity, on average, in response to sound sources located in contralateral versus ipsilateral space (Werner-Reiss and Groh 2008).

In terms of whether there is any functional and/or spatial organization of neuronal preferences for different regions of auditory space ("preferred binaural configuration"), recordings in cat AC suggest that the proportion of contralateral-preferring neurons differs across AC regions (Stecker and Middlebrooks 2003), with some areas even showing a preference for midline as opposed to contralateral sound source locations sounds (Higgins *et al.* 2010; Lee and Middlebrooks 2013). Imig and Adrián

(1977), Middlebrooks and Pettigrew (1981) and Rajan *et al.* (1990) report fine-grained spatial organization in cat A1 in the distribution of contralaterally- and ipsilaterally-preferring neurons. Additionally, Zhang *et al.* (2004) find that the preferred binaural configuration evoking the greatest response in the majority of EO type neurons[5] is for sounds with contralateral ILDs, while the preferred binaural configurations of EE units are evenly distributed across sounds with contralateral and with ipsilateral ILDs. Similarly, Imig and Adrian (1977) report that the degree of monaural contralateral bias ("aural dominance") expressed by neurons is related to the binaural interaction patterns they show in response to sounds varying in ILD, with the majority of neurons that exhibit a "suppressive" binaural interaction pattern (response to sound in the dominant ear greater than the response to binaural sound at the same intensity) displaying a preference for sound in the contralateral ear, while those neurons that exhibit a "facilitory" binaural interaction pattern (response to binaural sound greater than response to sound at the same level in the dominant ear) vary in terms of aural dominance.

With respect to potential hemispheric asymmetries, such that there is more contralateral bias in one hemisphere versus the other, very little can be deduced from the animal neurophysiological evidence, as many studies historically either do not report the hemisphere from which data are collected or systematically choose a single hemisphere in all of their subjects from which to record. Moreover, methodological difficulties typically prevent recording from neurons in both hemispheres of a single subject, thereby precluding within subject inter-hemispheric comparisons. As such, hemispheric asymmetries have typically not been a focus in neurophysiological investigations of AC responses to binaural cues.

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[5] The binaural response pattern of a neuron is classified as EO if the neuron responds to monaural stimulation of the contralateral ear but is not affected by stimulation of the ipsilateral ear, and as EE if it responds to monaural stimulation of both ears.

1.3.2 Form of neural code: mammalian data

A long-held theory about neural coding of auditory space put forth by Jeffress (1948) posits that binaural cues corresponding to locations in space are represented in the brain by unique groups of topographically-organized neurons narrowly tuned to sound source locations distributed throughout the azimuth (termed a "place code"), resulting in neural "maps" of auditory space. However, decades of research have not yielded any evidence for such spatiotopic maps in the lemniscal auditory system of mammals.[6] An alternative hypothesis could be that binaural cues are represented in the AC by a distributed rate code in which sound location in a given hemifield is coded by patterns of activation across binaural neurons broadly tuned to contralateral azimuth. However, given this coding scheme, the robust observations described above of unequal distributions of binaural neurons — with a majority tuned broadly to sound sources deep within contralateral hemispace and a minority tuned to ipsilateral hemispace — appear inconsistent with equally robust psychophysical evidence showing behavioral acuity for sound localization to be quite sharp, with the sharpest tuning at midline locations (reviewed in Phillips 2008 and Stecker *et al.* 2005b).

One leading hypothesis which serves to resolve these apparently incongruent observations posits an "opponent-channel" process (McAlpine *et al.* 2001; Phillips and Hall 2005; Stecker *et al.* 2005b) in which sound location is encoded — possibly in each hemisphere — by the *relative difference* in activity between contralateral- and ipsilateral-preferring subpopulations, which is maximal for midline locations. If this comparison takes place between the contralaterally- and ipsilatarally-tuned neural populations in each hemisphere, however, a logical corollary is that even though there may be comparatively greater cortical response to contralateral as opposed to ipsilateral sound sources, information about sound location in *both* hemifields should be

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[6] Evidence for a place code has been observed in the mammalian superior colliculus, thought potentially to subserve the integration of auditory information and visiotopic maps (Palmer and King 1982).

available to auditory spatial processing mechanisms in each hemisphere. This is at odds with the experimental lesion data (see Sections 1.2.1 and 1.2.2) showing sound localization deficits in contralesional hemispace subsequent to unilateral AC lesions. To resolve this incongruity, Stecker *et al.* (2005b) speculate that while AC mechanisms in each hemisphere may indeed represent auditory space in both hemifields, the output of these processes in each hemisphere may project to higher level-areas that are associated with the perception only of contralateral auditory space, thereby accounting for the lesion results.

In addition to the rate-dependent opponent-channel code described above, evidence suggests that temporal features of the neuronal response are also sensitive to sound-source location and in some AC regions carry as much or more spatial information than firing rate (Furukawa and Middlebrooks 2002; Stecker *et al.* 2003; Stecker and Middlebrooks 2003; Werner-Reiss and Groh 2008; Chadderton *et al.* 2009). Pattern-recognition analyses of neural responses to sound varying according to free-field location indicate that, despite being broadly tuned to auditory space, neurons in areas A1, A2, DZ, and PAF of cat AC can accurately code spatial location based on spike timing patterns, and further that the timing of the first post-stimulus spike carries the majority of the spatial information present in these patterns (Furukawa and Middlebrooks 2002; Stecker *et al.* 2003; Stecker and Middlebrooks 2003; Stecker *et al.* 2005a). PAF latencies in particular — despite being longer than in other areas — are most highly modulated by and transmit the greatest degree of information about auditory space (Stecker *et al.* 2003). Werner-Reiss and Groh (2008) confirm the likelihood that spike timing also plays a role in primate AC spatial coding strategies, observing that average first spike latencies of neurons in core areas of macaque AC are shorter in response to contralateral than to ipislateral sound sources. Chadderton *et al.* (2009) find similar results in rat A1, and further observe that EPSPs are also earlier for contralateral sounds, indicating that synaptic influences likely play a role in temporally-based spatial coding strategies.

1.3.3 Role of stimulus history: mammalian data

Another factor related to auditory spatial processing in the AC is the role that stimulus history likely plays in shaping binaural tuning. Stimulus-specific neural adaptation (SSA) — i.e., the attenuation of the response of neurons tuned to a particular stimulus dimension when sounds closely matched along that dimension are presented repeatedly, followed by response recovery when a deviant stimulus is presented — has been observed in mammalian core AC areas. Data suggest that SSA in the AC occurs simultaneously on multiple time scales, from milliseconds to tens of seconds, in association with a variety of stimulus dimensions, including interaural phase disparity (Malone *et al.* 2002), frequency, and amplitude (Ulanovsky *et al.* 2003; 2004). The effects of SSA appear potentially to include both reduced responsiveness to stimuli with parameter values at the same level as the repeating stimulus *and* enhanced responsiveness to sounds with parameter values outside of the repeating stimulus (particularly during the sustained portion of the neural timecourse) (Ulanovsky *et al.* 2003; 2004; Pienkowski and Eggermont 2009), serving in effect to sharpen tuning and enhance stimulus discriminability. Middlebrooks *et al.* (2009), for instance, observed that the tuning of discrete populations of neurons in cat AC responding separately to stimuli with varying sound sources locations interleaved in sequences — in configurations that would presumably be segregated perceptually ("stream segregation") — is substantially sharper in each population than had previously been observed in response to the same stimuli presented singly, presumably due to SSA-based mechanisms.

1.3.4 Joint or separate representation of ITD & ILD: mammalian data

At present, it is not clear whether ILD and ITD cues are represented separately in the cortex or whether they may be integrated (and if so, at what processing level) to create some overall percept of sound source location (reviewed in Johnson and Hautus 2010). At the level of the auditory brainstem, it is generally thought that the two cues are processed to a large extent in a segregated fashion, based on the anatomical characteristics and physiology of the lateral and medial nuclei of the superior olivary complex (LSO and MSO, respectively). The LSO on each side of the brain receives excitatory inputs from the ipsilateral ear and inhibitory inputs from the contralateral ear (via the medial nucleus of the trapezoid body, MNTB), and is populated predominantly by neurons tuned to high frequencies. Both of these characteristics provide a substrate well suited for but not necessarily exclusive to ILD tuning.[7] These anatomical observations are confirmed by neurophysiological recordings in LSO showing maximal sensitivity to ILD cues, though modest sensitivity to ITD and envelope ITD is also observed (reviewed in Stecker and Gallun 2012). In contrast, the MSO receives excitatory inputs from both ears and comprises primarily low-frequency neurons, creating an anatomically separate channel for ITD processing (Stecker and Gallun 2012). Evidence regarding whether or not ILD- and ITD-dominated processing streams remain separate at the level of the cortex is limited, and is primarily restricted to human EEG/MEG studies (Schröger 1996; Ungan *et al.* 2001; Johnson and Hautus 2010) (see Section 1.4.4 below).

1.3.5 Areal specialization for auditory spatial tuning: mammalian data

Motivated by a well-established hypothesis in the visual domain positing the existence in visual cortex of two anatomically and functionally distinct processing streams — one associated with visual pattern ("what") processing and the other with spatial ("where") processing — Rauschecker (1998) proposed a similar "dual-stream" hypothesis for auditory processing in the cortex in which there is a distinct rostral/anterior pathway sensitive to auditory patterns and a caudal/posterior stream sensitive to auditory spatial cues. The preliminary evidence for this hypothesis included lesion and

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[7] Physical ILDs between a listener's ears depends on the relationship between head size and sound wavelength; as a result, real-world ILD cues effectively only exist for higher frequency sounds with longer wavelenths.

anatomical tracer data suggesting the presence of distinct AC pathways as extensions of separate but parallel thalamocortical projection streams (Rauschecker *et al.* 1995), in addition to neurophysiological recordings showing enhanced sensitivity for conspecific calls in rostrolateral belt neurons (Rauschecker 1998). Subsequent investigations confirmed that neurons in macaque anterolateral areas selectively process conspecific calls, while those in caudolateral areas show greater spatial sensitivity (Rauschecker and Tian 2000). The presence of anatomically distinct processing streams received further support from Romanski *et al.* (1999) who demonstrated that rostral and caudal AC areas in non-human primates have distinct and highly specific projections to frontotemporal areas such that caudal areas project to spatially-related dorsolateral prefrontal cortex, and rostral AC areas to rostral and ventral prefrontal areas thought to subserve non-spatial functions (reviewed in Romanski et al. 1999).

However, Stecker and Gallun (2012) caution that observations regarding specialized processing domains in caudal relative to rostral AC may reflect quantitative rather than qualitative areal differences, as evidenced by a series of studies in cat AC demonstrating that neurons in *all* areas investigated (including A1, A2, AAF, DZ, and PAF) display some sensitivity to sound-souce location, though response characteristics in more caudal and dorsal regions (PAF and DZ) render them uniquely suited for processing sound location (Furukawa and Middlebrooks 2002; Stecker *et al.* 2003; 2005a; Harrington *et al.* 2008). In PAF (and to some extent DZ), spatial tuning — though still broad — is sharper than in A1 and other areas. Additionally, artificial neural network analyses suggest that at a population level PAF neurons carry more spatial information than other areas, due primarily to stronger spatial modulation of response latencies (see Section 1.3.2), along with the capacity of PAF neurons to maintain spatial tuning at high stimulus intensity levels, and the presence of a more balanced representation of space across PAF (with a greater proportion of neurons favoring ipsilateral space than in other areas) (Stecker *et al.* 2003; Stecker and Middlebrooks 2003). Neurons in DZ appear to favor sounds with midline locations (Lee and Middlebrooks 2013), mirroring findings in rat AC indicating particular regions with a preference for sounds with midline ILD cues (Higgins *et al.* 2010).

In further support of the dual-stream hypothesis, cortical cooling studies by Lomber and Malhotra (2008) (see Section 1.2.1) show a double dissociation in which temporary unilateral deactivation in posterior area PAF in cat AC induces acute and profound sound localization deficits in the contralateral hemifield, while deactivation of anterior area AAF instead results in auditory pattern discrimination deficits. Notably, however, Harrington (2002) found that surgical AC lesions in monkeys cause significant sound localization deficits only when encompassing the *entire* AC, not when restricted to either rostral or caudal fields. Harrington's data were collected from animals that had gone a significant period of post-lesion recovery, allowing for potential neural reorganization. The inconsistencies between his results and those of the Lomber group's may therefore reflect the quantitative rather than qualitative areal differences in auditory spatial coding across AC neurons, and illuminate the dynamic and plastic nature of processing of auditory space in the AC.

1.4 Neuroimaging and psychophysical evidence: human

1.4.1 Degree of contralateral bias & potential hemispheric asymmetries: human data

Partly because traditional fMRI designs and analyses do not provide detailed information about the fine-grained spatial resolution or time course of the response, many neuroimaging[8] investigations of binaural processing — in contrast to neurophysiological studies — focus instead on the degree of contralateral bias and potential differences across the hemispheres in response to auditory spatial cues. Based on the contralateral dominance routinely observed in animal neurophysiological and lesion data, the predominantly contralateralized anatomical pathways of the ascending auditory system, and the well-established contralateral cortical organization of visual and

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[8] In this document, the term "neuroimaging" will be used primarily to refer to fMRI studies, although data from research using EEG and MEG will also be discussed.

somatosensory spatial processing, it has long been presumed that cortical auditory spatial processing in humans is also contralaterally biased. Many of the early neuroimaging studies exploring this hypothesis used monaurally-presented sound stimuli, which consistently elicits a greater BOLD response in the hemisphere contralateral to ear of presentation, a result that has been replicated across a variety of stimuli, including syllables (Jäncke *et al.* 2002; Stefanatos *et al.* 2008), tone bursts (Woldorff *et al.* 1999), and amplitude-modulated tones (Scheffler *et al.* 1998). However, the validity of extrapolating results derived from monaural stimuli to binaural cue processing relies on the premise that binaural and monaural processing are highly related. Indeed, there is a clear relationship between binaural ILD and monaural sound in that modulating ILD values can be seen as equivalent to simply changing monaural level in each ear; extremely large ILD values, for instance, create a percept very similar to that elicited by monaural sound. There is some evidence in the animal neurophysiological literature to support a strong relationship between ILD and monaural sound; Harrington *et al.* (2008) found that the contralateral locations favored by binaural responses of cat AC neurons coincide with acoustic axis of cat pinnae, suggesting monaural effects. However, anatomical evidence indicates that mammalian subcortical (Pickles 2008) and perhaps cortical pathways for the processing of monaural sounds are separate from those for binaural signals (Imig and Adrián 1977), such that the contralateral response bias to monaural stimulation may simply reflect the contralateralized anatomical organization of the ascending auditory pathway, rather than any active processing mechanisms.

In contrast to the monaural stimulation data, the results derived from neuroimaging investigations of sensitivity to binaural spatial stimuli are surprisingly equivocal with respect to contralateral bias. Some studies do not find evidence of contralateral dominance, reporting that stimuli bearing ILD or ITD cues elicit roughly bilateral neural responses regardless of cue location (ILD: Zimmer *et al.* 2006, ITD: Woldorff *et al.* 1999; Ungan *et al.* 2001). However, it is possible that the ILD values used by

Zimmer et al. (±3.5 dB) were simply too small to drive a detectable contralateralized response, and the ITD values used by the Woldorff et al. and Ungan et al. (±2000 and ±1000μs, respectively) too far outside the physiologically-relevant range for humans.[9] Indeed, Ungan et al. (2001) did observe contralateral bias in the response to larger ILDs of ±20 dB, as did other studies in response to stationary ITDs smaller than ±700μs (Krumbholz *et al.* 2005a; Palomäki *et al.* 2005; Tiitinen *et al.* 2006; Krumbholz *et al.* 2007; Johnson and Hautus 2010) and "moving" (i.e., continuously varying) ITDs smaller than ±1000μs (Krumbholz et al. 2005b, 2007). In support of the speculation that there may be contralateral bias only for particular ranges of interaural values, von Kriegstein *et al.* (2008) observed contralateral dominance in the planum temporale for ITDs of ±500μs, but not for ±1500μs. von Kriegstein and colleagues speculate that – even though they evoke a lateralized acoustic percept — the representation of implausibly long ITDs of ±1500μs may be coded in some other more subtle way than the predominance of activity on one side of the brain.

Consistent with the human lesion data (see Section 1.2.2), a number of human neuroimaging studies have observed differences between hemispheres in degree of contralateral bias such that sound sources in left hemifield ("leftward" sound) activate RH more than LH, while "rightward" sounds elicit roughly bilateral responses. Correspondingly, LH is more sensitive to rightward sound, while RH demonstrates sensitivity to sound sources in both left and right hemifields. This general pattern has been seen in response to both stationary (Johnson and Hautus 2010) and moving (Krumbholz *et al.* 2005a; 2007) ITD stimuli, and to sound movement evoked using head-related transfer functions (HRTFs[10]) (Getzmann 2009). Similarly, Magezi and

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[9] Given the size of the human head, ecologically valid ITD levels extend to ∼ ±600 to ±800μs for humans, and ILD levels to ∼ ±20 to ±30 dB [Blauert 1983; von Kriegstein *et al.* 2008; Salminen *et al.* 2010b; Stecker and Gallun 2012].

[10] In contrast to manipulating ITD or ILD cues in isolation, which creates an intracranial percept of sound coming from locations inside the head, binaural HRTFs are filters simulating the full complement of acoustic spatial cues (ITD, ILD, and monaural cues), yielding a more realistic percept of auditory space outside the head.

Krumbholz (2010) — using EEG to measure responses to probe ITD stimuli after exposure to an adaptor ITD sound — found that the response was lateralized toward RH for stimuli presumably activating neurons tuned to leftward ITDs and was more bilateral for stimuli thought to drive neurons tuned to rightward ITDs (see Section 1.4.2). Notably, to the best of our knowledge, there have been to date no reports of a similarly robust pattern of response asymmetries for stimuli with ILD cues alone.

As noted, these neuroimaging results appear consistent with the clinical human lesion data, in which damage to the RH is associated with relatively severe localization deficits for ITD stimuli in both hemifields, while damage to the LH results either in deficits confined to the contralesional right hemifield (Clarke et al. 2000; Spierer et al. 2009) and/or in generally more mild deficits (Altman et al. 1979; Bisiach et al. 1984; Ruff et al. 1981; Zatorre & Penhune 2001) (see Section 1.2.2). Together, the neuroimaging and lesion data have been generally interpreted as an RH processing dominance for auditory space. Magezi and Krumbholz more specifically, however, speculate that the data — in the context of the opponent channel model in which auditory space is encoded by the balance of activation across two populations of neurons broadly tuned to contralateral and ipsilateral space — suggest rather that the two populations may differ across the hemispheres such that RH contains both a contralateral and an ipsilateral channel, and LH only a contralateral channel. Moreover, exploring possible hemispheric asymmetries in the response time course, Krumbholz *et al.* (2007) collected EEG data showing that the difference in latency between LH and RH responses was significantly greater for leftward as opposed to rightward ITD stimuli. Krumbholz and colleagues hypothesize that the LH ipsilateral response to leftward motion is comparatively slow because it relies on projections from the contralateral hemisphere via the corpus callosum, whereas a faster RH ipsilateral response to rightward motion may derive from direct intra-hemispheric ascending projections from subcortical structures.

The conclusion that RH is dominant for processing auditory space was also was the interpretation derived from a somewhat contradictory set of results generated by Palomäki *et al.* (2002; 2005), Salminen *et al.* (2010a), and Tiitinen *et al.* (2006) in a series of MEG studies. Measuring responses primarily to subject-specific HRTFs, the MEG results consistently show that while there is contralateral response bias to auditory space in both hemispheres, the dynamic range between responses to contralateral versus ipsilateral stimuli is wider in RH than LH, and widest for stimuli containing the full complement of spatial cues (ITD, ILD, and monaural) as opposed to ITD or ILD in isolation (although ITD responses exhibited a wider dynamic range than did ILD). Though less contralateral bias is seen in LH (Palomaki et al. 2005), response amplitudes are larger in RH than LH for both rightward and leftward sounds. Using an adaptation paradigm, Salminen et al. (2010) also demonstrated that the RH response to acoustic stimuli is attenuated more by a 3-D auditory adaptor stimulus located in contralateral left as compared to ipsilateral right hemispace, whereas the LH response is attenuated equally by both rightward and leftward adaptors. Salminen and colleagues interpret these results and the above MEG findings to suggest that the RH (presumably AC) is more highly tuned than is the LH to auditory space, hypothesizing — in direct contrast to Magezi and Krumbholz (2010) — that the LH may either contain two near-equal populations of contralaterally- and ipsilaterally-tuned neurons, or a very limited number of binaural neurons.

1.4.2 Form of neural code: human data

Recently, human neuroimaging studies investigating cortical processing of binaural cues have begun to address questions related to the form of the neural response to auditory space. Because neuroimaging methods yield neither direct nor fine-grained recordings of neuronal firing but instead measure signals indirectly reflecting the activity of large aggregations of neurons,[11] extracting data that illuminate

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[11] Relative to the experimental manipulation, fMRI measures local changes in blood flow within the brain associated with neural activity, and MEG/EEG measure the magnetic/electrical signal

neural coding strategies requires targeted design and analysis techniques. Using EEG and MEG, Magezi and Krumbholz (2010), Salminen *et al.* (2009) and Salminen *et al.* (2010b) employed an adaptation paradigm in which response to left-lateralized "probe" sounds was collected after exposure to a differently-located "adaptor" stimulus to test whether the response to location change better fits response models predicted by Jeffress' (1948) place code or is instead more consistent with an opponent-channel hypothesis. Magezi et al. and Salminen et al. reason that because the place code hypothesis posits an essentially uniform density of neurons narrowly tuned to locations throughout azimuthal space, it would predict that the degree of attenuation in the response to the probe should solely reflect the difference in location between adaptor and probe sounds (the closer together they are, the more response adaptation and the more attenuated the signal), regardless of the absolute location of the two sounds sources. Alternatively, the opponent-channel hypothesis — in which auditory space is encoded by the balance of activation between a larger group of neurons broadly tuned to contralateral sounds (with peaks deep inside contralateral space) and a smaller group broadly tuned to ipsilateral space — would predict that the response should be greatest/least adapted the more lateralized the probe is and/or the more centered the adaptor is (i.e., "outward" sound), and smallest/most adapted for location change toward midline (i.e., "inward" sound).

In the above "location change" studies, all probe sounds presented were lateralized in the left hemifield, on the basis of either HRTF (Salminen *et al.* 2009) or ITD (Magezi et al. 2010; Salminen et al. 2010) manipulations. The results from all three studies indicate that the response to change in sound location was the greatest for outward sound, consistent with the opponent-channel hypothesis. The research groups conclude that ITD is represented in human cortex by an opponent-channel code potentially inherited from subcortical processing centers, and that it is likely —

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outside the scalp generated by neural activity.

based on the HRTF results — that ILD is also represented in the same manner.

Salminen and colleagues report observing similar results in both RH and LH (although as expected — because probe sounds were only in the left hemifield — RH responses are significantly greater in magnitude than LH), offering support for the speculation by Stecker *et al.* (2005b) that there are majority contralaterally- and minority ipsilaterally-tuned populations in each hemisphere, given that the RH change responses to leftward sound likely reflect the activation of the majority population of contralaterally-tuned neurons, while the LH response depends on activation of the minority ipsilaterally-tuned units. In a slightly different interpretation, Magezi and colleagues report that the change response (N1) was lateralized toward the RH for outward stimuli, presumably activating neurons tuned to the leftward sound, but was bilateral for inward conditions, which were assumed to activate neurons tuned to rightward sound. The authors speculate that this result may be consistent with a hemispheric asymmetry in the balance of contralateral and ipsilateral channels, in which RH contains both channels but LH only a contralateral channel (see Section 1.4.1).

1.4.3 Role of stimulus history: human data

The neural effects of stimulus history — how the brain processes a probe stimulus as a function of previous adaptor sounds presented — are often collectively termed stimulus-specific adaptation (“SSA”), which specifically refers to the response attenuation observed to occur on multiple time scales as a consequence of stimulus repetition[12] (see Section 1.3.3). Adaptation paradigms (“fMRI$_a$”) have been employed in MR research as a methodological device to illuminate effects of experimental manipulations too subtle to capture using traditional paradigms, especially those that drive

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[12] It is worthwhile noting, however, that adaptation or attenuation of the neural response is not necessarily the only consequence of prolonged exposure to a stimulus. Neuronal facilitation/enhancement or other changes in the response pattern are also possible; however, adaptation has been the most commonly observed effect in neurophysiological recording studies.

changes in the BOLD response occurring at a sub-voxel resolution which may be averaged out at the sampling resolution typical of most fMRI studies (Grill-Spector and Malach 2001; Krekelberg *et al.* 2006). As described in Section 1.4.2 above, data from fMRI$_a$ experiments can also be employed to uncover relationships between sequential stimuli that reveal neural coding strategies. But importantly, variation in the neural response to a stimulus according to characteristics of the previous sound(s) is more than simply a methodological tool; it is itself likely a key mechanism in shaping the neural response to and indeed perception of a stimulus — highlighting the potential importance in real-world behaviors of change detection over coding of absolute stimulus values (Dahmen *et al.* 2010).

It is important therefore to characterize the effects of stimulus history on the cortical response to binaural cues. Neurophysiological recordings indicate the presence of SSA in mammalian AC in association with binaural processing (see Section 1.3.3). As to whether humans also exhibit sound location-dependent SSA, a number of neuroimaging studies report attenuation of the response in association with same-same (SS) as compared to same-different (SD) pairings of stimuli modulated according to sound-source location, using HRTF (Ahveninen *et al.* 2006; Deouell *et al.* 2007; Altmann *et al.* 2008) and ITD (Schadwinkel and Gutschalk 2010) stimuli. Notably, the common locus of the increased response for SD over SS stimuli seen in these studies is reported in the planum temporale, bilaterally. Based on the contralateral bias that appears to characterize cortical response to sound-source location (see Section 1.4.1), it is quite surprising that the change response is not also contralaterally biased. This may be explained in the Altmann *et al.* (2008) and Schadwinkel and Gutschalk (2010) studies by the fact that the change response results were for data collapsed across probe and adaptor pairs presented in *both* right and left hemispace which would be expected to show a bilateral response. Deouell *et al.* (2007), however, presented adaptor and probe stimuli that are both lateralized to the right hemifield (15° and 60° right of midline), and Ahveninen *et al.* (2006) used stimuli that were either centered or 45° rightward, both of which — based on previous evidence of contralateral bias — would be expected to yield response foci primarily in LH.

Schadwinkel and Gutschalk (2010) measured both the magnitude and the time course of the change response to harmonic tone complexes with interleaved sequences of leftward ($-687.5\mu s$) and rightward ($62.5\mu s$ – $687.5\mu s$) ITDs. The results indicate that for sequences in which the rightward ITD $>125\mu s$, there was a greater response (presumably due to diminished adaptation as the separation between the two sounds increased), specifically in the sustained component of the BOLD timecourse. Further, this was paralleled by an increased probability of the subjects perceiving the sequence as two segregated sound streams. This is similar to neurophysiological data recorded in cat AC (Middlebrooks *et al.* 2009) in which sharper tuning was observed in discrete populations of neurons responding separately to stimuli varying by sound-source location that were interleaved (in configurations presumably generating a percept of segregated streams) than had been previously seen in response to the same sounds presented singly (see Section 1.3.3). This would suggest that the neuroimaging results above reflect some mechanism involving stimulus history effects that sharpen tuning, and that this effect can be seen in the sustained component of the BOLD time course.

In a related study, Getzmann (2009) measured EEG responses to three different rates of auditory motion simulated by continuously varying binaural HRTFs. Based on the premise that auditory motion is computed from repeated discrete changes in sound source location (Smith *et al.* 2004), differential response patterns can be seen as reflecting varying amounts of release from adaptation of location-tuned neurons. At slower auditory motion velocities, potentially resulting in a relatively high degree of adaptation, Getzmann reported that the response was greatly reduced and RH activation predominated in response to auditory motion in both directions. At medium velocities, LH responded to rightward motion, while RH responded to both leftward and rightward motion (an asymmetric hemispheric activation pattern that has been previously observed, as reviewed in Section 1.4.1). At faster velocities eliciting the least adaptation, there was increased activation overall and roughly symmetrical contralateral response bias in each hemisphere. If the Getzmann data indeed reflect the involvement of adaptive mechanisms, they would appear to suggest that stimulus history effects related to sound source location differentially involve the LH, with release from adaptation at medium and fast rates of change sharpening sound source location tuning in LH.

Although, to the best of our knowledge, there are no neuroimaging studies examining the effects of adaptation to ILD-only cues on cortical sensitivity to sound location, a number of human psychophysics studies confirm that the presentation of ITD and ILD adaptor stimuli have similar effects on the perception of auditory space (Phillips and Hall 2005; Phillips *et al.* 2006; Vigneault-MacLean *et al.* 2007; Dahmen *et al.* 2010). A consistent result observed in these studies is that — in the presence of adapting binaural stimuli — the perceived midline is shifted toward the hemifield of the adaptor; correspondingly, the perceived laterality of probe sounds is shifted away from the adaptor. Phillips and Hall (2005) interpret this data as evidence for the opponent-channel model, which would predict that adapting either the contralaterally- and ipsilaterally-tuned neural populations will effectively enhance the contribution of the other, thereby shifting the point of perceived centrality. The results found by Phillips and Hall (2005) and Phillips *et al.* (2006) suggest that the contributions of ITD and ILD adaptation to perception of sound source location do not differ greatly in shape, magnitude or direction of effect. However, the data do suggest there may be a slight hemifield asymmetry for (high-frequency) ILD stimuli only, with the observed adaptation effect larger for stimuli in the left than the right hemifield, potentially consistent with Getzmann's (2009) HRTF-based auditory motion observations.

1.4.4 Joint or separate representation of ITD & ILD: human data

Although structural and neurophysiological evidence from mammals suggests that ILD and ITD cues are processed in essentially segregated paths at the level of the midbrain (see Section 1.3.4), there is less evidence about whether their processing is separated or integrated in the AC. In the few lesion studies that systematically explore the separate effects of unilateral lesions on the localization of sounds with ITD and of ILD cues, unique patterns of deficits for the two cues are observed. Spierer *et al.* (2009) report that — for sounds lateralized according to ITD — RH damage in humans is associated with localization deficits in both hemifields, and LH damage either with mild damage or damage confined to the right hemifield. For sounds lateralized according to ILD, both RH-and LH-damaged patients show mild localization deficits. Boester's (1994) results derived from experimental lesions in macaques appear to corroborate Spierer et al.'s findings (see Sections 1.2.1 and 1.2.2).

Another line of evidence from human psychophysical studies seems at first glance to suggest that information about ITD and ILD is integrated, showing that humans can counterbalance a lateralized percept of sound location based on one of the cues by lateralizing the other cue in the opposite direction, implying a "trading ratio" by which one cue can offset the other (Harris 1960; Hafter and Jeffress 1968). However, Hafter and Jeffress note that some of their subjects report perceiving separate "time images" and "spatial images," each with different trading ratios. Further, Hafter and Carrier (1972) report that for some subjects the percept created by the dichotic sound effectively "centered" by the above "trading" process still remains discriminable from that created by a true diotic sound, suggesting that ILD and ITD are processed separately at least in centers mediating conscious perception.

The neuroimaging evidence regarding whether or not ILD- and ITD-dominated processing streams remain distinct in human AC is restricted to a limited number of EEG/MEG studies, all of which suggest — on the basis of differing field topographies and/or interhemispheric dominance patterns associated with the responses to ILD and ITD — that the two cues are processed separately, at least at the level of the cortical response components measured (Schröger 1996 [MMN], Ungan *et al.* 2001 [N1], [M100], Tardif *et al.* 2006 [> 75 ms post-stimulus onset],Johnson and Hautus 2010). Interestingly, however, Johnson and Hautus (2010) also report — in contrast to the M100 results — that the object-related negativity (ORN) component (which has been identified as a physiological index of pre-attentive auditory scene segregation [reviewed in Johnson and Hautus 2010]) appears similar across dichotic pitch stimuli created using both ITD and ILD.[13] This would suggest that information common to the two cues may be combined at the level of auditory scene analysis.

1.4.5 Areal specialization for auditory spatial processing: human data

The dual-stream hypothesis positing an anterior AC specialization for auditory pattern processing and a posterior specialization for auditory spatial processing was originally proposed on the basis of anatomical and neurophysiological evidence in non-human mammals, and has subsequently received strong support from lesion/cortical cooling studies (see Section 1.3.5). Extending this model to humans, however, has not been without controversy. Belin and Zatorre (2000) alternatively suggest that the posterior pathway is associated with processing spectral motion rather than auditory space, and Zatorre *et al.* (2002) find posterior AC activation only in response to very specific configurations of auditory spatial stimuli. Moreover, the specific loci of the putative spatial processing pathway has been somewhat vague, and in both clinical lesion studies (reviewed in Clarke *et al.* 2005) and in a large meta-analysis of fMRI and PET studies (Arnott *et al.* 2004), the cortical region most strongly associated with auditory spatial processing was inferior parietal cortex, not posterior AC. A consistent factor in these studies and others that implicate inferior parietal

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[13] Dichotic pitch stimuli are broadband sounds containing an ITD or ILD restricted to a narrow band of frequencies such that the listener hears two concurrent spatially separated pitch percepts.

cortex in binaural processing appears to be the involvement of an auditory spatial task (Zatorre *et al.* 2002; Hart *et al.* 2004), suggesting that conscious perception of auditory space and/or spatio-motor integration may recruit inferior parietal areas. In their meta-analysis, Arnott *et al.* (2004) note that no activation is seen in posterior temporal areas for some studies measuring the response to auditory spatial cues.

However, more recent neuroimaging data, including the adaptation studies discussed in Section 1.4.3 (Ahveninen *et al.* 2006; Deouell *et al.* 2007; Altmann *et al.* 2008), do implicate planum temporale (PT) in auditory spatial processing (Warren and Griffiths 2003; Krumbholz *et al.* 2005a; von Kriegstein *et al.* 2008). Ahveninen *et al.* (2006) and Warren and Griffiths (2003) in particular, show compelling double dissociations in which PT but not anterior temporal areas respond/show response adaptation to sound location, while anterior temporal areas but not PT respond/show adaptation to pitch and phonetic sounds. The majority of the studies exploring cortical areal specialization for auditory spatial processing vary sound source location using HRTFs; there is far less evidence about regional specialization for ITD or ILD processing. Krumbholz *et al.* (2005a) implicate PT for ITD processing; less is known about ILD.

1.5 Purpose of the present study

In order to characterize the cortical representation of binaural sound in humans, the present set of experiments systematically measured the BOLD response to parametric modulation of ILD and ITD values. Previous studies using fMRI to investigate the processing of binaural sound in human AC have typically collected responses to only a few cue levels, therefore data establishing comprehensive binaural tuning curves are lacking. Given the evidence reviewed above suggesting that neural sensitivity to binaural cues varies significantly across cue types and cue values (see Sections 1.2.2, 1.3.3, 1.3.4, 1.4.1, 1.4.4), the measurement of separate parametric tuning curves for ILD and ITD may help mediate some of the inconsistencies in the literature regarding contralateral bias and possible hemispheric asymmetries. AC sensitivity to ILD and ITD is rarely examined in the same study, with the same experimental paradigm, equipment, and analysis techniques. Measuring tuning to both cues in virtually identical experiments allows for direct comparison of results across cues to identify processing similarities and differences that will help establish whether ILD and ITD are represented jointly or separately at the level of the AC.

Because the data further suggest that binaural tuning varies across AC regions (Sections 1.3.2, 1.3.5, 1.4.5) and that the degree of contralateral tuning may be quite modest (Section 1.3.1), the present study employs high-resolution surface-mapping of activation in regions of interest defined individually in each subject to better reveal both functional and areal processing patterns. The use of a “continuous-carryover” (Aguirre 2007) event-related fMRI$_a$ paradigm, in which every stimulus is presented briefly before and after every other stimulus, serves to further expose potentially modest effects by capturing non-adapted change responses that are presumably more robust than the adapted signal typically collected in traditional block presentation paradigms. Additionally, given the reports from some neurophysiological studies that there is spatial organization of binaural processing on a relatively fine-grained level (see Section 1.3.1), the use of fMRI$_a$ allows for the investigation of potential binaural tuning at a sub-voxel level that is unavailable using traditional fMRI paradigms.

Moreover, data collected in an fMRI$_a$ paradigm can provide systematic evidence characterizing the specific effects of stimulus history on binaural tuning. Although previous neuroimaging studies have explored the effects of stimulus history (Section 1.4.3), they all collected responses to modulation in sound-source location simulated by manipulating ITD or HRTF values, only for left hemifield sounds. In contrast, data collected in the present study allow for the systematic characterization of the effect of stimulus history on responses to ITD and to ILD over a parametrically-varied range of cue values simulating sound source locations in both hemifields. And finally, the use of fMRI$_a$ allows — in the manner of Magezi and Krumbholz (2010), Salminen *et al.* (2009), and Salminen *et al.* (2010b) (again using either ITD and HRTF stimuli) — for the testing of predictions about response to location change based on place code and opponent-channel models to help establish which form of coding best describes the representation of auditory space in human AC. To our knowledge, the present study would be the first to attempt to replicate the results of Magezi et al. and Salminen et al. using fMRI, and experimentally manipulating ILD independently of ITD.

The remainder of this document describes the experiments and results found in our investigation of human AC processing of ILD and ITD. Chapter 2 (Experiment 1) explores the functional equivalence of binaural ILD and monaural processing in human AC. Chapter 3 (Experiments 2 – 5) investigates the effects of parametric modulation of ILD and ITD values on the AC BOLD response, measuring tuning functions in pre-defined regions of interest, in each hemisphere, for each cue. Chapter 4 addresses the effects of stimulus history on tuning for the data collected in Experiments 2 and 4, and further examines whether the evidence supports or refutes the opponent-channel hypothesis. Chapter 5 briefly summarizes the findings across all the experiments and discusses future directions.

Chapter 2

EXPERIMENT 1: MONAURAL AND BINAURAL CONTRIBUTIONS TO ILD TUNING IN HUMAN AUDITORY CORTEX

2.1 Background

As reviewed in Chapter 1, the neuroimaging record to date does not consistently show the human cortical BOLD response to binaural stimulation to exhibit contralateral bias (i.e. greater response in the hemisphere contralateral to the location of the sound source), as would be predicted on the basis of mammalian lesion and neurophysiology results. Although fMRI studies measuring sensitivity to monaural sound consistently find a greater AC response contralateral to the side of stimulation (Scheffler *et al.* 1998; Woldorff *et al.* 1999; Jäncke *et al.* 2002; Suzuki *et al.* 2002; Stefanatos *et al.* 2008), similar patterns of contralateral bias in response to binaural cues are reported by some research groups (Krumbholz *et al.* 2005a; von Kriegstein *et al.* 2008), while others instead observe bilateral response patterns (Woldorff *et al.* 1999; Zimmer *et al.* 2006). These divergent neuroimaging results may be partly due to variation in cue values presented (von Kriegstein *et al.* 2008), or to the potentially modest level of contralateral bias present at the neural response level (Werner-Reiss and Groh 2008). Additionally, ambiguity regarding the degree to which tuning to auditory space is contralaterally biased in population-level measures such as fMRI may also result from the possible mix of excitation and inhibition contributed by multiple co-mingled neural populations with opposing tuning (i.e., contralateral- and ipsilateral-prefering, as observed by Stecker *et al.* 2005b; Werner-Reiss and Groh 2008).

The fundamental complexities of auditory spatial processing and the ascending auditory system likely guarantee complexity in the representation of binaural cues at the level of the cortex. The organization of the cochlea dictates that sound source location is not coded topographically according to place of stimulation on the basilar membrane receptor; instead, binaural representations must be computed in the brain, based on information from each ear. Additionally — though the main ascending auditory pathways from both monaural and binaural structures of the auditory brainstem are known to be dominated by contralateral anatomical projections (reviewed in Stefanatos *et al.* 2008; Johnson and Hautus 2010), the decussation patterns of the ascending auditory system are quite complex (see Figure 2.1). For ILD, which is derived from differences in acoustic energy arriving at each ear and therefore carries information both about binaural level differences and statistics of monotic gain in each ear, it is unclear to what extent tuning depends on active binaural processing mechanisms or passive anatomical inheritance of signal from the contralateral ear. Indeed, neurophysiological recordings in mammalian AC show that though a majority of neurons are binaurally sensitive (Kitzes 2008), many exhibit spatial tuning consistent with monaural gain (Harrington *et al.* 2008).

The aim of the Experiment 1 was therefore to investigate the relationship between cortical processing of monotic sound stimuli and spatial tuning to ILD. To what extent is ILD tuning based on monaural versus binaural input? Two prominent approaches that previous investigations have used to characterize the neural representations of binaural and monaural sound include measuring AC sensitivity to parametrically modulated binaural cues, and comparing AC responses to monotic stimulation of each ear independently versus diotic stimulation of the two ears together in order to quantify the degree and nature of binaural interaction (i.e., enhanced response to binaural relative to monaural stimulation, termed "facilitation," or reduced response to binaural relative to monaural stimulation, termed "suppression"). Due to methodological differences, however, it has been difficult to synthesize data from these two types of studies.

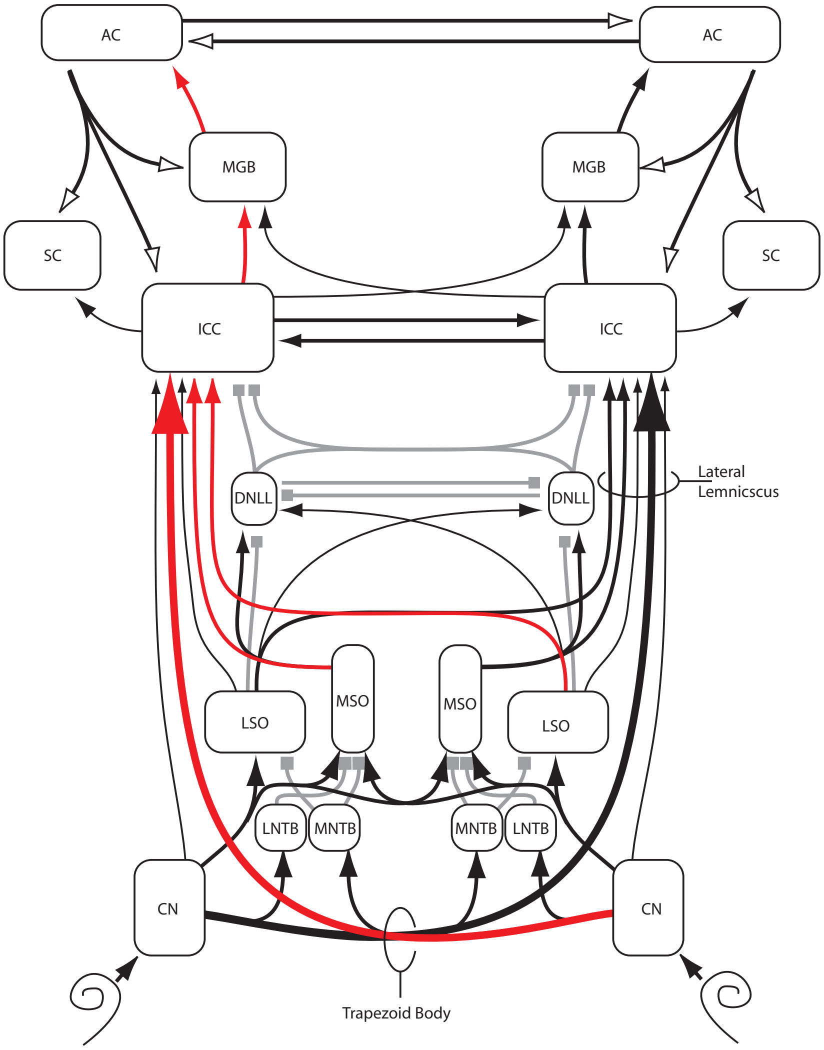

Figure 2.1: Ascending auditory pathway. Black and red: excitatory inputs; line weights indicate projection magnitudes. Gray: inhibitory projections. Contralateral pathways to left AC highlighted in red for illustration. Contralateral monaural inputs dominate. Major inputs to the inferior colliculus (ICC) include crossed monaural projections from cochlear nucleus (CN) and binaural projections from superior olivary nuclei (LSO and MSO).

In this experiment, therefore, we compared, in the same stimulus set, the BOLD response to monotic sound with the response to binaural stimuli comprising either a) diotic sound with equal intensities at each ear or b) dichotic ILD-bearing sound with parametrically varying intensity differences between ears. We investigated the relationship between tuning to monotic sound level and to parametric variation in ILD by characterizing and comparing the degree of contralateral bias present in the response to both types of stimuli. The results obtained in the present study confirm previous evidence that human AC response to monotic stimuli is stronger in the hemisphere contralateral to side of stimulation. Sensitivity to dichotic ILD-bearing sound is also seen to be contralaterally biased, albeit less strongly and consistently across AC regions. This attenuation in contralateral bias for binaural versus monaural stimulation appears to be partly because the response to ILD-bearing sound — though exhibiting a generally monotonic increase with perceptually increasingly contralateral stimuli — does not clearly show the expected monotonic decrease with increasingly ipsilateral sound. Instead, there is an "uptick" in the response to stimuli bearing ipsilateral ILD levels, particularly in right hemisphere core and posterolateral fields, with the presentation of extreme (20-30 dB) ILDs. We hypothesize that this non-monotonicity may reflect the excitatory contribution of ipsilaterally-tuned auditory spatial neurons. A direct comparison of the tuning to monotic gain and to ILD show that the degree of contralaterality in response to the two types of stimuli is only weakly related, suggesting that ILD is processed at least partially independently of monotic gain statistics, instead depending on active spatial tuning mechanisms.

To further investigate these potential mechanisms, we examined whether binaural interaction patterns show facilitation or suppression for diotic sound and for dichotic ILD-bearing stimuli. Binaural suppression suggests the involvement of some type of suppressive or inhibitory mechanism. Past evidence is mixed for facilitation (Scheffler *et al.* 1998) versus suppression (Jäncke *et al.* 2002; Krumbholz *et al.* 2005b; Stefanatos *et al.* 2008) in the human AC response to diotic sound. To our knowledge, there are no studies to date that have assessed binaural interaction patterns for dichotic ILD-bearing sound. Our results indicate that binaural suppression dominates AC processing of diotic sound, particularly in core and posterolateral AC fields. For parametrically-varied dichotic ILD-bearing stimuli, comparisons between response-ILD and monotic response level functions indicate that there is broadly ipsilaterally-tuned binaural suppression, with the greatest suppression occurring for ipsilateral ILD values of 10-20 dB, and the least for extreme (+/-30 dB) ipsilateral values and contralateral ILDs. This suggests the presence in posterolateral AC of an active, suppression-driven ILD tuning mechanism.

2.2 Methods

All procedures, including recruitment, consenting, and testing of human subjects followed the guidelines of the University of Washington Human Subjects Division and were reviewed and approved by the cognizant Institutional Review Board.

2.2.1 Subjects

Participating in the study were seven subjects, including five paid adults and two laboratory personnel. All self-reported as right handed, with normal hearing and no history of neurological disorder. Two of the participants were male; five were female; all were between 18-50 years old. Informed written consent was obtained from all paid participants.

2.2.2 Stimuli

The stimuli comprised trains of Gabor clicks (Gaussian-windowed tone bursts) in which each click consisted of a 4 kHz cosine multiplied by a Gaussian temporal envelope with $\sigma = 221\mu s$. The resulting spectral bandwidth was also Gaussian, with $\sigma = 750$ Hz (half-maximal bandwidth $\sim$ 1.8 kHz). The peak-to-peak interclick interval (ICI) was 3 ms. Click trains were synthesized at 48.848 kHz (Tucker-Davis

Technologies RP2.1, Alachua FL) and presented via piezoelectric insert earphones (Sensimetrics, Malden MA) surrounded by circumaural ear defenders.

Two stimulus parameters were manipulated: sound level and presentation rate (see Figure 2.2). Levels ranging from 55 to 85 dB SPL and “silent” (-10 dB SPL) were assigned independently in each ear such that BOLD measures were collected in response to stimuli varying parametrically according either to diotic intensity/average binaural level (ABL) (see positive diagonal of blue shaded cells) or to dichotic ILD (see negative diagonal of red-to-green shaded cells). Responses to monotic (yellow shaded cells) and silent stimuli (black shaded cell) were also collected. All dichotic ILD-bearing stimuli had an average binaural level of 70 dB SPL. All sound stimuli were presented at either of two rates: “slow” (tortoise symbol: 5 Hz or 5 trains of 32 clicks per second, inter-train gap randomly varying between 0–30 or 0–200 ms) or “fast” (hare symbol: 40 Hz or 40 trains of 4 clicks per second, inter-train gap varying randomly from 0–30 ms). Thus, the total acoustic energy present at either stimulus rate was equal over a 1 s period.

Click train stimuli were presented in 12 s blocks varying pseudorandomly according to level combination (monotic, ABL or ILD) by rate (slow or fast). Every fourth block was silent. Stimuli were presented in three five-minute runs, with each run comprising 57 blocks of stimulus presentation, resulting in a total of six presentations per sound condition and 42 presentations of the silent condition over the course of the entire imaging session. In order to remain attentive to the stimuli, subjects were asked to detect and to respond with a right forefinger button press to rare presentations (once per $\sim$ 13 s) of deviant pitch click trains resulting from shortened ICIs (2 ms).

2.2.3 Imaging

Imaging was performed with a Philips Achieva 3T scanner. Data for each participant were collected in a single imaging session lasting approximately one to two hours. A high-resolution T-1 weighted anatomical volume and three echoplanar functional

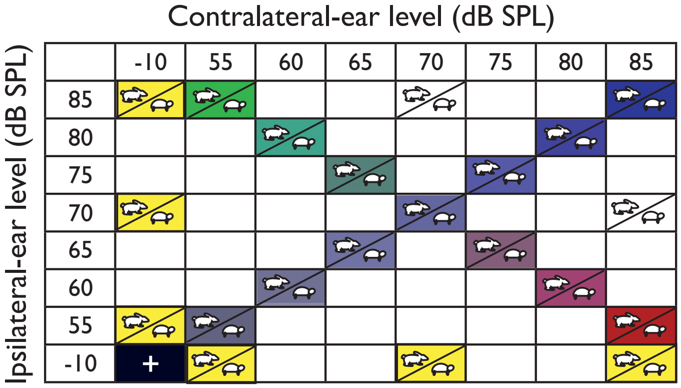

Figure 2.2: Binaural level and rate parameters of click train stimuli. Shading illustrates binaural level combinations used for testing sensitivity to average binaural level/ABL (shades of blue: positive diagonal) and interaural level difference/ILD (red to green: negative diagonal). Icons (tortoise/hare) represent slow and fast presentation rates. Monaural presentations indicated by yellow shading. Silent (-10 dB SPL in each ear) presentations indicated by black shaded cell labeled with "+". (Stimuli at 77.5 dB ABL, with ±15 dB ILD [cells with tortoise/hare icons and no shading] were also presented, but not analyzed in the present study.)

scans (3T, TR=12s, 32 slices, 3 x 3 x 4.5mm resolution) were collected. In order to minimize the effect of gradient scanner noise on auditory brain function, a sparse imaging paradigm (Edmister *et al.* 1999; Hall *et al.* 1999) was employed in which stimuli were presented in the relatively silent interval between single EPI volumes.

2.2.4 Analysis

Before preprocessing, the functional data were resampled to 1x1x1mm resolution in order to reduce sampling and movement noise (Kang *et al.* 2007). Preprocessing — comprising B0 unwarping, motion correction, high-pass filtering (.01 Hz) — was implemented using FSL 4.1 (FMRIB, Oxford, UK). Prior to analysis, each individual's 3D structural and functional data was extracted to the 2D cortical surface using Freesurfer 4.1 (Martinos Center for Biomedical Imaging, MGH, Boston), and then inflated to a common sphere. Anatomical normalization across individuals was performed on the spherical data by aligning the intersection of the superior temporal gyrus (STG) and the anterior-most transverse temporal gyrus or Heschl's gyrus (HG). For representational simplicity, spherical data were projected onto an equal-area Mollweide flat map (Woods *et al.* 2009), separately for each hemisphere in each individual.

Individual- and group-level parametric maps were derived from this 2D Mollweide data based on proportion of signal change across conditions. Statistical comparisons were conducted at the group level (mixed design treating subjects as a random factor) in 12 contiguous regions of interest (ROIs), plus a 13th all-inclusive ROI, located in the area of cortex surrounding the intersection of STG and HG, known to encompass human AC. These ROIs (see Figure 2.3) were based on the boundaries of human AC fields proposed by Woods *et al.* (2010), defined following careful consideration of the functional divisions observed in AC of non-human primates (Kaas and Hackett 2000; Petkov *et al.* 2006) and comparison of human AC BOLD sensitivity to variation in a wide array of features, including sound frequency, intensity, ear of presentation, and attentional modulation. The parcellation of Woods *et al.* (2010) represents our current best estimate of the functional parcellation of human AC, an estimate that is likely to change in response to future work in this area. In the current study, the ROIs defined in this way were used to quantify gross regional variation in the sensitivity of AC BOLD responses to binaural features and not to formally evaluate functional roles specific to AC fields. Analyses were performed in MATLAB 7.4 (Mathworks, Natick MA).

2.3 Results

2.3.1 Stimulus parametric maps of sensitivity to monotic and diotic stimuli

A cortical-surface map of group-average BOLD responses to monotic and diotic sound conditions (see Figure 2.4) was derived by identifying suprathreshold voxels showing greater than 1% signal change relative to silence, averaged across blocks presenting

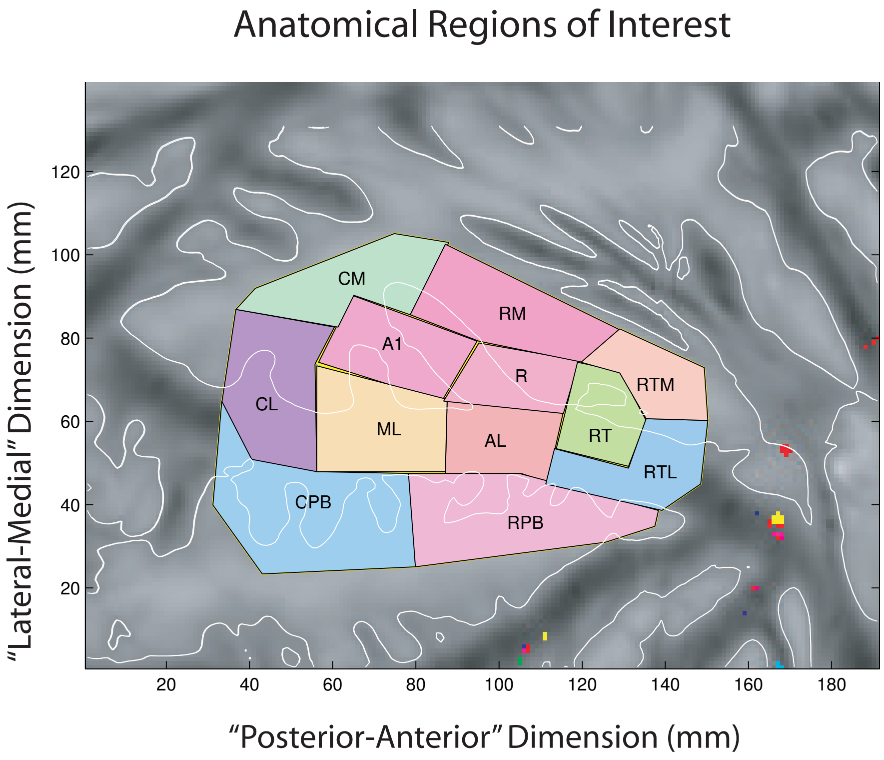

Figure 2.3: Anatomical regions of interest (ROIs) on a right hemisphere cortical surface, adapted from Woods et al. (2009). ROIs are defined on the basis of comparison to functional fields of macaque AC, relative to a spherically aligned curvature map of human AC. An additional ROI was defined to encompass the entirety of AC (all shaded regions combined). The large gyrus in the center of the image, extending over anterior A1 and posterior R fields, is Heschl's gyrus (HG). ROI abbreviations: A1: primary field; AL: anterolateral; CL: caudolateral; CM: caudomedial; CPB: caudal parabelt; ML: mediolateral; R: rostral; RM: rostromedial; RPB: rostral parabelt; RT: rostrotemporal; RTL: rostrotemperolateral; RTM: rostrotemporomedial.

sound either monotically to the contralateral (red shading) or ipsilateral (green shading) ear, or diotically (blue shading). Suprathreshold voxels selected were confined to those located within a functionally-defined region of cortex showing response to sound (all conditions combined relative to silent blocks). Voxels in which there existed overlapping suprathreshold responses to multiple sound conditions were coded according to color mixtures within an RGB color model, i.e., magenta, cyan, yellow, and white.

In both hemispheres, magenta shading — indicating overlapping sensitivity to diotic and contralateral monotic stimuli — was observed to dominate in areas surrounding Heschl's gyrus (HG), with a majority of suprathreshold voxels located posterior to HG. These results support previous findings of a contralaterally-biased response to monotic sound in human AC (Scheffler *et al.* 1998; Woldorff *et al.* 1999; Jäncke *et al.* 2002; Suzuki *et al.* 2002; Stefanatos *et al.* 2008), and further suggest that those cortical areas sensitive to monotic sound in the contralateral ear are also responsive to diotic stimuli. The white shaded regions evident posterior to HG in each hemisphere indicate additional overlapping suprathreshold sensitivity to ipsilateral monotic sound.

2.3.2 Contralateral bias in response to monotic stimulation

The degree of monotic contralateral bias, both across AC regions and across intensity, was quantified by computing a contralaterality index (CI) for group-average suprathreshold responses (greater than 50% of maximum signal change, relative to silent baseline) in each ROI (see Figure 2.5, top). CI was defined as the difference between the BOLD response to contralateral monotic and ipsilateral monotic stimulation, normalized by the sum of these responses, or:

$$CI = (C - I)/(C + I)$$

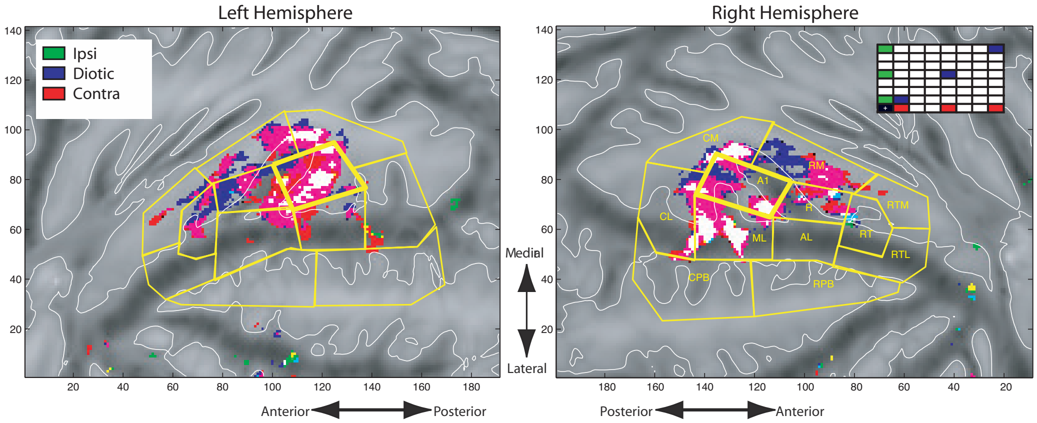

Figure 2.4: Cortical-surface maps of group-average BOLD responses to monotic and diotic sound. Colored shading overlaid on group-average left and right cortical surfaces indicates voxel-wise response greater than 1% signal change (relative to silence), averaged across blocks presenting sound monotically to the contralateral (red) or ipsilateral (green) ear, or diotically (blue). Overlapping suprathrehold responses to more than one sound condition appear as RGB mixture (magenta, cyan, yellow, white). Responses are averaged across subjects without spatial smoothing, and are masked by significant overall response to sound (all conditions combined). Box inset depicts stimulus conditions analyzed, based on color coding scheme established in Figure 2.2.

where C = response to monotic stimulation to the contralateral ear, and I = response to monotic stimulation to the ipsilateral ear. CI values range from -1 (indicating complete bias to ipsilateral stimulation) through 0 (indicating no bias) to +1 (indicating complete bias to contralateral stimulation). Consistent with previous reports (Scheffler *et al.* 1998; Woldorff *et al.* 1999; Jäncke *et al.* 2002; Suzuki *et al.* 2002; Stefanatos *et al.* 2008), most AC fields — excepting anterior regions of right AC — show contralateral response bias to monotic sound, somewhat greater in core than other AC regions (see Stefanatos et al. 2008), and in left hemisphere (LH) as opposed to right hemisphere (RH). Separate CIs for monotic stimulation at each intensity level presented (55, 70, and 85 dB SPL) were also computed, averaged across all AC ROIs (see Figure 2.5, bottom). Across hemispheres and at all intensities, CI> 0, further confirming that AC shows a general contralateral bias for monotic stimuli. This bias appears to be greatest at moderate to high intensities (70 to 85 dB) in LH.

2.3.3 Binaural interaction patterns

The nature of the AC BOLD response to binaural stimulation was investigated by comparing responses to monotic versus diotic and versus dichotic ILD-bearing stimulation.

2.3.3.1 Monotic versus diotic stimuli

Monotic and diotic responses were compared by deriving response-intensity functions plotting group-average % signal change in suprathreshold BOLD responses (greater than 50% of maximum signal change, relative to silent baseline) against intensity/ABL for sounds presented either monotically to the contralateral ear or diotically. Response-intensity functions were computed for individual ROIs see Figure 2.6, top) and for an overall mean of data from all AC ROIs combined (see Figure 2.6, bottom). The data, particularly in core A1 and overall mean AC ROIs, show roughly monotonic increases with ABL in both hemispheres for diotic stimuli, similar to results

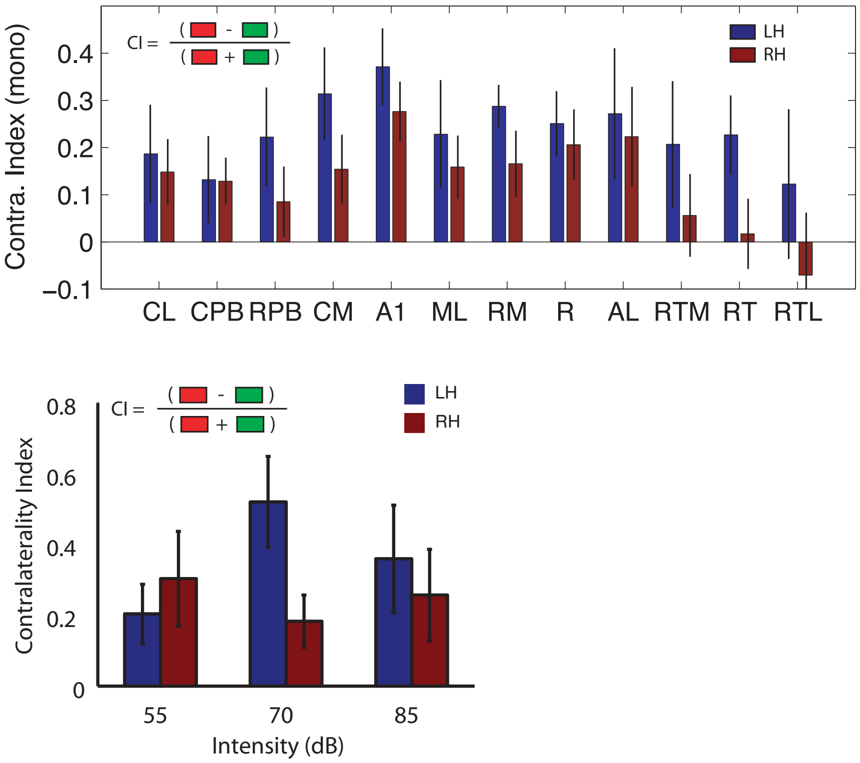

Figure 2.5: Contralaterality index (CI) for response to monotic sound. CI is computed as the ratio of contralateral minus ipsilateral BOLD response to the sum of contralateral and ipsilateral responses. Blue bars = left hemisphere, red bars = right hemisphere. Error barsindicate +/- 1 s.e.m. across subjects. Inset refers back to stimulus color coding scheme established in Fig 2. Top: Monotic CI values averaged across intensityplotted across regions of interest (ROIs). Bottom: Monotic CI values in all encompassing AC-average ROI plotted across intensity.

obtained by Sigalovsky and Melcher (2006). In the mean AC and many individual ROIs (e.g., A1, R, and ML bilaterally, and CL and CPB in RH), responses to diotic stimuli show steeper response-intensity functions than do those for monotic presentation. That is, at low to moderate intensities (55 to 70 dB SPL), binaural diotic responses are reduced compared to monotic responses, while at higher intensities (85 dB SPL), they are similar. This suggests that binaural suppression dominates in AC at low to moderate intensities.

The nature and degree of this binaural interaction for diotic stimuli were quantified by computing binaural interaction index (BI) values from the response-intensity data in the overall mean AC ROI (see Figure 2.7). BI was defined as the difference between BOLD % signal change in response to contralateral monotic and to diotic stimulation, equated in intensity at the contralateral ear, or:

$$BI = (C - D)/C$$

where C = % signal change response to monotic stimulation to the contralateral ear and D = % signal change response to diotic stimulation. BI ranges from -1 (indicating binaural suppression) through 0 (indicating no difference between the response to monotic and diotic stimuli, equated in intensity at the contralateral ear) to +1 (indicating binaural facilitation). BI values less than 0 are observed across intensity levels in both hemispheres (except in RH at high [85 dB] intensity), confirming that there is binaural suppression in human AC in response to diotic stimulation, particularly at low to moderate (55 to 70 dB) levels of presentation. In the mean AC ROI, suppression is greatest in LH at 70 dB.

2.3.3.2 Monotic versus dichotic ILD-bearing stimuli

Similar to the previous analysis, responses to monotic and dichotic ILD-bearing stimuli were assessed by comparing monotic response-level functions (% signal change in BOLD response to monotic sound to the contralateral ear plotted across intensity) to

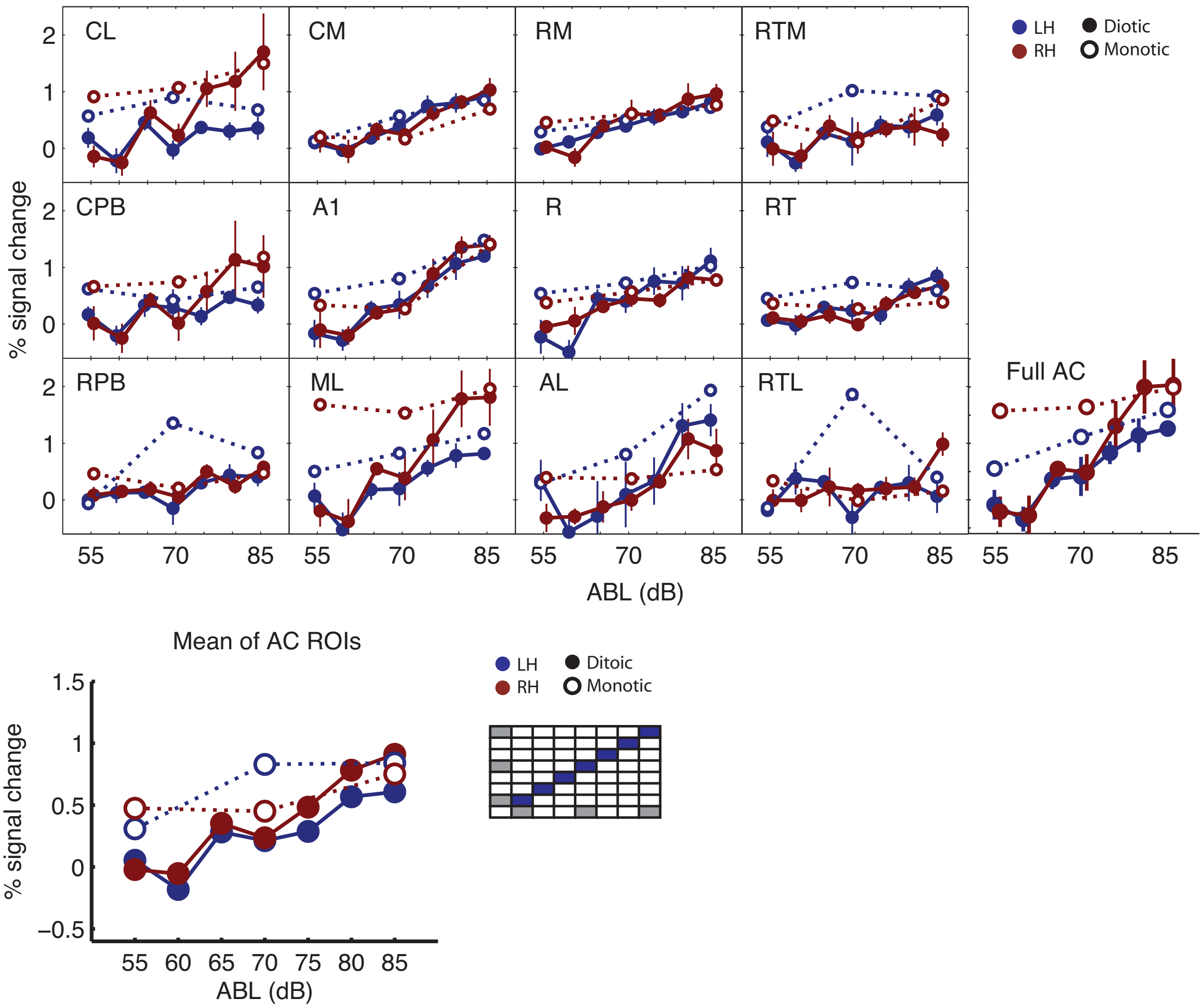

Figure 2.6: Response-intensity functions for monotic and diotic stimulation. Percent signal change in BOLD signal (relative to silence) plotted against average binaural level (ABL: blue shading in inset panel) for sounds presented diotically (filled symbols) or monotically to the contralateral ear (open symbols). Blue symbols = left hemisphere, red symbols = right hemisphere. Top: Monotic and diotic response-intensity functions in AC regions of interest (ROIs). Error bars indicate +/- 1 s.e.m. across subjects. Bottom: Monotic and diotic response-intensity functions for overall mean AC ROI. Individual ROIs separately baselined prior to averaging.

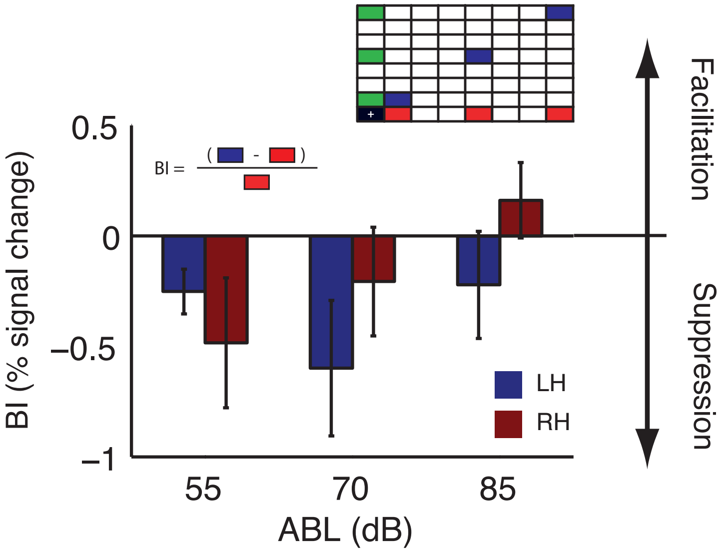

Figure 2.7: Binaural interaction index (BI) for diotic stimuli in mean AC, across intensity levels. BI is plotted as the % signal difference in the response to contralateral monotic (red cells in inset panel) and diotic stimuli (blue cells in inset panel), equated in intensity at the contralateral ear. Blue bars = left hemisphere, red bars = right hemisphere. Error bars plot +/- 1 s.e.m. across subjects.

response-ILD functions (% signal change in response to dichotic stimulation plotted across parametrically-varied ILD). Again, response-ILD and monotic response-level functions were computed individually for AC field ROIs (see Figure 2.8, top) and for an overall mean of AC ROIs combined (see Figure 2.8, bottom). Dichotic ILD-bearing stimuli varied by 10 dB increments from -30 dB ILD (louder at left ear or "leftward") to +30 dB ILD (louder at right ear or "rightward"), but maintained an average binaural level of 70 dB.

For parametrically varied dichotic ILD-bearing stimuli, comparisons between response-ILD and monotic response level functions indicate that there is broadly ipsilaterally-tuned binaural suppression — particularly in core and posterolateral (A1, ML, and CL) regions — with greatest suppression at ipsilateral ILD values of 10-20 dB. This suggests the existence in posterolateral AC of an active, suppression-driven ILD tuning mechanism.

Response-ILD functions demonstrate a contralateral cortical bias in which generally greater responses can be seen in the hemisphere contralateral to side of ILD presentation, a pattern that is particularly clear in A1. With respect to binaural interaction patterns, a consistent difference across ROIs between the BOLD response to monotic and to dichotic ILD-bearing stimuli is evident only at midline (0 dB) through ipsilateral ILD values of 10-20 dB, where binaural suppression dominates. There is little to no suppression for extreme (+/-30 dB) and contralateral ILDs.This pattern is suggestive of broadly ipsilaterally-tuned binaural suppression. Suppression in the overall mean AC ROI is quantified by calculating a binaural interaction index for responses to dichotic ILD-bearing stimuli across midline (0 dB ILD) and eccentric ILD levels (-30 and +30 dB ILD) (see Figure 2.9). In this case, BI is defined as the difference between BOLD % signal change in response to dichotic ILD and contralateral monotic stimulation, equated to contralateral ear intensity during corresponding binaural presentations, or:

$$BI = (C - D)/C$$

where C = % signal change response to monotic stimulation to the contralateral ear and D = % signal change response to dichotic ILD-bearing stimulation. BI<0 indicates binaural suppression, whereas BI>0 indicates binaural facilitation. BI values for the overall mean AC ROI confirm that there is binaural suppression in response to midline ILD (0 dB ILD) stimuli — particularly in LH — but not to extreme left or right-favoring ILD stimuli (-30 or + 30 ILD). Looking at the response-ILD functions for individual ROIs (Figure 2.8, top), such suppression-driven ILD tuning appears to be strongest bilaterally in posterolateral (CL, CPB, ML) and core A1 regions.

2.3.4 Tuning to parametric variation in ILD

Across AC ROIs, tuning to parametric variation in ILD can be observed in Figure 2.8 (top), which plots % signal change (relative to silence) in the BOLD response across ILD values. As previously noted, in most ROIs — but particularly in core A1 — a contralateral response bias is seen in which RH responds more to contralateral leftward than to ipsilateral rightward stimuli. The opposite is true for LH. The BOLD response in each hemisphere appears generally to monotonically increase with increasingly contralateral ILD values, presumably as the sound stimuli are perceptually lateralized more eccentrically in contralateral auditory space. Interestingly, however, there is not such a clear monotonic decrease for increasingly ipsilateral ILD stimuli. Instead, in a number of regions — notably core A1 and posterolateral CL and CPB, particularly in RH — there is a "uptick" in the magnitude of the response to ipsilateral ILD stimuli, often at extreme +/- 30 dB ILD, but sometime at more central ipsilateral ILD values.

Similar to the contralaterality analyses for monotic stimuli described previously, the level of contralateral bias in response to ILD stimuli can be quantified by computing contralaterality index (CI) values in each ROI (see Figure 2.10). CIs were determined by calculating for each hemisphere the difference between the BOLD response to stimuli bearing contralaterally-lateralized ILDs (C) and to stimuli bearing

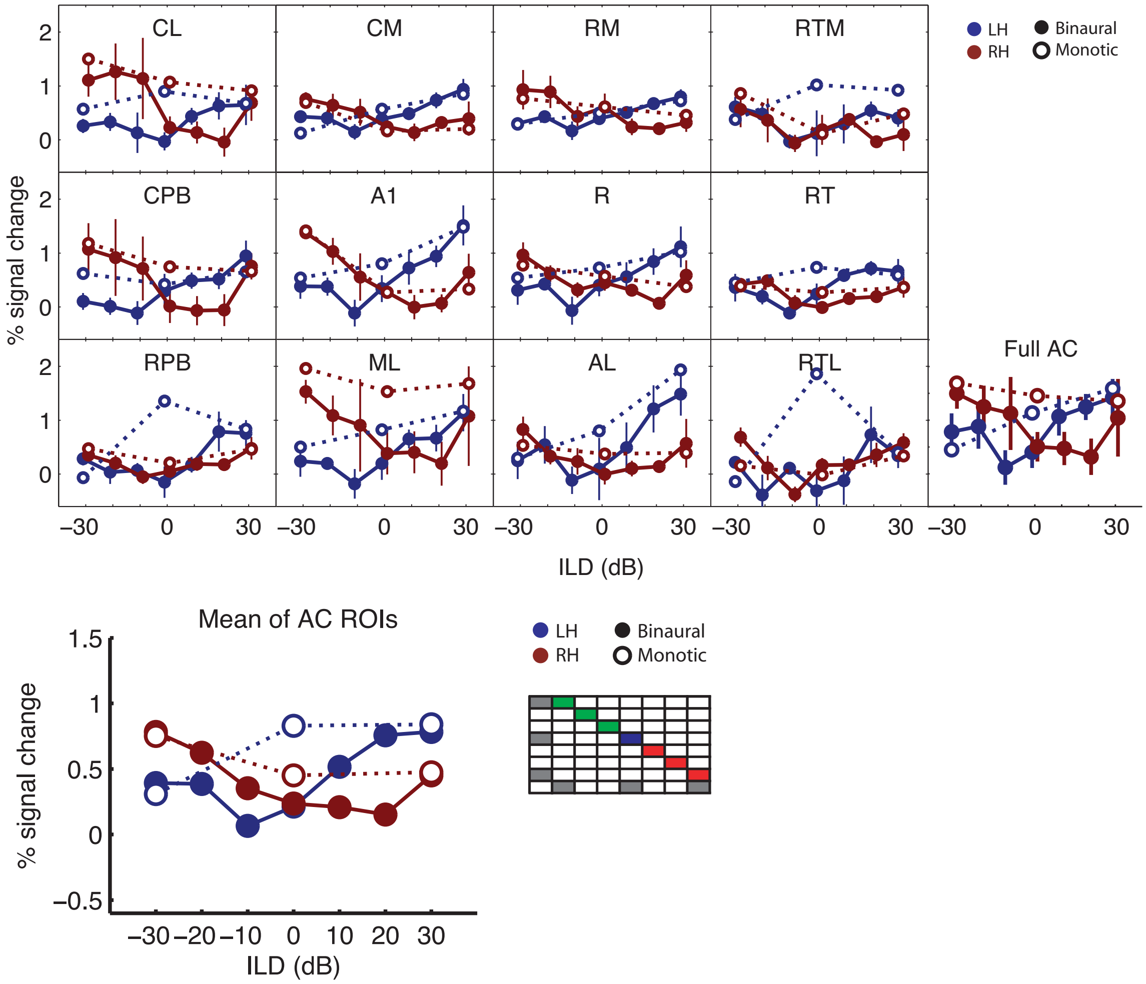

Figure 2.8: Response-ILD and monotic response-level functions. Percent signal change in BOLD signal (relative to silence) plotted against interaural level difference (ILD: red-to-green shaded cells in inset panel) for sounds presented dichotically (filled symbols), varying in ILD from -30 dB (louder at left ear) to +30 dB (louder at right ear) and delivered at an ABL of 70 dB SPL. Also plotted is % signal change for contralateral monotic stimuli equated to contralateral ear intensity during corresponding binaural presentations (open symbols). Blue symbols = left hemisphere, red symbols = right hemisphere. Top: Response-ILD and monotic response-level functions in AC regions of interest (ROIs). Error bars indicate +/- 1 s.e.m. across subjects. Bottom: Response-ILD and monotic response-level functions in overall mean AC ROI. Individual ROIs separately baselined prior to averaging.

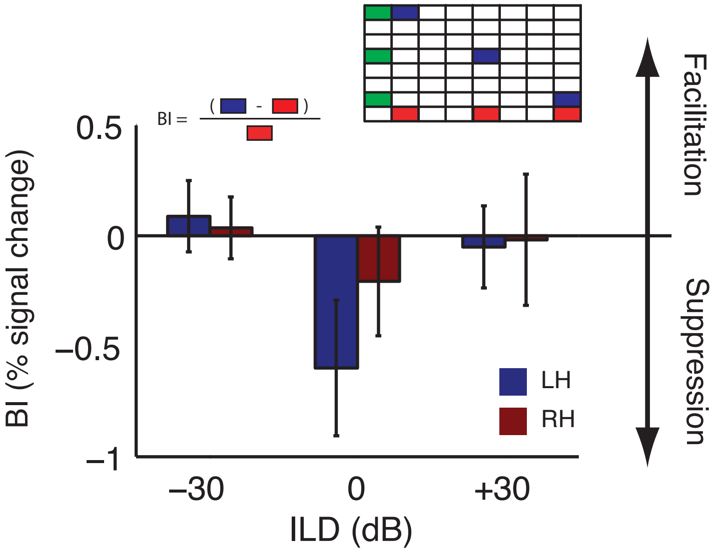

Figure 2.9: Binaural interaction index (BI) for overall mean AC response to dichotic ILD-bearing stimuli (ILD = -30 db [extreme left], 0 dB [midline], +30 dB [extreme right]. BI is plotted as the % signal difference in the response to contralateral monotic (red cells in inset panel) and dichotic ILD-bearing stimuli (blue cells in inset panel), equated to contralateral ear intensity during corresponding binaural presentations. Blue bars = left hemisphere, red bars = right hemisphere. Error bars plot +/- 1 s.e.m. across subjects.

ipsilaterally-lateralized ILDs (I) (averaged across responses to +/- 10, 20, and 30 dB ILD), normalized by the sum of these responses:

$$CI = (C - I)/(C + I)$$

Again, CI values range from -1 (indicating complete bias to ipsilateral ILD stimuli) through 0 (indicating no bias) to +1 (indicating complete bias to contralateral ILD stimuli). For most AC ROIs, in both hemispheres, CI $>$ 1, denoting a contralateral response bias to ILD. Positive CI values are greatest in A1 and R core fields and adjacent regions, medially and laterally (CM, ML, and RM). In a number of far anterior (RTM and RTL) and to a lesser extent posterior (CL) fields, the CI values either are near 0, indicating no response bias to auditory space, or — in some RH anterior regions — are less than 0, suggesting an ipsilateral response bias. A comparison of these dichotic ILD CI values versus those for monotic stimuli (Figure 2.5, top) suggests that AC responses to monotic sound are more consistently and strongly contralaterally biased than are responses to ILD-bearing dichotic stimuli.

To further quantify the relationship between contralateral bias to monotic sound and ILD tuning, the correlation in each AC ROI between CI values for BOLD responses to contralateral monotic stimuli and the response-ILD slope for contralateral ILD values was computed (see Figure 2.11). ILD slope was computed by fitting a linear regression line to responses for ILD ranging between 0 and 30 dB contralateral, separately for each combination of subject, ROI, and hemisphere. Correlation between contralateral monotic CI and ILD slope instead of ILD CI values was explored so that the relationship measured would reflect each region's response to contralateral sound only (in order to eliminate the non-monotonic effect in the response to ipsilateral stimulation). A significant correlation was observed only in CPB (R^2=0.33, $p < .05$), suggesting that — at least as reflected in contralateral CI and ILD-slope values — AC tuning to monotic gain is not strongly related to ILD tuning.

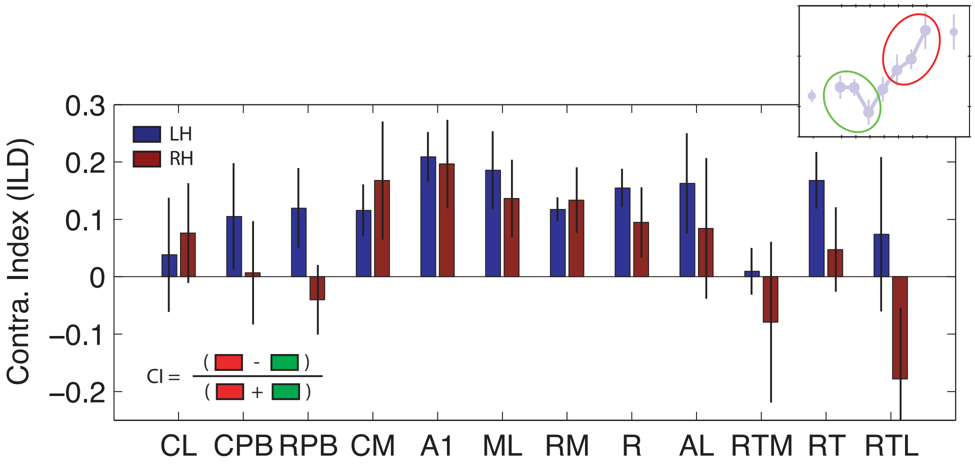

Figure 2.10: Contralaterality index (CI) for response to dichotic ILD-bearing sound across AC ROIs. CI was computed as the ratio of average responses to contralateral (red circled stimulus values in inset panel) minus ipsilateral (green circled stimulus values in inset panel) stimuli, normalized by the sum of these responses. CI values were computed separately for each combination of subject, ROI, and hemisphere. Bar heights and error bars plot mean CI +/- 1 s.e.m. across subjects. Left hemisphere = blue bars, right hemisphere = red bars. Values greater than 0 indicate contralateral tuning in a majority of ROIs.

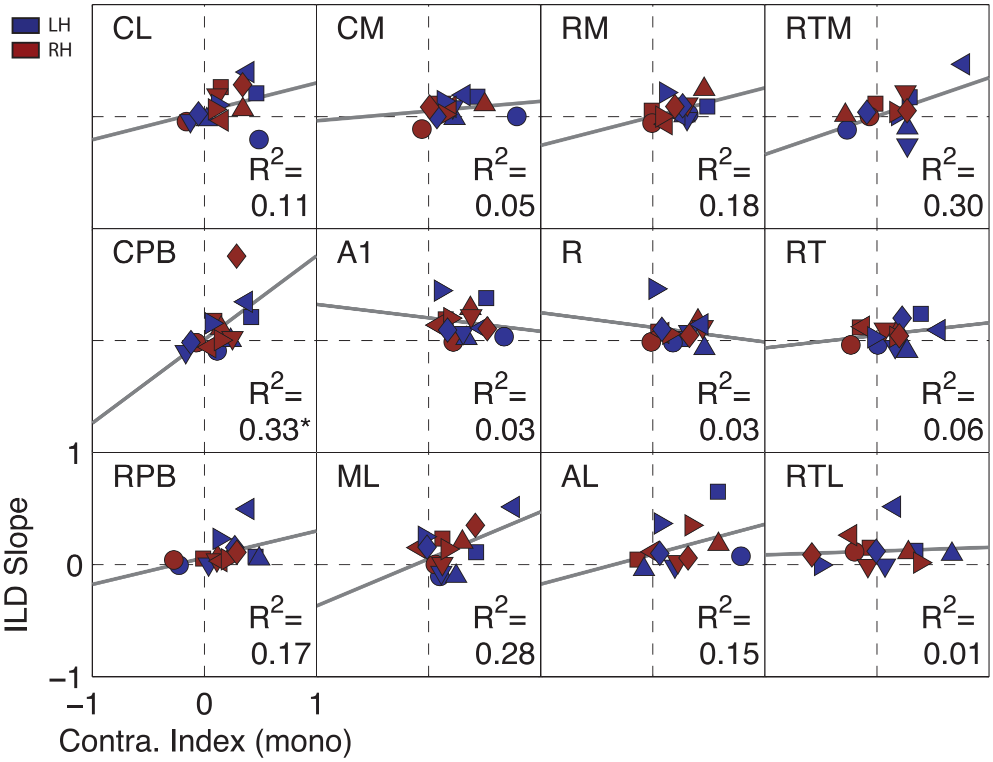

Figure 2.11: Correlations between contralaterality indices (CI) obtained from responses to monotic stimulation (horizontal axis) and response-ILD slopes for contralateral ILD values (vertical axis). ILD slope was computed by fitting a linear regression line to responses for ILD ranging between 0 and 30 dB contralateral, separately for each combination of subject, ROI, and hemisphere. In each panel, blue and red symbols plot values measured in left and right hemispheres, respectively, of individual listeners. Lines indicate linear regression slopes; statistically significant correlations ($p < .05$) are indicated by asterisk (*).

2.3.5 Effects of stimulus presentation rate

Stimulus specific neural adaptation (i.e., reduced firing in response to repeated versus novel stimulation) has been observed in neurophysiological recordings in mammalian AC (Malone *et al.* 2002; Ulanovsky *et al.* 2003; Pienkowski and Eggermont 2009). Based on the premise that attenuation of the BOLD response in human AC with increasing rates of stimulus presentation (Harms and Melcher 2002) may be indicative of a general response adaptation in the human AC, we explored the effect of stimulus presentation rate on ILD tuning in the present study. All stimuli were presented at both fast (40 Hz) and slow (5 Hz) rates, and differences in response magnitude (as measured by % signal change relative to silent baseline) between slow and fast presentation rates were calculated across levels of ILD in each ROI (see Figure 2.12). Across ROIs, hemispheres, and ILD levels, there is clear modulation of response by presentation rate, with difference values positive overall, corresponding to greater activation for slow than fast presentation rates. Difference values near or below 0 were seen predominantly in anterior regions (e.g., RT, RPB, and RTL), with the most positive values seen in core and posterior and lateral belt regions (e.g., A1, CL, ML, and AL), suggesting that these areas are more adaptive to presentation rate. Across levels of ILD, this presentation rate effect appears to be enhanced for moderate ILD values of 10-20 dB and reduced for small (0 dB) or large (+/- 30 dB) ILD values. Computed for voxels across the entire AC region (Figure 2.12, far right), the presentation rate effect appears greatest in RH in response to sound sources in the contralateral left hemifield, whereas in LH the presentation rate effect is similar in magnitude for sounds lateralized to both hemifields. These results suggest that there may be an overall hemispheric asymmetry in response adaptation.

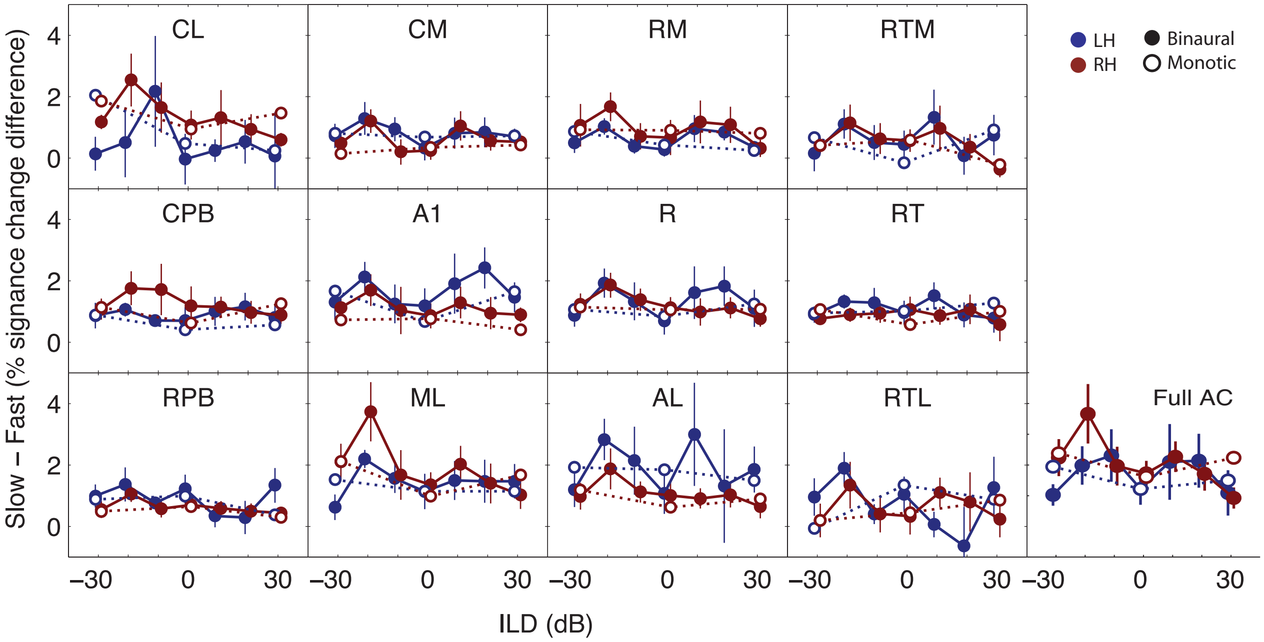

Figure 2.12: Modulation of BOLD response by stimulus presentation rate. Plotted for each ROI are are difference values in response magnitude (% signal change from baseline) to slow (5 Hz) versus fast (40 Hz) presentations of monotic (open symbols) and dichotic ILD-bearing (closed symbols) stimuli, across ILD level. Blue symbols = left hemisphere; red symbols = right hemisphere.

2.4 Discussion

2.4.1 Contralaterally biased AC response to monotic sound

The contralaterally-biased response to monotic sound seen in the current study is consistent with previous evidence showing that monotic presentation to either ear yields a greater BOLD signal in AC contralateral to side of stimulation (Scheffler *et al.* 1998; Woldorff *et al.* 1999; Jäncke *et al.* 2002; Suzuki *et al.* 2002; Stefanatos *et al.* 2008). We interpret this monotic response pattern to be a reflection of the predominantly contralateral anatomical projections ascending from each ear, absent the influence of any active binaural processing mechanisms. When collapsed across intensity, we observed monotic contralateral bias to be greater in core A1 than in other ROIs tested. The greater contralateral bias seen in the A1 response to monotic sound may derive from the presumably higher proportion of direct input to this region from ascending lemniscal thalamic projections (i.e., ventral portion of medial geniculate body [MGBv]) relative to other AC regions receiving comparatively more corticocortical, interhemispheric, and non-lemniscal corticothalamic (e.g., medial and dorsal MGB) projections (de la Mothe *et al.* 2006a;b; Lee and Winer 2008). The more heterogenous projections to and from non-core areas engender a more highly processed signal, potentially moderating the inherent contralateral dominance of the ascending monaural pathway.

The contralateral bias seen in A1 and a number of other ROIs is also greater in LH than in RH, possibly reflecting a greater contralaterality in anatomic projections from the right auditory periphery to left AC than vice versa. This asymmetry in response contralaterality appears to be level-dependent. It is strongest at 70 dB, while at 55 and 85 dB, there is little difference between left and right AC with respect to degree of bias. Additionally, contralateral bias may be stimulus-dependent. Stefanatos et al. (2008) found a slightly higher contralaterality index value in RH than in LH in response to monotic syllable stimuli at 95 dB. The hemispheric discrepancy between this result and our data may be due to the high intensity of stimulus presentation in the Stefanatos study and/or because the speech stimuli used elicited a large response in LH regardless of ear of presentation.

2.4.2 Binaural suppression dominates AC response to diotic sound and shapes AC tuning to ILD

The cortical surface map data obtained in the present study (Figure 2.4) indicate a pattern of voxels surrounding Heschl's gyrus sensitive to both diotic and contralateral monotic presentation of click train stimuli. The "horseshoe" shape of the BOLD response pattern — surrounding HG with a predominance of suprathreshold responses in posterior AC areas — may reflect sensitivity to the 4000 Hz center frequency of the stimuli, consistent with the tonotopic gradients previously observed in human AC (e.g., Woods *et al.* 2009), that indicate increased responsiveness to high frequency tones surrounding HG, with dominant posterior foci.

Neurons with similar responses to monotic and diotic stimuli are typically labeled "E0" type responders, signifying that input to the ipsilateral ear neither enhances nor reduces the response to contralateral ear input. In assessing whether the data from the present study reflect an E0 response pattern, it is important to note that the BOLD signal represents voxel averages summing over the responses of hundreds of thousands to millions of neurons (Logothetis 2008). It is therefore not possible to determine whether commensurate responses to monotic and diotic sound co-occur within single neurons or are instead included in the summed sub-voxel responses of separate populations of neurons. Moreover, our map of suprathreshold responses to diotic and contralateral monotic stimuli does not provide information about magnitude differences between the two conditions. Indeed, examining such differences by comparing response-intensity curves and binaural interaction index values for monotic versus diotic presentations reveals level-dependent binaural suppression for diotic stimuli in human AC, suggesting an "EI" rather than E0 response pattern. That is, at low to moderate intensities (55 to 70 dB), there is reduced sensitivity to diotic versus monotic sound in the overall mean AC ROI. In the individual ROIs, this pattern is particularly evident in core A1 and posterolateral ML, CL, and CPB. This result is consistent with previous fMRI (Jäncke *et al.* 2002; Krumbholz *et al.* 2005b; Stefanatos *et al.* 2008) and MEG (reviewed in Stefanatos et al. 2008) data showing binaural suppression for a variety of sound stimuli, including speech syllables, tones, and noise. Consistent with our results, Krumbholz et al. observed this suppression in core regions on HG, and in planum temporale, posterior to HG. In contrast, however, Scheffler *et al.* (1998) observed binaural facilitation for tones. This discrepancy may be due to the high intensity (95 dB) of their stimulus presentation, which — based on the current data — may attenuate or eliminate binaural suppression.

Our data suggest an EI pattern in which the diotic voxel-wise response is reduced relative to the contralateral monotic response. Jäncke *et al.* (2002) and Krumbholz *et al.* (2005b) observed the same pattern, with Krumbholz and colleagues reporting an 18% suppression of the binaural relative to the contralateral monotic response. As Krumbholz et al. note, the smaller diotic than contralateral response suggests that the reduction for diotic stimulation cannot solely result from passive saturation, but must to some degree be produced by active suppression. Krumbholz and colleagues hypothesize that this suppression stems from a mechanism involving inhibition by the ipsilateral input response on the response to contralateral input. Such a mechanism is consistent with neurophysiological recordings of EI-type neurons in and above the inferior colliculus (reviewed in Krumbholz *et al.* 2005b).

Krumbholz et al. additionally note that the lack of facilitation observed across studies is quite surprising given that the level in one ear for monotic sound is the same absolute value as the level in each ear for the diotic stimuli. Psychophysical data indicate that diotic sounds are perceived to be louder than corresponding monotic sounds (Marks 1980), an effect known as "binaural summation," and increased loudness has been shown to result in increased AC BOLD signal (Sigalovsky and Melcher 2006).

Jäncke *et al.* (2002) suggest that the lack of increased response observed in association with binaural summation may be due both to inhibitory mechanisms described above and possible top-down attentional influences.

For dichotic ILD-bearing stimuli, our data show broadly ipsilaterally-tuned binaural suppression, with the greatest suppression at ipsilateral ILD values of 10-20 dB, and less at contralateral ILDs. There appears to be little binaural interaction in response to sounds with large level differences between the ears (-30 and +30 dB ILD). We hypothesize that this ILD-dependent binaural suppression may serve as a mechanism shaping AC tuning to ILD. Our results suggest this mechanism is particularly strong in core A1 and posterolateral (CL, CPB, and ML) areas, as these regions are where the most suppression for centered/diotic stimuli was observed. This would be consistent with prior evidence that posterior AC regions subserve auditory spatial processing (e.g., Rauschecker and Tian 2000, Arnott et al. 2004).

2.4.3 Contralateral bias in AC tuning to ILD: relationship between monotic and ILD tuning

The tuning curves derived from the BOLD response to parametrically-varied dichotic ILD-bearing stimuli suggest that the AC response to ILD is generally contralaterally biased. As with the response to contralateral monotic level, the BOLD signal increases monotonically with increase in contralateralized ILD values, a pattern particularly evident in core A1 and posterolateral regions CL, CPB, and ML. The contralaterality index values for the ILD response, however, are less consistently positive (i.e., less indicative of strong contralateral bias) than are those for monotic stimulation. One reason for the attenuated contralaterality index values for ILD appears to be the lack of a clear monotonic decrease in response to increasingly ipsilateral ILD stimulation. Instead, there is an enhanced BOLD response to extreme ipsilateral ILD values, particularly in RH regions A1, CL and CPB. We speculate that this escalation is due to the increased excitatory response in ipsilaterally-tuned neurons as ipsilateral ILD values increase. This effect may be accentuated in posterolateral regions due potentially to a concentration of neurons sensitive to auditory space — contralaterally- but also ipsilaterally-tuned — a scenario that may be associated with the increased influence of a suppression-driven ILD tuning mechanism in posterolateral regions based on ipsilateral inhibition, as hypothesized by Krumbholz and colleagues.

This observed rise in response to extreme ipsilateral stimulation may partially account for data from prior fMRI studies showing weak to no contralateral bias in response to binaural stimuli (Woldorff *et al.* 1999; Krumbholz *et al.* 2005a; Zimmer *et al.* 2006), although a number of these studies presented ITD as opposed to ILD-modulated stimuli. If sound source location is indeed encoded in the AC by an interplay of excitatory and inhibitory responses of contralaterally- and ipsilaterally-tuned neurons consistent with the "opponent-channel" hypothesis (McAlpine *et al.* 2001; Stecker *et al.* 2005b), this representation may be quite difficult to capture with fMRI measures which do not differentiate excitatory versus inhibitory activity.

Though responses to contralateral monotic level and to contralateral ILD values both increase monotonically, contralaterality index values derived from data across the entire ILD-response curve appear to reflect a more complex mix of responses in contralaterally- and ipsilaterally-tuned populations. Because of this, our questions regarding the relationship between ILD tuning and response to monotic gain are best captured in our data by the correlation between monotic contralaterality index values and contralateral ILD slope. This correlation reached significance only in region CPB, suggesting that ILD processing is not highly related to statistics of monotic gain, but instead reflects actual spatial tuning.

2.4.4 Response adaptation to ILD greatest in lateral belt fields

Consistent with other fMRI studies, we observed greater AC response for stimuli presented at slow (5 Hz) versus fast (40 Hz) rates (Giraud *et al.* 2000; Harms and Melcher 2002), a difference we interpret as arising from decreased response adaptation at slower presentation rates. This adaptation effect was strongest in lateral belt fields CL, ML, and AL, consistent with prior evidence that core AC fields exhibit a more tonic response to repeating stimuli, while non-core fields respond in a phasic manner suggestive of response adaptation (Harms *et al.* 2005; Seifritz *et al.* 2002). In most ROIs, the greatest adaptation observed was at 10-20 dB ILD. In the AC average response, the RH adaptation was stronger for contralateral ILD stimuli, while in the LH, the degree of adaptation was similar for contralateral and ipsilateral sound. These data are generally consistent with neurophysiological observations of a predominating population in AC of contralaterally-tuned neurons and a smaller population that is ipsilaterally-tuned, although it suggests a possible hemispheric asymmetry similar to that observed by Salminen *et al.* (2010a). Salminen and colleagues found that MEG responses to noise were more attenuated in RH by preceding ("adaptor") sound in the contralateral left as opposed to ipsilateral right hemifield, while the LH response was equally affected by adaptors in either hemifield. Krumbholz *et al.* (2005a) also observed a reduction of the AC BOLD response in posterolateral planum temporale to non-moving (i.e., repetitive) auditory spatial stimuli, but no reduction for virtually "moving" sounds, suggesting auditory adaptation. Krumbholz and colleagues suggest that planum temporale is specialized for processing auditory motion sensitivity, and that this is subserved by adaptation to invariant sound features. We speculate that enhanced adaptation at 10-20 dB ILD (in RH, particularly for sound in the contralateral hemispace) may serve to sharpen auditory spatial tuning and thereby enhance stimulus discriminability, especially moderately large ILD levels.

2.5 Conclusions

In conclusion, our data show that response-ILD and monotic response-level BOLD tuning functions both evidence an increased response for contralateral over ipsilateral sound, i.e., binaural sound carrying an ILD indicative of a contralateral sound source or monotic sound in the contralateral ear. However, the relationship between the contralateral bias patterns shown by the responses to the two different types of sound are not closely related, indeed, responses to binaural stimuli are suppressed relative to monotic sound. This suggests that ILD sensitivity seen in the BOLD signal does not depend primarily on mechanisms related to monotic gain, but instead relies on active binaural processing mechanisms.

Our investigation of binaural interaction patterns for for ILD-bearing dichotic stimuli suggest that AC tuning to ILD is shaped by suppression of the response — particularly in posterolateral AC regions — to sounds with ILD values from 0 to 10-20 dB, but not extreme values of ±30 dB. We speculate that this inhibition is generated in sub-cortical centers by suppressive mechanisms associated with the response of ipsilaterally-tuned neurons acting on the excitatory response of contralaterally-tuned neurons. The reduction in suppression at ±30 dB ILD may possibly be a product of an increased excitatory response of ipsilaterally-tuned neurons at these extreme ILD values, which can be observed in the response-ILD functions.

The finding of contralateral tuning to ILD in the current study — in contrast to those studies that have observed a more bilateral response to ILD (Zimmer *et al.* 2006) or ITD (Woldorff *et al.* 1999) — could derive from the fact that responses were measured to a large number of parametrically-varied ILD values, from centered to eccentric, and were examined separately in multiple regions of interest in the auditory cortex. The functions derived show that tuning to ILD varies considerably by ILD level and by region. Both because the processing of binaural cues appears likely to involve a complex interplay of excitatory and inhibitory relationships between multiple populations of neurons, and because the contralateral dominance of the binaural processing system may in fact be quite minimal,on a neural level, observing a contralateral bias effect in the BOLD response to binaural cues may be dependent on careful stimulus selection and principled region of interest analyses.

Chapter 3

EXPERIMENTS 2–5: TUNING TO ILD AND ITD IN HUMAN AUDITORY CORTEX

3.1 Background

Much remains unclear about human cortical processing of binaural spatial cues. Animal lesion and neurophysiology data suggest that auditory space is processed preferentially in posterior AC (Rauschecker and Tian 2000; Furukawa and Middlebrooks 2002; Stecker *et al.* 2003; 2005a; Lomber *et al.* 2007; Harrington *et al.* 2008; Lomber and Malhotra 2008), and is dominated in each hemisphere by tuning to sound sources located in the contralateral hemifield (Middlebrooks and Pettigrew 1981; Jenkins and Masterton 1982; Thompson and Cortez 1983; Kavanagh and Kelly 1987; Rajan *et al.* 1990; Brugge *et al.* 1996; Heffner 1997; Stecker and Middlebrooks 2003; Mickey and Middlebrooks 2003; Werner-Reiss and Groh 2008). The human neuroimaging evidence, however, is more ambiguous about the dominance of contralateral tuning in AC processing of auditory space, with some studies showing a contralaterally-biased response to binaural stimuli (Krumbholz *et al.* 2005a; Palomäki *et al.* 2005; Krumbholz *et al.* 2007; von Kriegstein *et al.* 2008; Stecker and McLaughlin 2011; Johnson and Hautus 2010) and others equivalent responses in both hemispheres (Woldorff *et al.* 1999; Zimmer *et al.* 2006).

In those neuroimaging studies that do report contralateral bias, a relatively consistent finding — at least for sound stimuli lateralized by ITD or HRTF cues — is that there are hemispheric asymmetries in degree of contralateral dominance such that the left hemisphere (LH) exhibits a more contralaterally biased response to auditory space than does the right hemisphere (RH) (Krumbholz *et al.* 2005a; 2007; Getzmann

2009; Johnson and Hautus 2010).[1] These observations are supported by human lesion studies showing that RH damage/disruption is associated with localization deficits for ITD stimuli in both left and right hemispace, while LH damage/disruption is associated with deficits restricted to contralesional right hemifield sounds or generally more mild deficits (Altman *et al.* 1979; Ruff *et al.* 1981; Bisiach *et al.* 1984; Clarke *et al.* 2000; Zatorre and Penhune 2001; Spierer *et al.* 2009). Although there is relatively little animal data focusing on hemispheric processing differences or separately investigating the contribution of ITD versus ILD cues to cortical processing of auditory space, a macaque lesion study conducted by Boester (1994) showed that — while unilateral AC lesions do not cause deficits in discrimination of ILD-mediated sound source locations — they do result in elevated discrimination thresholds for ITD sounds in the contralesional hemifield, apparently more so for LH than RH lesions. In addition to suggesting a possible hemispheric asymmetry in the processing of ITD, the results from the above studies moreover imply that ILD and ITD are processed differently in the cortex. The question of whether the two cues are processed jointly or separately is also plagued by disparate levels of evidence available across the species; there is some human neuroimaging data to suggest they are processed separately in the cortex (Schröger 1996; Ungan *et al.* 2001; Tardif *et al.* 2006; Johnson and Hautus 2010), while there is little animal research beyond the Boester study to support or refute this conclusion.

The existing fMRI evidence related to human cortical processing of binaural sound is derived primarily from studies that sample auditory space sparsely, presenting relatively few binaural cue levels. Moreover, processing of ITD and ILD is rarely investigated within the same study with identical methodological and experimental paradigms. These factors have made it difficult to draw broader conclusions about

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[1] Results of MEG studies conducted by Palomäki *et al.* (2002; 2005), Salminen *et al.* (2010a),and Tiitinen *et al.* (2006) suggest the contrary, however, finding that RH is more highly modulated by auditory spatial cues.

tuning across auditory space, and to directly compare ILD and ITD processing. The aim of the present study was therefore to collect the BOLD fMRI response to parametrically modulated ILD and ITD cues in order to first assess whether the BOLD signal is indeed tuned to these cues, and then to measure tuning functions for each cue in pre-defined regions of interest (ROIs). Such tuning functions will provide systematic evidence about how binaural processing in human AC varies across cue values, cue types, and cortical areas — and whether hemispheric asymmetries are evident in any of these parameters. This data will help address some of the continuing questions related to binaural processing in human AC, specifically: whether there is contralateral tuning to ILD and ITD, whether tuning in either hemisphere is more contralaterally biased ("hemispheric asymmetry"), whether auditory space is processed preferentially in distinct AC regions, and whether ILD and ITD are represented jointly or separately at the level of the cortex.

In the present series of experiments, the BOLD fMRI signal was measured in response to the presentation of parametrically modulated ILD and ITD cues. Experiments 2 and 3 respectively modulated ILD and ITD cues carried by narrowband Gabor click trains with a 4 kHz carrier frequency and .5 kHz click rate/envelope frequency (designated "ILD_{GCT}" and "ITD_{GCT}"). Because this stimulus is characterized by a high carrier frequency and a strongly modulated envelope, salient ILD and ITD cues[2] can be presented within the same stimulus. *GCT* stimuli have been used previously by a number of groups employing psychoacoustic methods (Hafter and Buell 1990; Saberi 1996; Stecker and Hafter 2002; Stecker and Brown 2010) and by our lab in previous neuroimaging studies (Stecker and McLaughlin 2011). The psychoacoustic record demonstrates that listeners can localize sound based on ILD or ITD cues in *GCT* stimuli, presumably for ITD by attending to envelope as opposed

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[2] Based on the "duplex theory" of sound localization (Rayleigh 1907), ITD cues are most salient at low frequencies (the arrival of sound signals from the two ears cannot be differentiated from subsequently arriving sound waves at higher frequencies) and ILD cues at high frequencies (an object the size of the human head generates negligible ILDs at lower frequencies).

to fine structure temporal information.

To our surprise, however, initial analyses the data from Exp. 2 and 3 showed clear contralateral tuning in the AC BOLD response to ILD_{GCT}, but no such tuning to ITD_{GCT}. We therefore followed up with two additional experiments to test whether the apparent absence of tuning to ITD in the BOLD signal was specific to the ITD_{GCT} stimulus, perhaps due to reduced AC sensitivity to envelope as opposed to fine structure ITD, or to reduced salience of the ITD_{GCT} cue because of the high carrier frequency and relatively fast click modulation rate. Experiment 4 presented the same parametrically modulated values of ITD carried by broadband noise burst trains ("ITD_{NBT}"), and Experiment 5 the same ITD cues carried by lowpass noise ("ITD_{LPN}"), both of which stimuli carry highly salient envelope and fine structure ITD cues. "ITD_{LPN}" was included to control for the possibility that subjects' auditory spatial processing systems could be predominantly driven by the centered (0 dB) *ILD* cue present and particularly salient at the higher frequencies in the broadband *NBT* stimulus. (See further description of carrier stimuli below in Section 3.2.2.) All four experiments were carried out separately, but used the same experimental design, equipment, and imaging paradigm. In order to facilitate visualization and comparison of results, however, the methods, analyses, and results for all four experiments are presented jointly herein.

Binaural level-response functions plotted for BOLD responses collected showed clear contralateral tuning in both hemispheres to ILD_{GCT}, particularly in posterior AC regions and Heschl's gyrus, and modest contralateral tuning in the LH to ITD_{NBT} and ITD_{LPN} stimulation. Because they showed the most tuning, more extensive ROI-based averaging analyses were carried out on the responses to ILD_{GCT} and ITD_{NBT} stimuli, which confirmed the initial finding of robust posterior contralateral tuning to ILD in both hemispheres, but also revealed a hemispheric asymmetry in which LH was slightly more sensitive to ILD than was RH. This same asymmetry was more evident in the response to ITD_{NBT}, which exhibited contralateral tuning only in LH.

Tuning was observed primarily in posterior regions and Heschl's gyrus, but there was also modest sensitivity in anterior regions for both cues. Although the degree of AC tuning differed greatly between ILD_{GCT} and ITD_{NBT}, the present results did not yield compelling evidence to suggest that ILD and ITD are processed separately at the level of the AC. Disparities across parameters differentiating responses to the two cues, i.e., presence of contralateral tuning and hemispheric response asymmetries in contralateral bias, may simply be an artifact of the weaker tuning to ITD_{NBT}, rather than the differential effects of distinct processing mechanisms.

3.2 Methods

3.2.1 Subjects

Ten subjects between 18 and 35 years old participated in each experiment (Exp. 2: 5 female, Exp. 3: 5 female, Exp. 4: 6 female, Ex 5: 7 female), however, the data for one subject was eliminated from Exp. 5 due to stimulus presentation problems in the MR scanner. Over the course of all four experiments 25 total subjects were involved. (A number of subjects participated in multiple experiments.) Inclusion criteria were: normal hearing (thresholds < 20 dB HL between 500–8000 Hz), adequate performance on psychoacoustic sound localization tests using ITD and ILD cues, right-handedness (score $> +40$ on the Edinburgh Handedness Inventory [Oldfield 1971]), no experience with tonal language, no known history of neurological disorder, and no contraindication to MR scanning. Informed written consent was obtained from all participants. All procedures, including recruitment, consenting, and testing of human subjects followed the guidelines of the University of Washington Human Subjects Division and were reviewed and approved by the cognizant Institutional Review Board.

3.2.2 Stimuli

Each of the four experiments consisted of modulation of a binaural cue carried by an underlying sound stimulus, which varied across the experiments. (See Figure 3.1.) The ILD_{GCT} and ITD_{GCT} stimuli used in Exp. 2 and 3, respectively, were trains of Gabor clicks: Gaussian-filtered impulses created by multiplying a 4 kHz carrier frequency cosine by a Gaussian temporal envelope with $\sigma = 221\mu s$, resulting in a bandwidth of 1.8 kHz half-max. The peak-to-peak interclick interval (ICI) was 2 ms (generating a click rate envelope frequency of .5 kHz), and the presentation rate was 4 trains of 16 clicks/s (4 Hz). Exp. 4 employed ITD_{NBT} stimuli comprising trains of 16 x 1 ms white noise bursts with a 10 ms inter-burst interval, resulting in an envelope frequency of 100 Hz. Exp. 5 presented ITD_{LPN} stimuli employing a two-octave (250–1000 Hz) noise bursts with a duration of 160 ms and on/off ramps of 20 ms.

The four underlying sound stimuli carried parametrically modulated binaural cues, with nine different cue values. In Exp. 2, the ILD_{GCT} cues were modulated according to values ranging from ±30, ±20, ±10, ±5 to 0 dB ILD, in addition to which a "silent" condition (the same underlying stimulus presented at an average binaural level or intensity of -10 dB) was also included. The various stimuli presented in Experiments 3–5 all carried ITD-only modulations ranging from ±1500, ±800, ±500, ±200, and $0\mu s$ ITD, and again included a silent condition. With the exception of the ITD value of $\pm 1500\mu s$, the set of binaural cues presented roughly cover the ecologically-valid range for humans for ILD and ITD.[3] The extreme ITD value of $\pm 1500\mu s$ was included in order to replicate aspects of a previous study in which cortical tuning was observed for ITD levels of ±500 but not $\pm 1500\mu s$ (von Kriegstein *et al.* 2008).

In each experiment, the sound stimuli were presented at an average binaural level

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[3] Given the size of the human head, ecologically valid ITD levels extend to $\sim \pm 600$ to $\pm 800\mu s$ for humans, and ILD levels to $\sim \pm 20$ to ±30 dB (Blauert 1983; von Kriegstein *et al.* 2008; Salminen *et al.* 2010b; Stecker and Gallun 2012).

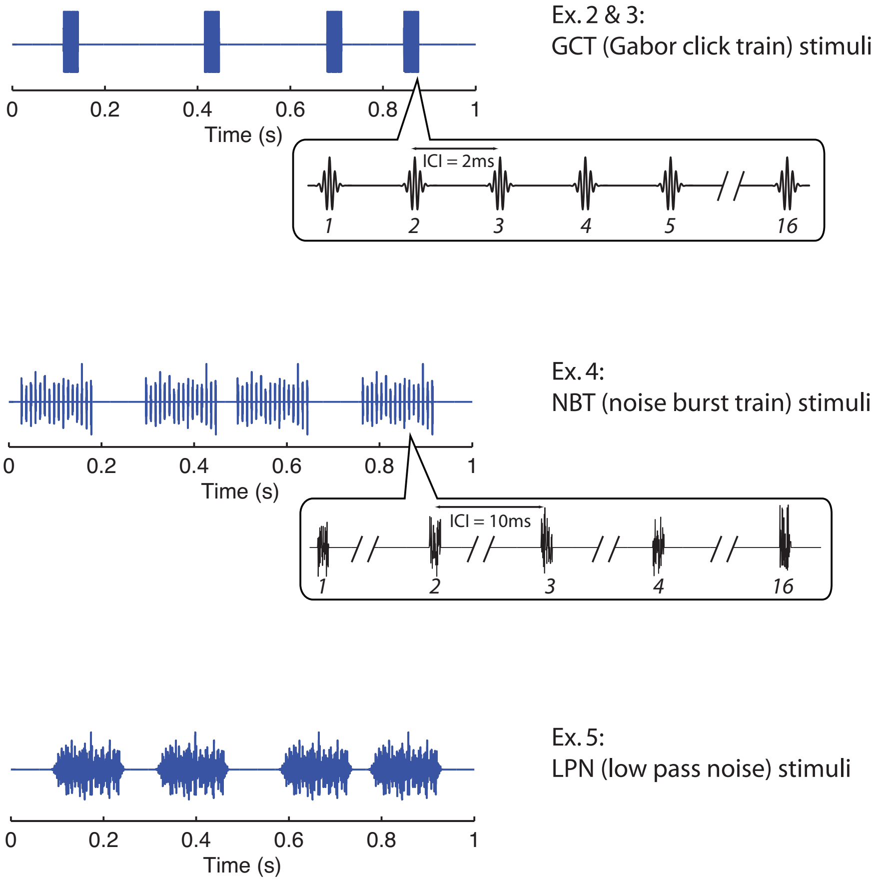

Figure 3.1: Time-frequency representations of the underlying acoustic stimuli employed in each experiment.

(ABL) of 80 dB SPL. For the ILD_{GCT} stimuli in Exp. 2, ILD levels were generated by increasing intensity in one ear while attenuating it by an equal amount in the other, thereby maintaining a constant ABL. All stimuli were 1 s in duration, occurring randomly within a 3 s stimulus window such that the interstimulus interval was jittered from 0–5 s (Matlab 7.4). Based on a continuous carryover paradigm (Aguirre 2007), each stimulus condition was presented both preceding and following every other condition for the same number of trials, thereby completely balancing for stimulus history effects. (See Figure 3.2.) Presentation of the binaural cue value conditions was thus pseudorandomly counterbalanced over 201 stimulus trials per run. Stimuli were synthesized using TDT System 3 signal-processing hardware (Tucker-Davis Technologies, Alachua FL) and presented via piezoelectric insert earphones (Sensimetrics S14, Malden MA) surrounded by circumaural ear defenders to reduce scanner noise.

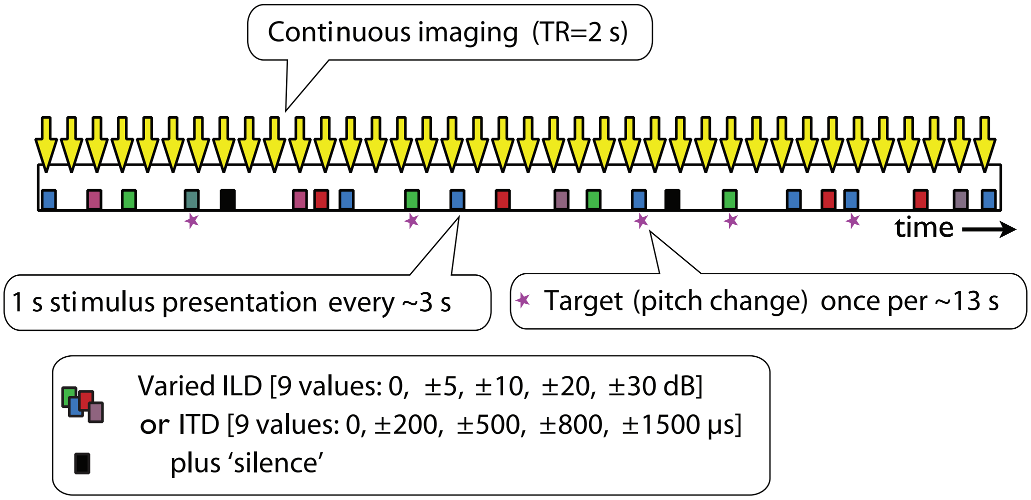

Figure 3.2: Event-related continuous-carryover paradigm, following Aguirre (2007).

3.2.3 Imaging

Imaging was performed with a Philips Achieva 3T scanner. In each of the four experiments, 10 participants underwent one scanning session (for a total of 40 sessions) lasting $\sim$ 90 minutes. A high-resolution T1-weighted whole-brain structural scan was acquired for registration with the functional scans and for extraction to the individual's cortical 2-D surface. Four echo-planar functional scans — each taking $\sim$ 8 minutes — were then acquired using a continuous event-related imaging paradigm (TR=2s, 42 slices, 2.75 x 2.75 x 3mm resolution). In contrast to Exp. 1, which employed a sparse imaging acquisition sequence, Exp. 2–5 used a continuous imaging paradigm. Robust sound-related activity was observed in pilot experiments using continuous imaging . (See Figure 3.3.)

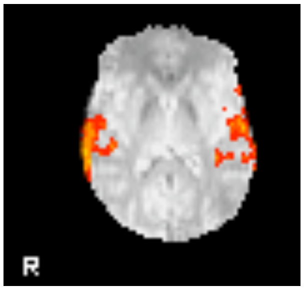

Figure 3.3: Pilot data from a single subject, collected using a continuous imaging paradigm (TR=2). Color map shows response ($p < .01$, uncorrected) to ILD_{GCT} stimulation vs. silence.

In each experiment, two of the four functional scans acquired were the parametrically modulated binaural manipulations described above, resulting in 2 x 201 stimulus presentations per subject. (The exception was Exp. 5, in which each subject participated in one functional run presenting ITD_{LPN} stimuli.) During functional scans, in order to maintain vigilance and attention to the sounds, subjects were asked to respond by right-handed button press to an infrequent pitch change (created by slightly varying the standard inter-click or inter-burst interval, and occurring randomly at an average rate of $\sim 13s$), orthogonal to the experimental manipulation. In order to minimize eye movements that may elicit confounds in the functional data, subjects were also asked to keep their eyes open and to fixate on a visual center cross displayed on a screen in the scanner via a rear projection system.

3.2.4 Analysis

Auditory cortex is located on the supratemporal cortical surface, which is a highly enfolded region of the brain in humans, exhibiting a high degree of variability both across individuals and across hemispheres within the same individual. Therefore, to ensure accurate spatial registration of the functional to structural data, we projected each individual's 3-D functional data to his/her individualized 2-D cortical surface, which provides a more accurate, subject-specific mapping of gyral and sulcul anatomy. This was accomplished by extracting each subject's 3-D structural scan, prior to analysis, to his/her subject-specific 2-D cortical surface using Freesurfer 4.1 (Martinos Center for Biomedical Imaging, MGH, Boston), which generated 3-D to 2-D registration matrices. The functional data for each run were then pre-processed, consisting of high-pass filtering (.01 Hz), motion correction, B0 unwarping, and skull-stripping carried out using the FEAT tool in FSL 4.1 (FMRIB, Oxford, UK). Noise components were identified based on independent component analyses implemented in FSL's MELODIC, and removed from the data using the regfilt function in FSL. The pre-processed data for each run were then entered into a experimental model in which the predictors were the nine levels of binaural cue value presented, silence, pitch target, and response to target. The predictor timecourses were convolved with the canonical hemodynamic response function and submitted to a first-level univariate GLM analysis in FEAT.

Using this individual first-level data, two types of analyses were conducted for each experiment: voxel-wise mapping and ROI-based averaging. For the mapping analyses, the first-level results were combined across runs for each subject by implementing higher-level fixed-effects analyses in FEAT. Each subject's cross-run 3-D functional data was projected to his/her individual 2-D cortical surface in Freesurfer using the pertinent 3D to 2D registration matrix and then morphed onto Freesurfer's template 2-D surface (FSaverage). Once the data were in a common 2-D space, spatial smoothing at 5 mm (FWHM) was applied, and a higher-level random-effects group GLM analysis was implemented in Freesurfer on the 2-D surface. (See Figure 3.4.) Except where noted, results are displayed on FSaverage at $p < .05$, corrected for multiple comparisons based on False Discovery Rate (FDR) corrections both across the whole-brain and across right and left hemisphere AC ROIs (defined on FSaverage by merging the superior temporal and transverse temporal gyrus regions specified in Freesurfer's Desikan-Killiany atlas [Desikan *et al.* 2006]).

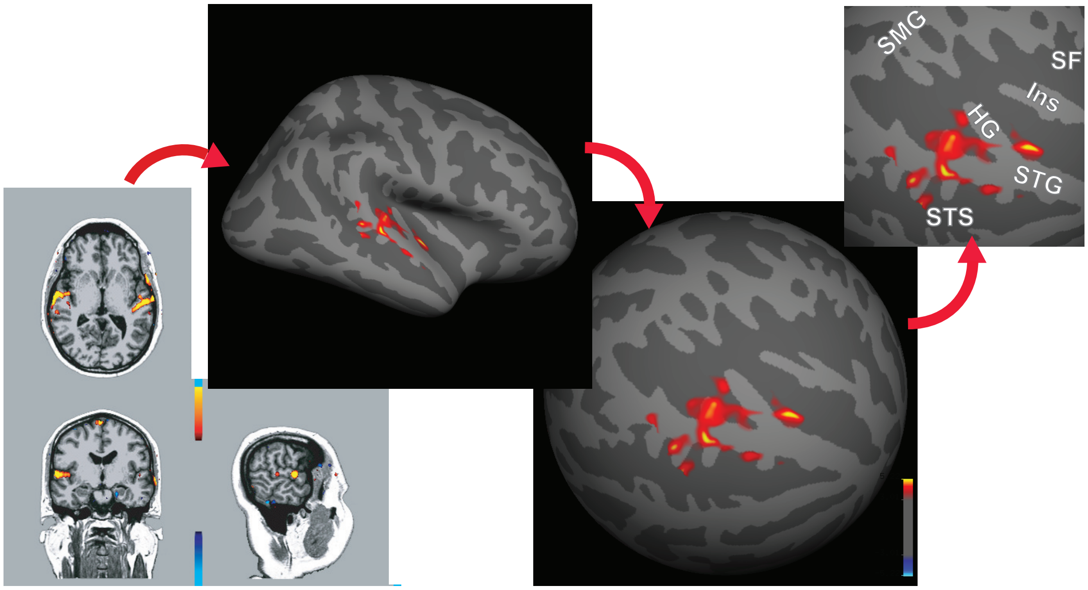

Figure 3.4: Voxel-wise mapping analysis. First-level individual 3-D functional data projected to individual's cortical 2-D surface, then morphed to Freesurfer's template 2-D surface (FSaverage) for higher-level group analysis.

For the ROI-based analyses, the AC was parcellated into three main regions in each hemisphere: Heschl's Gyrus (HG), anterior superior temporal gyrus (aSTG), and posterior superior temporal gyrus (pSTG). Subject-specific ROIs were created in Freesurfer by first defining the three regions on Freesurfer's template 2-D surface (FSaverage), based on the Desikan-Killiany atlas. The pre-defined transverse temporal gyrus region was used for HG, while the superior temporal region (which excludes HG) was subdivided into anterior (aSTG) and posterior (pSTG) ROIs with the boundary crossing STG at its intersection with HG. Then these template regions drawn on FSaverage were projected to each individual's cortical surface, creating subject-specific 2-D ROIs, which were then morphed onto the individuals' functional 3-D volumes. (See Figure 3.5.) Then, for the contrasts in the experimental model defined in FEAT, the mean BOLD signal was calculated from each subject's functional 3-D FEAT data in each of the three ROIs. For each individual, beta weights were averaged across the sound-responsive ($z > 2.3$, uncorr) voxels in each ROI. Group averages and standard error of the mean (S.E.M) across subjects were then calculated.

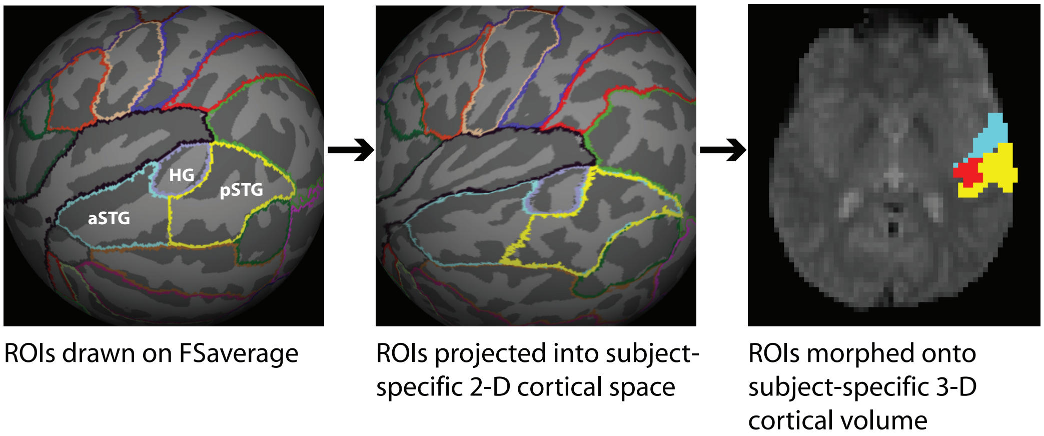

Figure 3.5: Creation of subject-specific ROIs: anterior superior temporal gyrus (aSTG), Heschl's gyrus (HG), and posterior superior temporal gyrus (pSTG).

3.3 Results

The group response to sound (all binaural level conditions added together) was mapped in AC ROIs in each hemisphere for the data from each of the four experiments. (See Figure 3.6a). The sound response in AC was highly robust for ILD_{GCT} and ITD_{NBT} stimuli, but slightly weaker for ITD_{GCT}. Subjects may not have perceived the ITD modulation carried by the ITD_{GCT} stimuli as well as they perceived the binaural modulations carried by ILD_{GCT} and ITD_{NBT}, leading potentially to increased habituation of the ITD_{GCT} response. For ITD_{LPN}, there was no significant AC response to sound when corrected for multiple comparisons, which we attribute primarily to a lack of power due to the reduced number of subjects and runs. The sound response across the whole brain was also mapped for each stimulus type (see Figure 3.6b), showing that the majority of the responses were confined to AC, and did not extend substantially to other cortical regions.

3.3.1 Binaural level response functions and hemifield-level tuning

For each underlying sound stimulus, binaural-level response functions are plotted in three ROIs: aSTG, HG, and pSTG. (See Figure 3.7.) The values plotted are based on mean beta-weights across all sound-responsive voxels in each ROI, averaged across subjects. For the ILD_{GCT} stimuli, the HG and pSTG tuning curves evidenced contralateral bias, as seen by the enhanced LH response to increasingly rightward ILD levels, and enhanced RH response to increasingly leftward ILDs. These tuning curves essentially replicate those measured for ILD_{GCT} in Exp. 1 using a sparse imaging paradigm. Also replicating the findings from Exp. 1, tuning to ILD was nonmonotonic in that the BOLD response did not decrease with increasingly ipsilateral cue levels; instead the response to extreme ipsilateral ILDs increased slightly (though less so than for contralateral ILDs). Systematic hemispheric differences in degree of contralateral bias were not evident in the ILD_{GCT} tuning curves.

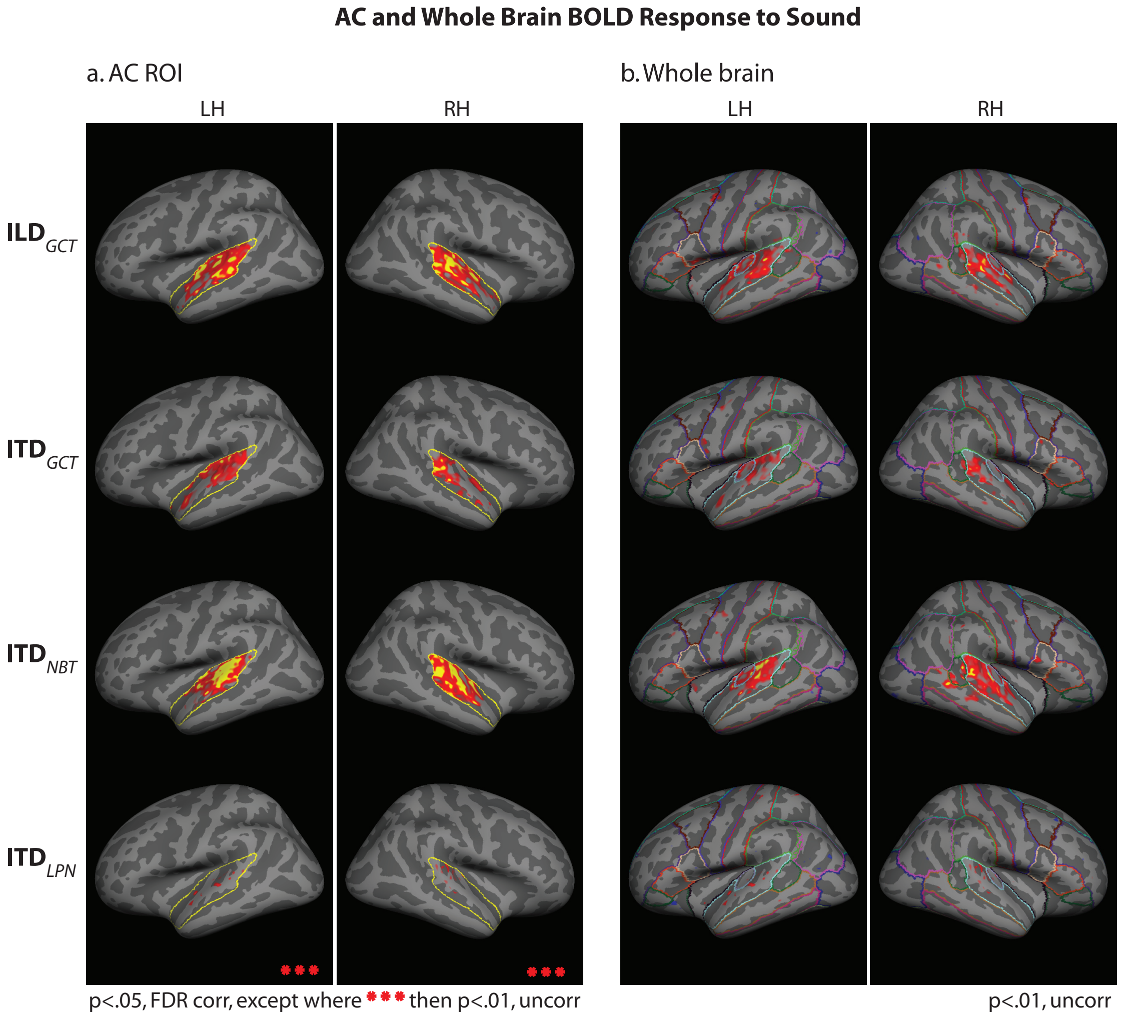

Figure 3.6: Group BOLD response to sound across experiments, displayed on Freesurfer's template 2-D surface (FSaverage). a) Response masked by AC ROI (outlined in yellow), $p < .05$, FDR corrected for multiple comparisons within AC. b) Whole-brain response, $p < .01$, uncorrected. Desikan-Killiany parcellation (Freesurfer 4.1) shown by colored outlines, for reference.

In contrast, obvious tuning to ITD was not evident in any of the ITD-based binaural level-response functions, except perhaps in the pSTG LH responses for ITD$_{NBT}$ and ITD$_{LPN}$ stimuli, which appear to exhibit a monotonic relationship to increasingly rightward ITD cues. From the tuning curves, it can also be observed that, for ITD$_{GCT}$ stimulation, LH was greater than RH response for all sound stimuli in all three ROIs, though particularly so in HG. Additionally, for all four underlying stimulus types, the response levels across the aSTG tuning curves were lower than the HG and pSTG levels.

To further investigate the hemifield-level tuning differences apparent in the binaural-level response functions, average response values are plotted in each ROI, for each sound stimulus type for three "hemifield spatial conditions" comprising leftward (L3), centered (C3), and rightward (R3) cue values. (See Figure 3.8.) For the ILD$_{GCT}$ stimuli, L3 cue values are -30, -20, and -10 dB; C3 values are -5, 0, and 5 dB; and R3 values are 10, 20, and 30 dB. For all of the ITD-based stimulus types, the $\pm 1500\mu s$ data points were excluded from this analysis because this cue lies outside the ecologically valid range of ITDs associated with human-sized heads. The ITD L3 cue values are therefore -800, -500, and -200μs; C3 values are -200, 0, and 200μs; and R3 values are 200, 500, and 800μs. Significant differences are noted, based on t-tests between RH versus LH responses for left and right hemifield spatial conditions (cross hemisphere/within condition or *"inter-hemispheric"* contrasts), and between responses to L3 versus R3 stimulation for each hemisphere (within hemisphere/cross condition or *"intra-hemispheric"* contrasts).

For the ILD$_{GCT}$ stimuli, the inter-hemispheric contrast (comparing LH and RH responses to sound located in a given hemifield) was significant in aSTG for R3 stimuli (p = .0169) and trended toward significance for C3 stimuli (p = .0703). No inter-hemispheric contrasts reached significance in HG for ILD. However, in pSTG, the inter-hemispheric contrasts were significant for L3 (p = .0271) and trended toward significance for R3 (p = .0761). The ILD intra-hemispheric contrasts (indicating

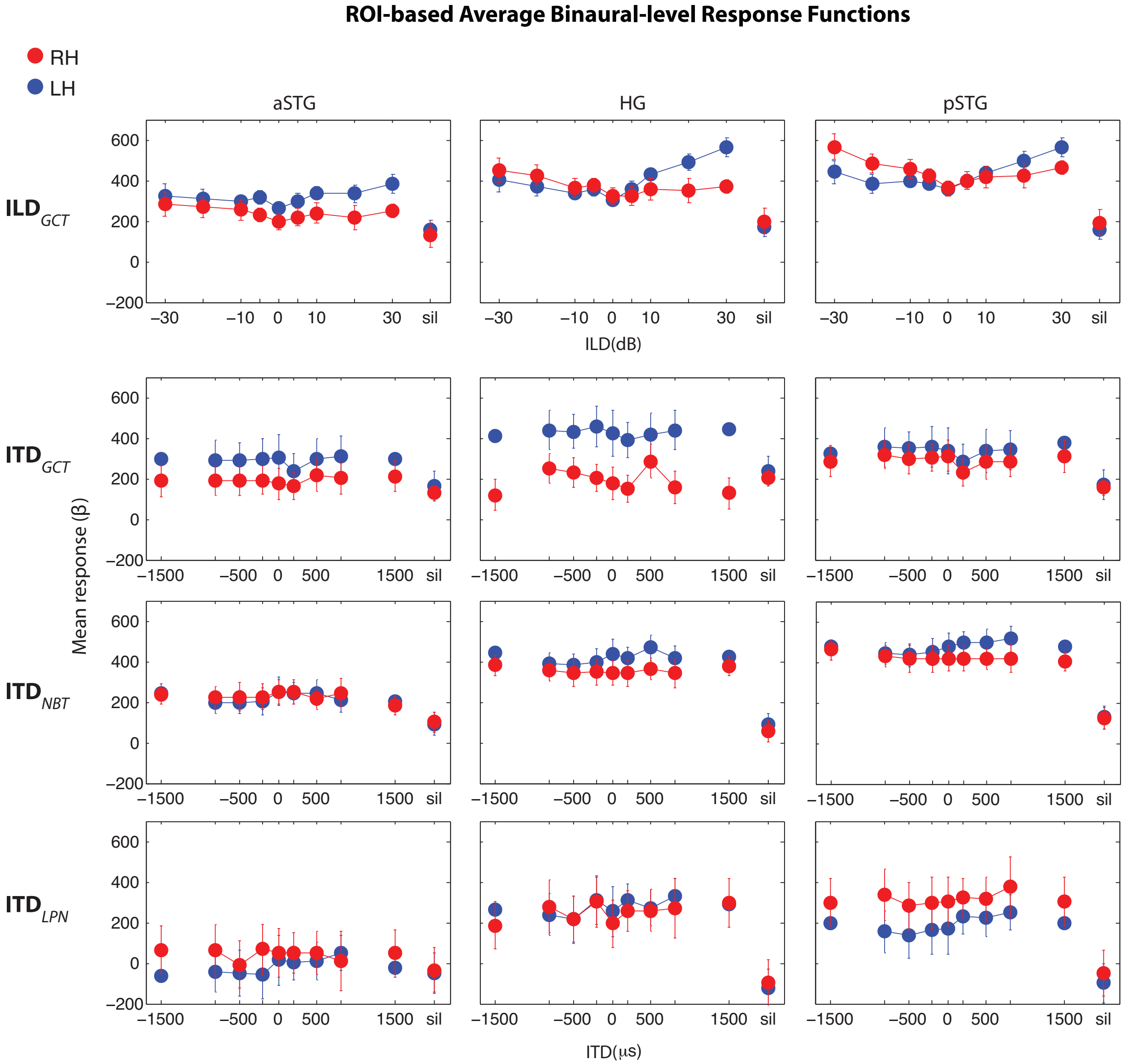

Figure 3.7: Binaural level-response functions plotted in aSTG, HG, and pSTG ROIs. Mean beta-weights for all binaural cue levels and silence are calculated for each subject across sound-responsive voxels ($z > 2.3$, uncorr) in each ROI, as defined individually on each subject's cortical surface. Data points plotted are group averages, and error bars are standard error of the mean (S.E.M.) across subjects. Sounds coming from the left side of auditory space are by convention represented as negative values, and sounds from the right as positive values. Blue points = LH responses; red points = RH responses.

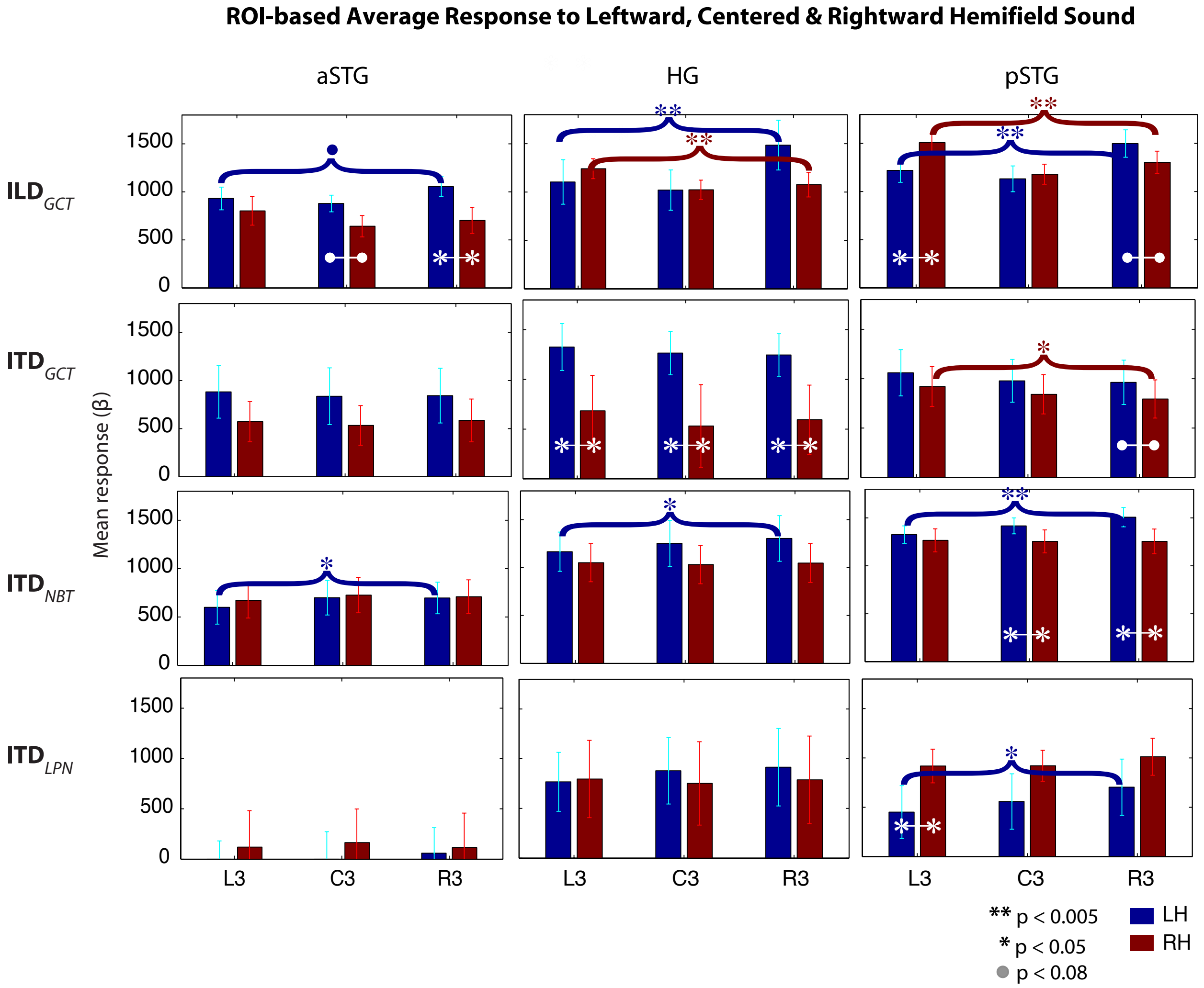
ROI-based Average Response to Leftward, Centered & Rightward Hemifield Sound

Figure 3.8: Average response values for the three leftward (L3), centered (C3), and rightward (R3) binaural cues, in each ROI, for each sound stimulus type. L3 is defined as -30, -20, & -10 dB for ILD$_{GCT}$ stimuli, and -800, -500, & -200μs for all ITD stimuli; C3 as -5, 0, & 5 dB for ILD, and -200, 0, & 200μs for ITD; and R3 as 10, 20, & 30 dB for ILD, and 200, 500, & 800μs for ITD. Error bars represent standard error of the mean (S.E.M.) across subjects. Blue bars = LH responses; red bars = RH responses. White lines extending across LH and RH bars = significant differences (or those showing a trend toward significance) between RH vs. LH responses for each spatial condition (inter-hemispheric contrast). Horizontal braces ⏞ extending across grouped binaural cue values = significant differences (or those showing a trend toward significance) between responses to L3 vs. R3 stimulation for each hemisphere (intra-hemispheric contrast). Significance levels shown at $p < .005$ (**), $p < .05$ (*), and $p < .08$ (•).

that a given hemisphere responds differently to leftward versus rightward sound) was highly significant in both HG and pSTG in both hemispheres (HG LH: $p = .0014$, HG RH: $p = .0043$, pSTG LH: $p = .002$, and pSTG RH: $p = .0014$). No clear hemispheric asymmetry was evident in these intra-hemispheric contrasts for ILD.

For the ITD_{GCT} stimuli, the inter-hemispheric contrast was significant in HG for L3 ($p = .0175$), C3 ($p = .0361$), and R3 ($p = .0224$), but this appears to reflect the high LH versus low RH response across all spatial values, rather than auditory spatial tuning. The ITD_{GCT} intra-hemispheric contrast in pSTG was significant for RH ($p = .0328$), but not LH. In contrast, for ITD_{NBT}, the intra-hemispheric comparison was significant for the LH response in all three ROIs (aSTG: $p = .0295$, HG: $p = .0081$, pSTG: $p = .0016$), indicating that LH but not RH processing of ITD_{NBT} was contralaterally biased across regions. The inter-hemispheric contrast was significant for ITD_{NBT} only in pSTG for R3 and C3 stimuli (R3: $p = .0076$, C3: $p = .0351$). For the ITD_{LPN} data, the intra-hemispheric comparison was again significant in LH but not RH pSTG ($p = .0146$). The inter-hemispheric contrast for processing L3 ITD_{LPN} stimuli was also significant in pSTG ($p = .0295$). As seen in the binaural level-response functions, the overall response across cue values was lower in aSTG than in HG and pSTG for all four underlying stimulus types.

The responses to the hemifield spatial conditions — L3, C3, and R3 — were additionally submitted to a voxel-wise mapping analysis in which the results of each subject's individual GLM analysis were projected to his/her 2-D cortical surface then to Freesurfer's template 2-D surface (FSaverage) for group GLM analysis, with results masked and FDR corrected for multiple comparisons in AC. (See Figure 3.9.) The bulk of the responses for all three hemifield spatial conditions across all four underlying stimulus types was localized in posterior AC regions. Again, the responses to the ITD_{LPN} conditions did not survive correction for multiple comparisons, but at $p < .01$, uncorrected, the responses – like those to the other underlying stimulus types – were primarily in posterior AC areas.

As in the ROI-based average analyses, the intra-hemispheric contrast — indicating whether a given hemisphere responds differently to leftward versus rightward sound — was examined. In this mapping analysis, a significant differential BOLD response ($p < .05$, FDR corrected) to contralateral versus ipsilateral sound was seen only for the ILD$_{GCT}$ stimuli in both LH and RH. The loci of this differential response was posterior to HG in LH, and both posterior and anterior to HG in RH. The uncorrected maps ($p < .01$) are shown for all of the ITD-based stimulus conditions, and appear to confirm the ROI-based averaging analysis in showing, at least for ITD$_{NBT}$ and ITD$_{LPN}$, weak contralateral tuning in LH, primarily in posterior areas. It is not surprising that the mapping analysis yielded weaker results for the intra-hemispheric contrasts than did the ROI-based analysis, given that the mapping analysis takes into account the response in *all* AC voxels — including those not responsive to sound — in aSTG, HG and pSTG regions combined, and corrects for multiple comparisons across all such voxels.

3.3.2 ILD$_{GCT}$ and ITD$_{NBT}$ level-response functions and pairwise contrasts

To investigate in more detail the binaural tuning suggested by the hemifield spatial condition analyses (Section 3.3.1), inter- and intra-hemispheric contrasts were tested for matched pairs of cue values across left and right hemifields for ILD$_{GCT}$ and ITD$_{NBT}$ stimulation only, as these conditions showed the strongest and most consistent tuning effects in the hemifield analyses. The “pairwise” inter-hemispheric contrasts were t-tests comparing the LH versus RH response to ±30db, ±20dB, and ±10dB for ILD$_{GCT}$, and to $\pm1500\mu s$, $\pm800\mu s$, and $\pm500\mu s$ for ITD$_{NBT}$. The intra-hemispheric contrasts were t-tests comparing a given hemisphere’s response to contralateral versus ipsilateral stimulation at particular cue values: 30v-30, 20v-20, and 10v-10 dB for ILD$_{GCT}$, and 1500v-1500, 800v-800, and 500v-500μs for ITD$_{NBT}$. (See Figure 3.10.) The $\pm1500\mu s$ data points were included in this analysis to replicate aspects of a study by von Kriegstein *et al.* (2008) in which contralateral tuning was

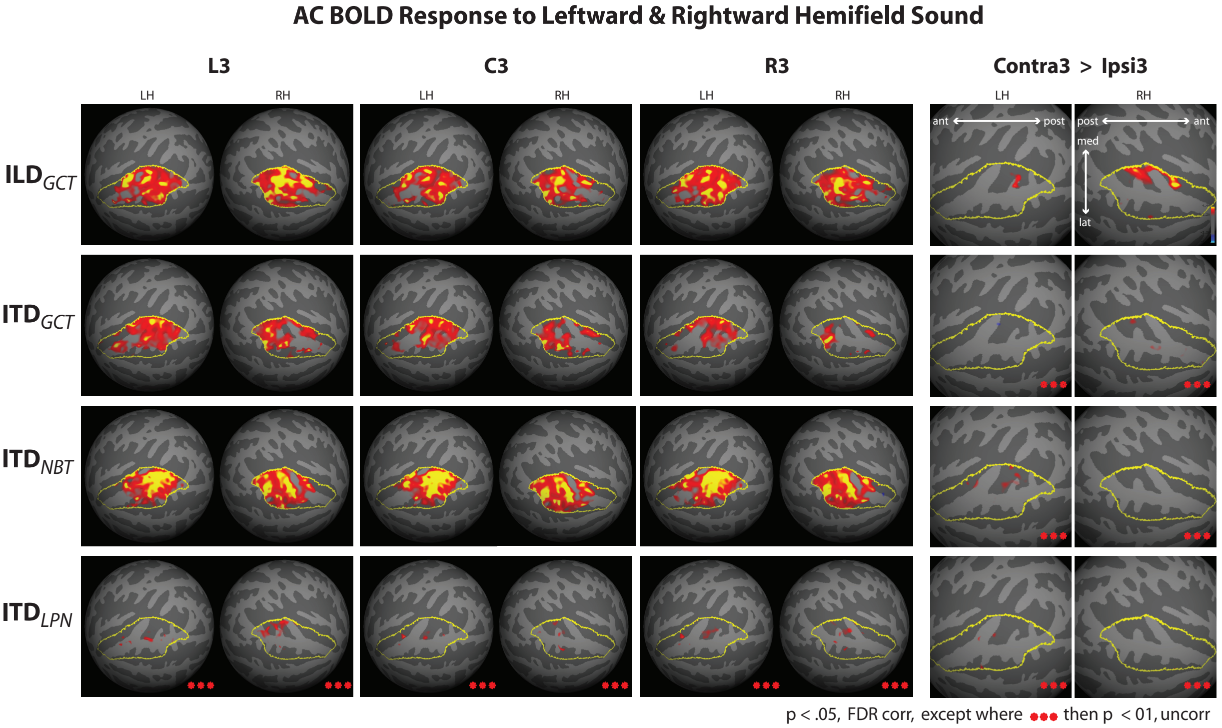

Figure 3.9: Group AC BOLD response in each stimulus condition to the three leftward (L3) and three rightward (R3) binaural cues, and also to the difference in response to the Contralateral 3 vs. Ipsilateral 3 cues. Voxel-wise responses displayed on Freesurfer's template 2-D surface (FSaverage) at $p < .05$, corrected for multiple comparisons (FDR) in AC (outlined in yellow), except where noted.

observed to ITD carried in lowpass noise stimuli at ±500 but not $\pm 1500\mu s$.

For ILD$_{GCT}$, the inter-hemispheric contrasts between LH versus RH responses were significant in pSTG for leftward -30 db ($p = .0159$) and -20 db ($p = .0241$), and rightward 20 db ($p = .0517$) and 30 db ($p = .0224$); in HG for no cue values (although the difference between LH and RH responses to 30 dB trended toward significance at $p = .0737$); and in aSTG for all of the rightward cue values (10 dB: $p = .0234$, 20 dB: $p = .0297$, 30 dB: $p = .0137$). The intra-hemispheric pairwise contrasts for ILD$_{GCT}$ show that the LH response to rightward stimulation differed significantly from the response to leftward stimulation at all levels tested in both pSTG (30v-30 dB: $p = .0091$, 20v-20 dB: $p = .0212$, 10v-10: $p = .0248$) and HG (30v-30 dB: $p = .0128$, 20v-20 dB: $p = .024$, 10v-10: $p = .0122$), and for 10v-10 db ($p = .0107$) in aSTG. In contrast, a significant difference in the RH response to leftward versus rightward stimulation was seen only in the pSTG for the -30v30 dB contrast ($p = .0391$), with a trend toward significance for the -10v10 dB contrast ($p = .0577$).

For ITD$_{NBT}$ stimulation, the pairwise inter-hemispheric contrasts were significant only in pSTG for the three far rightward sound levels ($1500\mu s$: $p = .0117$, $800\mu s$: $p = .0035$, and $500\mu s$: $p = .0069$), reflecting differentiation in LH and RH responses apparently generated by tuning in the LH response to increasingly rightward ITDs. Unlike ILD$_{GCT}$, the LH intra-hemispheric contrasts for ITD$_{NBT}$ were not consistently significant in any region, although the LH response was significantly greater for $800\mu s$ than for $-800\mu s$ ($p = .003$) in pSTG, and also for 500v-$500\mu s$ ($p = .0460$) in HG. Interestingly, the only significant RH intra-hemispheric contrasts for the ITD$_{NBT}$ stimuli were for -1500v$1500\mu s$ in pSTG ($p = .0449$) and aSTG ($p = .0048$). Therefore, the present results in LH but not RH are consistent with the von Kriegstein *et al.* (2008) observations of contralateral tuning in both hemispheres at ITD values of ±500 but not at $\pm 1500\mu s$.

The pairwise intra-hemispheric contrasts above were also subject to a voxel-wise mapping analysis. (See Figure 3.11.) As seen with previous analyses, the mapping

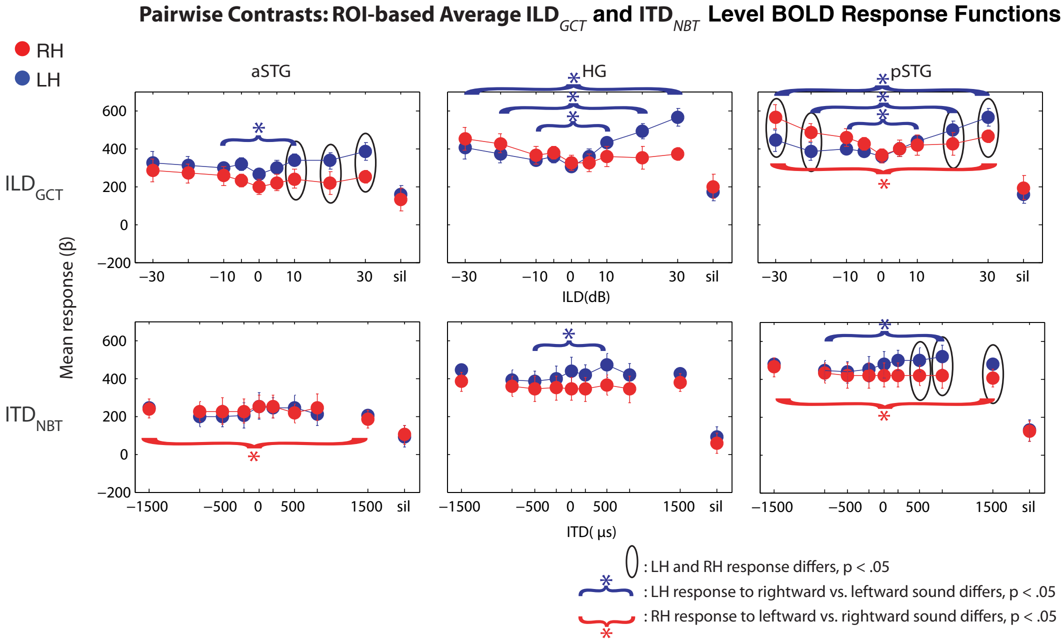

Figure 3.10: Significant pairwise contrasts identified on group binaural level-response functions plotted in aSTG, HG, and pSTG for ILD$_{GCT}$ and ITD$_{NBT}$, as per Figure 3.7. Error bars = standard error of the mean (S.E.M.) across subjects. Blue points = LH responses; red points = RH responses. Ellipses encircling LH and RH points = significant difference between LH vs. RH responses to stimulation at a given binaural cue level ("inter-hemispheric" contrast). Upward horizontal braces $\overbrace{\quad\quad}$ extending across matched cue values in left and right hemifields = significant difference in LH response to rightward vs. leftward stimulation (LH "intra-hemispheric" contrast). Downward horizontal braces $\underbrace{\quad\quad}$ extending across matched cue values in left and right hemifields = significant difference in RH response to leftward vs. rightward stimulation (RH "intra-hemispheric" contrast). Significant contrasts: $p < .05$.

analysis yielded less robust results for the intra-hemispheric contrasts than did the ROI-based average analysis, showing for ILD$_{GCT}$ stimuli significantly greater LH response to rightward versus leftward sound at 30v-30 db and 20v-20 db ($p < .05$, FDR corrected), and significantly greater RH response to leftward versus rightward sound at -30v30 dB ($p < .05$, FDR corrected). For both the LH and RH intra-hemispheric contrasts at ±30 dB, the largest region of differential response was posterior to HG, but the RH contrast was also significant in a cluster of voxels anterior to STG. The LH intra-hemispheric contrasts at 20v-20 dB elicited response loci posterior to HG and also on the anteromedial border of HG. For ITD$_{NBT}$ stimuli, the only intra-hemispheric contrast that reached significance is the LH response to 800v-800μs, with voxels located in posterior regions, paralleling the most significant intra-hemispheric contrast found in the ROI-based average analyses.

3.3.3 Leftward and rightward biased response models for ILD$_{GCT}$ and ITD$_{NBT}$

Based on a presumably simplified model in which, at a population level, neurons tuned to contralateral auditory space show increased activity with increasingly contralateralized sound, and neurons tuned to ipsilateral space show the opposite response pattern, two contrast vectors were constructed from the binaural cue values included as predictors in the GLM analysis. A "leftward-biased" vector modeled a linear increase in the BOLD response to increasingly leftward stimulation, and a "rightward-biased" vector modeled a linear increase in response to increasingly rightward sound. (Responses to ±1500μs were not included in the ITD model.) As with previous analyses, these contrasts were submitted both to ROI-based average and voxel-wise mapping analyses. The results of the ROI-based averaging analysis show the group average beta-weights across sound-responsive voxels in aSTG, HG, and pSTG representing the fit to these two models for ILD$_{GCT}$ and ITD$_{NBT}$ stimuli. (See Figure 3.12.) Again, as for hemifield spatial condition and pairwise analyses, the results for both the inter-hemispheric contrasts (differences in LH versus RH response fits to the leftward-biased model and

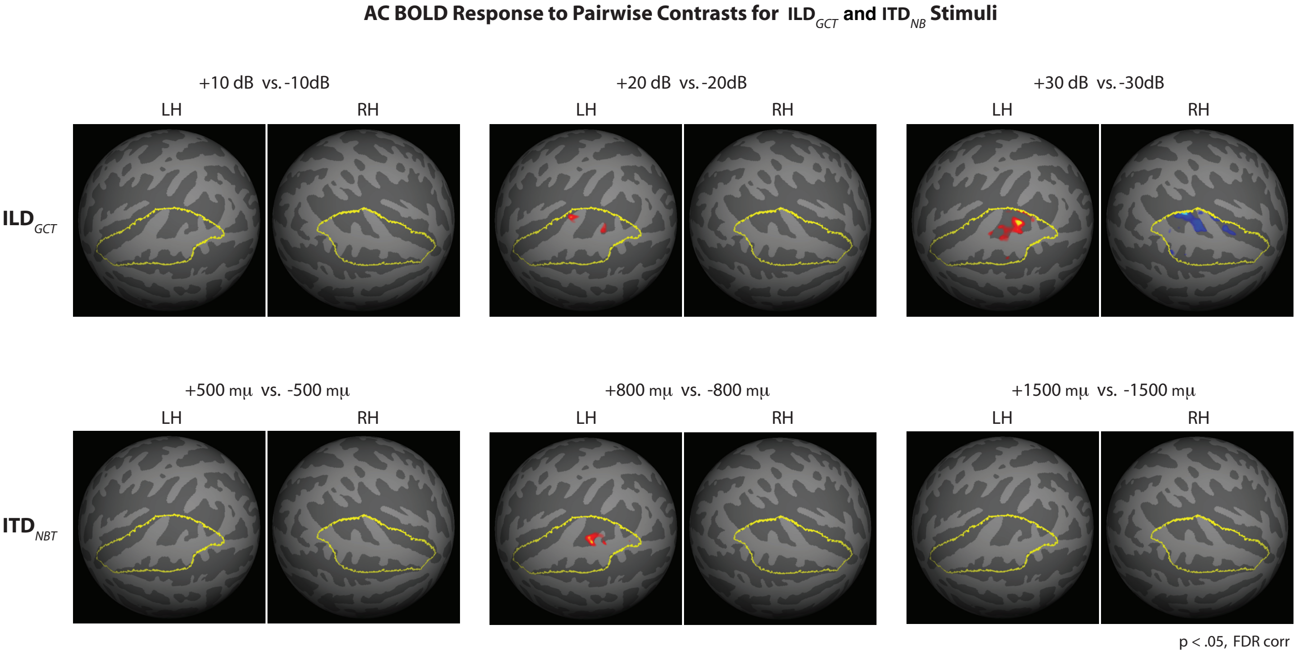

Figure 3.11: AC voxels responding significantly ($p < .05$, FDR corrected in AC, outlined in yellow) to pairwise contrasts: contralateral vs. ipsilateral stimulation at ±10 dB, ±20 dB, and ±30 dB for ILD$_{GCT}$ stimuli, and at $\pm 500 \mu s$, $\pm 800 \mu s$, and $\pm 1500 \mu s$ for ITD$_{NBT}$ stimuli. Red/yellow voxels = greater response to rightward stimulation. Blue voxels = greater response to leftward stimulation.

to the rightward-biased model) and intra-hemispheric contrasts (differences in a given hemisphere's response fit to the leftward vs. rightward-biased model) are reported.

For ILD$_{GCT}$, the inter-hemispheric contrasts show that the RH fit in pSTG was significantly better than the LH fit to the leftward-biased model (p = .0001), and conversely, the LH fit was significantly better than that of the RH to the rightward-biased model (p = .0007). In HG and aSTG, this inter-hemispheric comparison was significant only for the LH fit to the rightward-biased model (HG: p = .00005, aSTG: p = .0117), although the RH response fit to the leftward-biased model trended toward significance in both regions (HG: p = .0906, aSTG: p = .0716). The intra-hemispheric contrasts show that in pSTG, both the LH and the RH fit to the contralaterally biased model were significantly greater than to the ipsilateral model (LH: p = .0041, RH: p = .0138). This comparison was also significant for LH in HG (p = .0076) and trended toward significance for RH (p = .0687). Neither the LH nor RH intra-hemispheric contrast was significant in aSTG.

For ITD$_{NBT}$, the inter-hemispheric contrast shows that the RH fit was significantly greater than the LH fit to the leftward-biased model in pSTG (p = .0028) and in HG (p = .0372). The LH fit was significantly greater than the RH to the rightward-biased model only in pSTG (p = .0096). The only intra-hemispheric contrast that was significant showed that the LH response fit was significantly greater to the rightward as opposed to the leftward-biased model in pSTG (p = .0078), though there was a trend toward significance for the same LH intra-hemispheric contrast in HG (p = .0708).

The voxel-wise mapping analysis of the response model fits (see Figure 3.13) shows that for ILD$_{GCT}$ a large posterior area of RH AC exhibited a strong response fit with the leftward-biased model, while no voxels in LH AC showed a significant fit. Conversely, a large posterior area of LH AC evidenced a strong response fit with the rightward-biased model, while no voxels in RH AC exhibited a significant fit. For ITD$_{NBT}$, no voxels in either hemisphere showed a significant fit to either model.

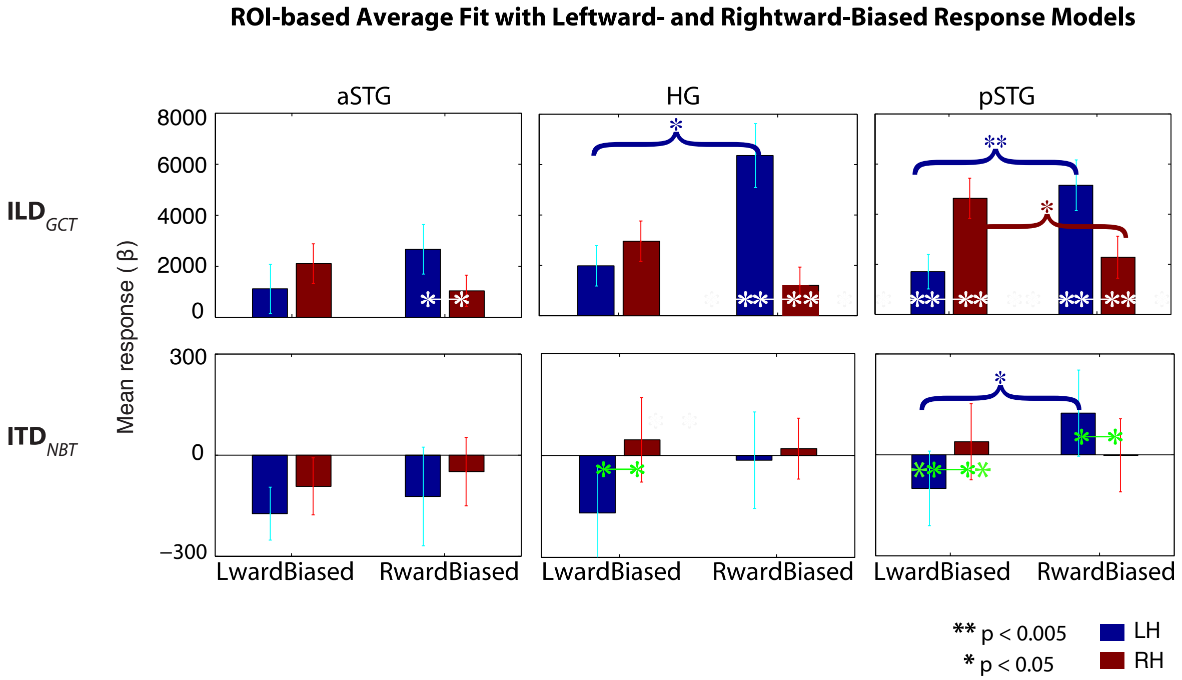

Figure 3.12: Group average fit to leftward-biased (linear increase with increasingly leftward sound) and rightward-biased (linear increase with increasingly rightward sound) response models. Plotted across aSTG, HG, and pSTG for ILD$_{GCT}$ and ITD$_{NBT}$ stimuli. Error bars represent standard error of the mean (S.E.M.) across subjects. Blue bars = LH responses; red bars = RH responses. White or green lines extending across LH and RH bars represent “inter-hemispheric” contrasts or differences in LH vs. RH response fits to leftward-biased or to rightward-biased models. Horizontal braces ⏞ extending across grouped binaural cue values represent “intra-hemispheric” contrasts or differences in fit to leftward-biased vs. leftward rightward-biased models for a given hemisphere. Significance is reported at $p < .005$ (**) and $p < .05$ (*).

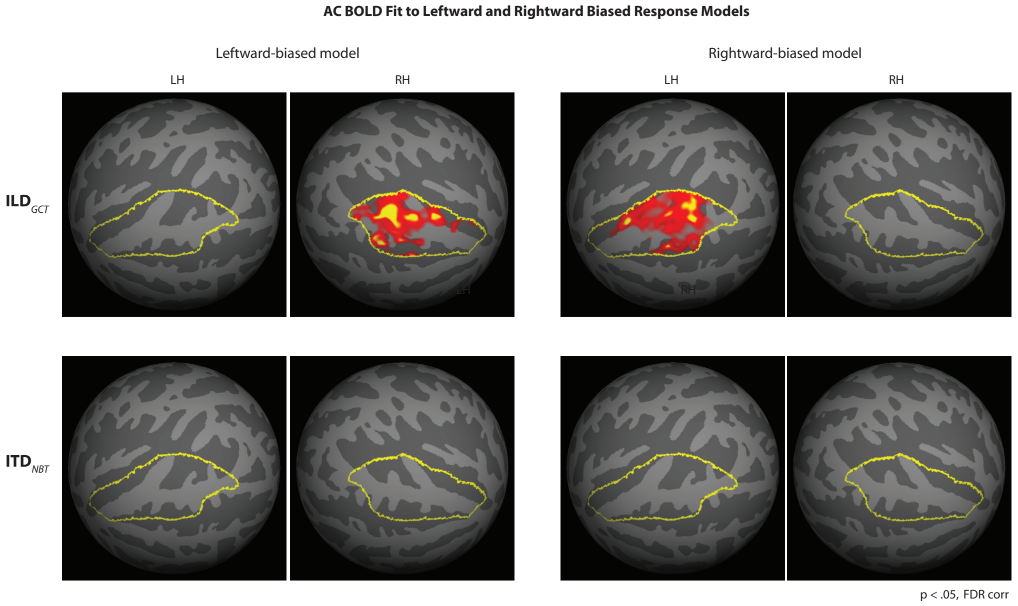

Figure 3.13: AC voxels showing a significant fit ($p < .05$, FDR corrected in AC ROI, outlined in yellow) in group mapping analysis to either leftward-biased (linear increase with increasingly leftward sound) or rightward-biased (linear increase with increasingly rightward sound) response models.

3.4 Discussion

3.4.1 Clear contralateral tuning in AC to ILD; modest contralateral tuning to ITD

The binaural level response functions plotted for ILD_{GCT} display clear contralateral tuning to ILD, primarily in pSTG and HG. They also suggest weak tuning in aSTG, which is confirmed by the hemifield-level intra-hemispheric comparisons indicating a greater BOLD response to contralateral than ipsilateral ILD in both hemispheres, in both pSTG and aSTG. The intra-hemispheric pairwise t-tests more specifically show that there is greater response to contralateral 30 than to ipsilateral -30 dB ILD, and likewise to contralateral 20v-20 dB ILD and 10v-10 dB ILD, most consistently in LH in both pSTG and HG. Overall, the intra-hemispheric contrasts, which compare responses to leftward versus rightward ILDs within a given hemisphere, appear to yield more consistent results than do the inter-hemispheric contrasts, which compare

LH and RH responses to a given ILD value. This is suggestive of a within-hemisphere code for ILD-mediated auditory space, particularly in HG and pSTG.

In contrast, the ITD level-response functions do not evidence obvious contralateral tuning to any of the ITD-based stimulus conditions, although LH responses in pSTG to ITD_{NBT} and ITD_{LPN} stimuli exhibit a weak monotonic relationship to ITD. It also appears that there is modulation of the LH response by ITD in HG in these two stimulus conditions, however, the function is far less monotonic. The hemifield t-tests confirm that the LH response to these ITD stimuli is contralaterally biased — greater for rightward than leftward sound — in pSTG, HG, and aSTG for ITD_{NBT}, but only in pSTG for ITD_{LPN}. The support offered by the pairwise comparisons for LH contralateral tuning to ITD_{NBT} stimuli in pSTG and HG is less convincing than the hemifield results, but a significantly greater response to contralateral than ipsilateral sound lateralized by $800\mu s$ ITD in LH pSTG can be seen, along with a greater response to contralateral $500\mu s$ versus ipsilateral $500\mu s$ in LH HG. Likewise, fitting the data to the contralaterally-biased response model described in Section 3.3.3 also indicates that the ITD_{NBT} stimuli only weakly fit the model in pSTG (the best fit is in LH to the rightward-biased model), while in contrast there is a high degree of fit for ILD_{GCT} stimuli in pSTG in both hemispheres, and also in LH HG.

The conclusion that the AC BOLD response is clearly contralateralally biased for ILD, but is less so for ITD, is also apparent in the voxel-wise maps of the above comparisons. Voxels that show significantly more response to contralateral versus ipsilateral sound are evident only in the ILD_{GCT} condition; no such differences are revealed in any of the ITD stimulus conditions. Likewise, the maps of voxels fitting the contralaterally-biased response models show for ILD_{GCT} that in RH there is a large area of AC exhibiting a high degree of fit to the leftward-biased model but no RH voxels fitting the rightward-biased model, while in LH the opposite pattern is seen, with a large number of voxels fitting the rightward-biased model and none fitting the leftward model. In contrast, for ITD_{NBT}, no voxels in either hemisphere significantly fit either the leftward or rightward biased model.

Based on BOLD responses to ITD carried by lowpass noise, von Kriegstein *et al.* (2008) concluded that the processing of ITD is contralaterally-biased for ecologically-valid ITD values of $\pm 500\mu s$, but not for "long" ITDs of $-1500\mu s$. The present results are consistent with this hypothesis only for LH processes, which responded more to rightward ITDs of 800 and $500\mu s$ than to leftward ITDs of the same values, but show a bilateral response to $1500\mu s$. The results for the RH response to ITD, however, contradict the findings of von Kriegstein et al., exhibiting a contralaterally biased response to long ITDs of $-1500\mu s$, but not -800 or $-500\mu s$. The effect observed in the present study is strongest for contralateral dominance in the LH response to $800\mu s$ ITD, suggesting perhaps that the conclusions of von Kriegstein and colleagues are an accurate description of ITD processing in LH, which in the present data is more tuned to ITD than is RH. It is unclear why von Kriegstein et al. did not observe this LH-dominant hemispheric asymmetry in ITD processing, but given that it is a relatively robust finding in the present study and has been shown previously in a number of other neuroimaging (Krumbholz *et al.* 2005a; Getzmann 2009; Johnson and Hautus 2010) and clinical lesion studies (Spierer *et al.* 2009), it appears to be a reasonable working hypothesis for AC processing of ITD.

The observed contralateral tuning in AC for ILD stimulation is consistent with findings in the animal neurophysiology literature (Phillips and Irvine 1981; Zhang *et al.* 2004; Higgins *et al.* 2010) and in a limited number of human fMRI (Stecker and McLaughlin 2011), EEG (Ungan *et al.* 2001), and MEG (Palomäki *et al.* 2005) studies. It was quite surprising, however, to find in the present results considerably less contralateral tuning to ITD than ILD, regardless of the underlying ITD stimulus — ITD_{GCT}, ITD_{NBT}, or ITD_{LPN} — employed. Although there are relatively few animal neurophysiology studies of cortical ITD processing, contralateral dominance is reported in the AC neural response to ITD (Reale and Brugge 1990; Fitzpatrick *et al.* 2000), in addition to which a number of human neuroimaging studies show contralateral bias in the population response to ITD (Krumbholz *et al.* 2005a; 2007; von Kriegstein *et al.* 2008), with some even reporting increased contralateral bias for ITD as opposed to ILD stimuli (Palomäki *et al.* 2005; Johnson and Hautus 2010).

The fact that ITD_{GCT} stimulation elicited minimal contralateral tuning is potentially explained by the fact that the high carrier frequency and fast modulation rate of the stimulus render the ITD cues less salient (an effect possibly exacerbated by scanner noise), although psychoacoustic studies demonstrate ITDs carried in this stimulus can be used to successfully localize sound. Moreover, it is presumed that subjects use envelope ITD cues to localize this stimulus, and there is some evidence that envelope ITD may be processed by different mechanisms than fine structure ITD (Dreyer and Delgutte 2006) which may be less strongly represented in AC. ITD_{NBT} and ITD_{LPN} — both of which carry salient fine structure ITD cues — exhibit somewhat more contralateral tuning than does ITD_{GCT} stimuli, but the contralateral dominance is still quite modest. For ITD_{LPN}, this may be due to reduced power resulting from the lower number of subjects and runs per subject. It is less obvious, however, why contralateral tuning to ITD_{NBT} stimulation is so minimal. It could be that the hypothesized rate-based opponent-channel code for ITD, reliant on increased neural activity for contralateral as opposed to ipsilateral stimulation, may in fact entail only a modest response differential across sound source hemifields (Werner-Reiss and Groh 2008), particularly for relatively simple, static acoustic stimuli, and/or without active attention to the spatial attributes of the sounds (i.e., a spatial task). Indeed, most previous neuroimaging studies that did observe more contralateral dominance in the response to ITD either involved a spatial task (Johnson and Hautus 2010), presented virtually moving stimuli (Krumbholz *et al.* 2005a; 2007), and/or found a relatively weak contralateral effect for ITD with static stimulation (Palomäki *et al.* 2005; Krumbholz *et al.* 2005a). Krumbholz *et al.* (2005a), for instance, only saw contralateral bias in the response to ITD for static sound stimulation at a relaxed statistical threshold ($p < .001$, uncorrected) in an ROI-limited analysis.

Cortical coding of ITD — possibly more than ILD — may in fact depend on engagement of attentional mechanisms through active attention to sound source location, a possibility we plan to investigate in future experiments. Additionally, the BOLD response may not be well suited for capturing cortical coding for ITD, which may rely on an interplay between excitation and inhibition generated by opponent contralateral and ipsilateral channels (Stecker *et al.* 2005b), or on a temporal code (Furukawa and Middlebrooks 2002; Stecker *et al.* 2003; Stecker and Middlebrooks 2003; Werner-Reiss and Groh 2008; Chadderton *et al.* 2009) — neither of which is well reflected in the BOLD signal. Given that naturally-occuring sound is almost always dynamically changing, it is also likely that stimulus history systematically affects binaural coding, a factor that may render it important whether stimuli are heard repeatedly (as in typical in fMRI block designs) or are presented in a more dynamic paradigm. The effects of stimulus history on the present results will be investigated in Chapter 4. Finally, it is possible that the above elements may play an important role in ILD as well as ITD encoding, and that the considerable contralateral tuning seen for ILD may partly reflect the contribution of anatomically-based contralateral monaural processing mechanisms in relevant to ILD (see Exp. 1) but not ITD processing, rendering the actual binaural contribution to contralateral ILD tuning observed herein as similarly modest as that seen for ITD.

3.4.2 Hemispheric asymmetries: greater contralateral bias in LH for ITD_{NBT} and to a lesser degree for ILD_{GCT}

Consistent with other neuroimaging (Krumbholz *et al.* 2005a; Johnson and Hautus 2010; Getzmann 2009) and clinical lesion studies (Spierer *et al.* 2009), the LH response to ITD_{NBT} stimulation showed contralateral bias — more response to contralateral rightward than ipsilateral leftward stimuli — while the RH response was essentially bilateral. This asymmetry for ITD_{NBT} can be seen in the ROI-based hemifield-level analysis which showed across all ROIs that only LH responded more to contralateral than ipsilateral stimulation; in the pairwise analysis which yielded the same result specifically for 800μs ITD in pSTG and 500μs ITD in HG; and in the response model analysis which showed that the fit for the LH response was better for the rightward- as opposed to the leftward-biased model, while the converse was not true for RH. Interestingly, the RH actually exhibited more contralateral bias than did LH only at 1500μs. One hypothesis is that this RH response reflects *perception* of the -1500μs stimulus, which is perceived as clearly lateralized. This would be consistent with the conclusions of Spierer *et al.* (2009) that RH is involved in higher-order processing of auditory space, while LH is more associated with basic coding of spatial cues, at least for ITD.

As mentioned above, there are some groups who have not observed asymmetries in contralateral bias in the response to auditory space, notably von Kriegstein *et al.* (2008). One intriguing possibility is that the processing asymmetry may be related to stimulus history effects, as suggested by EEG results from Getzmann (2009) showing that such an asymmetry was not seen in the response to HRTF stimuli presented at a slow or fast rate (presumably generating quite high or low degrees, respectively, of adaptation), while the typical asymmetry of increased contralateral bias in LH was seen for stimuli presented at a medium rate. The stimuli used by von Kriegstein et al. (2008) were presented repeatedly in blocks of 8 s, while the present data were presented for 1 s in random order in an event-related paradigm, possibly generating differential response patterns consistent with Getzmann's results.

A hemispheric asymmetry in the degree of contralateral bias in response to ILD$_{GCT}$ is less obvious in the present data, as there is no real indication of such an asymmetry in the ILD-level response functions, or the hemifield-level ROI-based averaging analysis or maps. However, the pairwise comparisons indicate that the LH response is greater to rightward as opposed to leftward ILDs at all cue levels tested in both pSTG and HG, while the RH responds more to leftward vs rightward sound only in pSTG at the 30 dB ILD level. This asymmetry is also seen in the response model fits for

ILD, which show that LH responses fit the rightward- better than the leftward-biased model in both pSTG and HG (highly significantly so in pSTG), while the converse is true for RH only in pSTG. This greater degree of contralateral bias in the LH as opposed to the RH response to ILD is not evident to any compelling degree in any of the voxel-wise maps plotted, highlighting the observation that, in the present study, the brain maps of voxels responding to given conditions (even when corrected for multiple comparisons only in AC voxels) appear to reveal only relatively gross effects that are better illuminated by average response to conditions of interest in more precise, theoretically-relevant ROIs.

3.4.3 Areal specialization in posterior regions

In the present study, the responses to ILD and ITD cues were seen mainly in posterior AC regions, as has been shown previously in other animal and human studies of auditory spatial processing (Rauschecker and Tian 2000; Warren and Griffiths 2003; Stecker *et al.* 2003; Krumbholz *et al.* 2005a; Ahveninen *et al.* 2006; Deouell *et al.* 2007; von Kriegstein *et al.* 2008). Tuning was seen to ILD_{GCT} and ITD_{NBT} in pSTG and HG, but less so in aSTG, throughout all the analyses but particularly in the binarual-level response functions, the ROI-based averaging pairwise comparisons, and response model fits. Additionally, the hemifield and pairwise maps plotting differential responses to contralateral over ipsilateral sound consistently show the effect to be located posterior to HG, either in the transverse temporal sulcus (mostly in RH) or on the posterior tranverse gyrus (primarily in LH). However, these maps do additionally show binaural tuning anterior to HG, especially in RH. Anterior tuning to ILD and ITD — while far weaker than in posterior areas — is also exhibited in ROI-based averaging analyses. In the hemifield analysis, the intra-hemispheric comparison shows that the LH response to both ILD_{GCT} and ITD_{NBT} is contralaterally-biased in aSTG, while in the pairwise analysis, LH aSTG consistently responds more than does RH to all contralateral rightward ILD values tested, and more to rightward 10 dB than leftward -10 dB ILD. It appears therefore, that the preferential posterior coding of binaural sound is a matter of degree rather than of kind, as suggested by Stecker and Gallun (2012) (see Section 1.3.5).

3.4.4 No compelling evidence for separate representations of ILD and ITD in auditory cortex

Although there is some prior evidence to suggest that ILD and ITD are represented separately at the level of the AC (Schröger 1996; Ungan *et al.* 2001; Tardif *et al.* 2006; Johnson and Hautus 2010), the present results do not provide compelling evidence to support this hypothesis. At first glance, the binaural-level response functions, the hemifield maps, and the response fit maps all appear to indicate that the AC is tuned to ILD_{GCT} but not to ITD_{NBT}. However, upon closer analysis, the data suggest that there is some tuning to ITD, and that disparities across the parameters appearing to differentiate ILD from ITD processing — i.e., presence of contralateral tuning and hemispheric asymmetries in contralateral bias — could be due simply to weaker tuning of ITD_{NBT} by the same mechanisms that process ILD_{GCT} (i.e., the seemingly greater hemispheric asymmetry for ITD may simply be revealed only at reduced response levels), rather than the differential effects of distinct processing mechanisms.

Chapter 4

EXPERIMENTS 2 AND 4: EFFECT OF STIMULUS HISTORY ON TUNING TO ILD AND ITD IN HUMAN AUDITORY CORTEX

4.1 Background

The analysis of the direct effects of ILD$_{GCT}$ and ITD$_{NBT}$ stimulation in Exp. 2 and 4 (see Chapter 3) found contralateral tuning in the BOLD AC response to ILD, but more modest tuning in the response to ITD. Additionally, an asymmetry was observed in which the left hemisphere (LH) response was more contralaterally biased than that of the right hemisphere (RH), an effect particularly apparent in the response to ITD but also revealed in more detailed analyses of the ILD data. To further investigate the processing of binaural cues in human AC, the following analyses were conducted to address the history effects of preceding binaural "adaptor" sounds on BOLD sensitivity to the ILD$_{GCT}$ and ITD$_{NBT}$ "probe" cues in the data from Exp. 2 and 4. The aim was to assess for each cue type the relationship between stimulus history and contralateral tuning, including hemispheric asymmetries in degree of contralaterality.

Auditory stimulus history effects — i.e., how the brain processes a particular dimension of a probe sound as a function of previous adaptor sounds — range from attenuation to enhancement of the probe response when probe and adaptor are matched across the dimension in question. Although stimulus history effects likely involve a complex interplay of adaptation, facilitation and other mechanisms, attenuation has been the most commonly observed effect of stimulus repetition in neurophysiological recording studies. Stimulus-specific adaptation ("SSA") is thought to play a role in the detection of sound change, a crucial element in the encoding of sound given the inherently dynamic nature of the signal. Neurophysiological recordings indicate that SSA takes place in mammalian AC on multiple time scales, from milliseconds to tens of seconds, in association with a variety of stimulus dimensions, including interaural phase disparity (Malone *et al.* 2002), frequency, and amplitude (Ulanovsky *et al.* 2003; 2004). The effects of SSA include both reduced responsiveness to stimuli with parameter values similar to the repeating stimulus and enhanced responsiveness (particularly during the sustained portion of the neural timecourse) to sounds with parameter values different from the repeating stimulus (Ulanovsky *et al.* 2003; 2004; Pienkowski and Eggermont 2009), serving to sharpen tuning and enhance stimulus discriminability. Middlebrooks *et al.* (2009), for instance, observed sharper tuning in discrete populations of cat AC neurons responding separately to stimuli varying by sound-source location that were interleaved in configurations presumably generating a percept of segregated streams than had been previously seen in response to the same sounds presented singly (see Section 1.3.3).

A number of human neuroimaging studies have reported response attenuation in association with repeated (SS or "same-same") compared to non-repeated (SD or "same-different") pairings of stimuli modulated according to ITD or HRTF values (Ahveninen *et al.* 2006; Deouell *et al.* 2007; Altmann *et al.* 2008; Schadwinkel and Gutschalk 2010), suggesting that humans also exhibit sound location-dependent SSA. Schadwinkel and Gutschalk (2010) observed a greater response in the sustained component of the BOLD timecourse to leftward probe ITD stimuli when they were preceded by rightward adaptor stimuli with ITD values $>125\mu s$. This was paralleled by an increased probability of the subjects perceiving the acoustic sequence as two segregated sound streams. Results from Exp. 1 of the current study, in which the response to ILD stimulation was greater at slower presentation rates presumably reflective of reduced adaptation, suggest that stimulus history effects play a role in ILD as well as ITD processing. This is supported by human psychophysical studies showing an effect of stimulus history on perceived laterality of probe sounds for both ITD and

ILD adaptor stimuli (Phillips and Hall 2005; Phillips *et al.* 2006; Vigneault-MacLean *et al.* 2007; Dahmen *et al.* 2010).

It is not clear whether ITD and ILD processes are affected differently by stimulus history, although results of psychophysical studies (Phillips and Hall 2005; Phillips *et al.* 2006) suggest that ITD and ILD adaptors have similar effects on the perception of sound source location. Phillips and colleagues do report that the stimulus history effect they observed was larger for high-frequency ILD stimuli in left as opposed to right hemifield, suggesting a hemifield asymmetry in the stimulus history effects associated with ILD. Getzmann (2009) observed differential effects across hemispheres in the EEG response to different rates of virtual auditory motion velocity (created by manipulating HRTF values), potentially reflecting varying degrees of adaptation of location-tuned neurons. At faster rates of motion, presumably eliciting less adaptation, both hemispheres responded similarly to leftward and rightward sound; at more moderate rates of motion, LH responded primarily to rightward sound while RH responded to sound in both hemifields, consistent with the hemispheric asymmetry observed in Exp. 2 and 4 in response to ILD_{GCT} and ITD_{NBT} stimulation, in addition to findings in other neuroimaging (Krumbholz *et al.* 2005a; Johnson and Hautus 2010; Getzmann 2009) and clinical lesion (Spierer *et al.* 2009) studies.

The continuous carryover presentation paradigm (Aguirre 2007) used in Exp. 2 and 4, in which every stimulus precedes and follows every other stimulus for the same number of trials, renders the present data particularly useful for investigating stimulus history effects. Because stimulus presentation was carefully balanced to control for history effects, the data can be analyzed as a whole to examine responses presumably independent of stimulus history ("direct effects"), or can be parceled out to investigate the effects of different stimulus history conditions at the level of individual cue values or collapsed across hemifields. Moreover, with this data set, the effects of stimulus history can be investigated across binaural cue types and across parametrically varied binaural cue values.

Investigating the change response in these data also affords the opportunity to re-examine the findings obtained in our prior analysis of the direct effects of ILD and ITD modulation on the AC BOLD response (see Chapter 3) in the context of an "fMRI$_a$" adaptation paradigm. These paradigms are used in MR research as methodological devices to illuminate effects of experimental manipulations too subtle to capture using traditional methods, particularly effects occurring at a sub-voxel resolution which may be averaged out at the sampling resolution typical of most fMRI studies (Grill-Spector and Malach 2001; Krekelberg *et al.* 2006). Investigating the change response may illuminate sensitivity, especially to ITD, not revealed in the direct-effects analyses in Chapter 3.

Lastly, the ILD$_{GCT}$ and ITD$_{NBT}$ data collected in Exp. 2 and 4 offer the opportunity to exploit the response to sound location change to investigate hypotheses about neural coding strategies in a manner similar to Magezi and Krumbholz (2010), Salminen *et al.* (2009) and Salminen *et al.* (2010b). These groups measured EEG and MEG responses to location change to determine whether observed response patterns better fit response models predicted by Jeffress' (1948) place code or were instead more consistent with an opponent-channel hypothesis. The investigators reasoned that because the place code hypothesis posits an essentially uniform density of neurons narrowly tuned to locations throughout azimuthal space, it would predict that the degree of attenuation in the response to a probe stimulus should solely reflect the magnitude of the difference between adaptor and probe sounds (the closer together the two sounds are, the more response adaptation or attenuation of the signal), regardless of the absolute location of the two sounds sources. Alternatively, the opponent-channel hypothesis — in which auditory space is encoded by the balance of activation between a larger group of neurons broadly tuned to contralateral sounds (with peaks deep inside contralateral space) and a smaller group broadly tuned to ipsilateral space — predicts that the response should be greatest the more lateralized the probe is relative to the adaptor ("outward" sound source location change), and smallest for location change toward midline (or “inward” change).

The studies by Salminen and colleagues and Magezi and colleagues found that the response to sound location change mediated by ITD or HRTF cues was the greatest for outward sound, consistent with the opponent-channel hypothesis. Both groups concluded that ITD is represented in human cortex by an opponent-channel code potentially inherited from subcortical processing centers, and that it is likely — based on the HRTF results — that ILD is also represented in the same manner. The current data offer the opportunity to replicate these studies using fMRI measures of response to both ILD and ITD stimuli, presented from multiple locations in both right and left hemifields.

4.2 Methods

4.2.1 Subjects

Ten subjects participated in Experiment 2 (ILD_{GCT}) and 10 in Experiment 4 (ITD_{NBT}), the portions of the current study for which data were analyzed in the present investigation of stimulus history effects on ILD and ITD tuning. Recruitment of subjects and information about subject characteristics is described in Chapter 3, which addresses the analysis of the data with respect to direct effects of ILD and ITD modulation on the BOLD response in human AC.

4.2.2 Stimulation and Imaging Methods

Experimental methods and imaging paradigm employed are also described in Chapter 3. Briefly, Exp. 2 (ILD_{GCT}) presented Gabor click train stimuli (4 kHz carrier frequency, bandwidth of 1.8 kHz half-max, 2 ms inter-click interval) modulated by ILD values ranging from ±30, ±20, ±10, ±5 to 0 dB ILD (plus a silent condition). Exp. 4 (ITD_{NBT}) presented noise burst train stimuli (16 x 1 ms white noise bursts) modulated by ITD values from ±1500, ±800, ±500, ±200, to $0 \mu s$ ITD (again including a silent condition). Sound stimuli were presented at an average binaural level (ABL) of 80 dB SPL, and were 1 s in duration with an interstimulus interval jittered from 0–5 s (Matlab 7.4). Based on a continuous carryover paradigm (Aguirre 2007), each stimulus condition was presented both preceding and following every other condition for an equal number of trials, thereby completely balancing for stimulus history effects. Stimuli were synthesized using TDT System 3 signal-processing hardware (Tucker-Davis Technologies, Alachua FL) and presented via piezoelectric insert earphones (Sensimetrics S14, Malden MA) surrounded by circumaural ear defenders to reduce scanner noise. Subjects were asked to respond by right-handed button press to infrequent pitch changes, and to fixate their eyes on a visual center cross displayed on a screen to minimize eye movements. A structural scan and 4 functional EPI scans were collected for each subject using a continuous imaging paradigm (3T, TR=2s, 42 slices, 2.75 x 2.75 x 3mm resolution).

4.2.3 Analysis

The methods used to pre-process and analyze the direct effects of ILD_{GCT} and ITD_{NBT} modulation are described in Chapter 3. The same methods, including ROI-based averaging and voxel-wise mapping analyses, were also employed in the present investigation of stimulus history effects. For the ROI-based averaging analyses, subject-specific ROIs were created in functional space. Three regions — Heschl's Gyrus (HG), anterior superior temporal gyrus (aSTG), and posterior superior temporal gyrus (pSTG) — were defined in Freesurfer 4.1 (Martinos Center for Biomedical Imaging, MGH, Boston) on the Freesurfer's template 2-D surface (FSaverage), based on the Desikan-Killiany atlas (Desikan *et al.* 2006). The pre-defined transverse temporal gyrus region was used for HG, while the superior temporal region (which excludes HG) was subdivided into anterior (aSTG) and posterior (pSTG) ROIs with the boundary crossing STG at its intersection with HG. These template regions drawn on FSaverage were projected to each individual's cortical surface, creating subject-specific 2-D ROIs, which were then morphed onto the individuals' functional 3-D volumes. Individual analyses were run using the general linear model ("GLM") in the FEAT tool in FSL 4.1 (FMRIB, Oxford, UK), and the mean BOLD signal for the contrasts in the model was calculated from each subject's functional 3-D FEAT data in each of the three ROIs. For each individual, beta weights were averaged across the sound-responsive voxels ($z > 2.3$, uncorrected) in each ROI. Group averages and standard error of the mean (S.E.M) across subjects were then calculated.

For the mapping analyses, first-level individual GLM results were combined across runs using higher-level fixed-effects analyses in FEAT. Each subject's cross-run 3-D functional data was projected to his/her individual 2-D cortical surface (previously generated by extracting each subject's data to the 2-D surface in Freesurfer) using the pertinent 3D to 2D registration matrix and then morphed onto Freesurfer's template 2-D surface (FSaverage). Once the data were in a common 2-D space, spatial smoothing at 5 mm (FWHM) was applied, and a higher-level random-effects group GLM analysis was implemented in Freesurfer on the 2-D surface. Except where noted, results are displayed on FSaverage at $p < .05$, corrected for multiple comparisons based on False Discovery Rate (FDR) corrections both across the whole-brain and across right and left hemisphere AC ROIs (defined on FSaverage by merging the superior temporal and transverse temporal gyrus regions specified in the Desikan-Killiany atlas).

4.3 Results

4.3.1 Stimulus specific adaptation for ILD_{GCT} and ITD_{NBT}

ROI-based average ILD_{GCT} and ITD_{NBT} level-response functions were plotted in aSTG, HG, and pSTG ROIs for same/different ("SD") and same/same ("SS") adaptor/probe combinations. (See Figures 4.1, B and 4.2, B. Triangles connected by solid lines indicate responses to SD stimulation, small circles connected by dotted lines represent SS stimulation.) For ILD, the response across ROIs to SS (or repeated) stimulation was attenuated in both hemispheres compared to SD responses at centered and moderate rightward probe sound values. In contrast, the response to SS stimulation was enhanced compared to SD responses for probe sounds in the left hemifield. Paired t-tests were used to test the differences at each ILD value between SS and SD responses. Because the effects involved may be quite subtle, p values up to .01 are reported; however, p values less than .05 are *italicized*. The SD response was greater than the SS response at rightward 10 dB ILD in pSTG LH (p = *.0360*) and RH (p = .0870), in HG RH (p = *.0423*), and in aSTG LH (p = .0530) and RH (p = *.0310*). In contrast, the SS response was greater than the SD response in pSTG LH at leftward -30 (p = .0711) and -5 (p = *.0438*) dB ILD; in HG LH at -20 (p = .0818) and -5 (p = .0670) dB ILD, and in aSTG LH at -20 dB ILD (p = .0650) and aSTG LH (p = *.0012*) and RH (p = *.0415*) at -5 dB ILD. Comparing the SD response functions to those generated by direct-effects analysis of the full data (see Figure 4.1, A, "Preceded by all sound"), it is evident that the shapes of the functions and relationship of LH to RH responses are quite similar. It does appear, however, that in HG the SD functions for LH and RH responses to leftward sound are more strongly differentiated than are the LH and RH responses in the "Preceded by all sound" function, suggesting that analysis of the SD change response serves to reveal sharper tuning in HG to leftward ILD sound than was observed in the direct-effects analysis.

For ITD$_{NBT}$, the response across ROIs to repeated/SS stimulation was enhanced in both hemispheres compared to the response to SD sound at centered/moderate and extreme rightward ITD values. T-tests show that the SS response was greater than the SD response at $-200\mu s$ ITD in pSTG LH (p = *.0171*) and RH (p = *.0209*), at $-200\mu s$ ITD for HG LH (p = *.0452*) and RH (p = .0768), at $200\mu s$ ITD in for HG RH (p = .0965), at $1500\mu s$ ITD in HG LH (p = *.0204*) and RH (p = *.0496*), and at $-200\mu s$ ITD in aSTG LH (p = *.0253*) and RH (p = *.0476*). The functions for

SD ITD tuning are again quite similar to direct-effects functions for the entire data set, although it appears that the slope of the SD response to leftward sound may be steeper in both RH and LH.

In order to assess the hemifield-level effects of stimulus history, ILD and ITD level-response functions were plotted across ROIs for probe sounds preceded by leftward, centered, and rightward sound. (See Figures 4.1, C and 4.2, C. Green bars indicate binaural values of adaptor stimuli.) For ILD$_{GCT}$, leftward adaptor sounds included those with ILD values of -30, -20, & -10 dB; centered included ILDs of -5, 0, & 5 dB; and rightward included ILDs of 10, 20, & 30 dB. For ITD$_{NBT}$, leftward adaptors were those with ITD values of -800, -500, & -200μs; centered were values of 0μs: and rightward included ITDs of 200, 500, & 800μs.[1] Comparing the hemifield stimulus history functions for ILD$_{GCT}$ with the direct-effects functions for the entire data set (Figure 4.1, A), it can be observed that the stimulus history functions are again quite similar in terms of shape and hemispheric relationships to the direct-effects functions; however, the effect previously evident in the SD tuning functions in which the LH and RH responses in HG to leftward sound were more differentiated than in the direct-effects analysis is seen here more specifically for leftward probe sounds preceded by rightward (and to a lesser extent, centered) adaptors. Consistent with the findings reported in Chapter 3, the response to ITD$_{NBT}$ was diminished compared to the response to ILD, and contralateral tuning is not clearly observable in any of the tuning curves. However, in pSTG and HG, both the shape of the LH response function for probes preceded by leftward sound and the shape of the RH function for probes preceded by rightward sound appear to be slightly more contralaterally tuned than do the direct-effects response functions.

To more closely examine the effects of stimulus history suggested by the binaural

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[1] The ±1500μs ITD value lies outside the ecologically valid range of ITDs associated with human-sized heads: it was included in the present study to replicate aspects of a previous study involving cues of ±500 and ±1500μs (von Kriegstein *et al.* 2008).

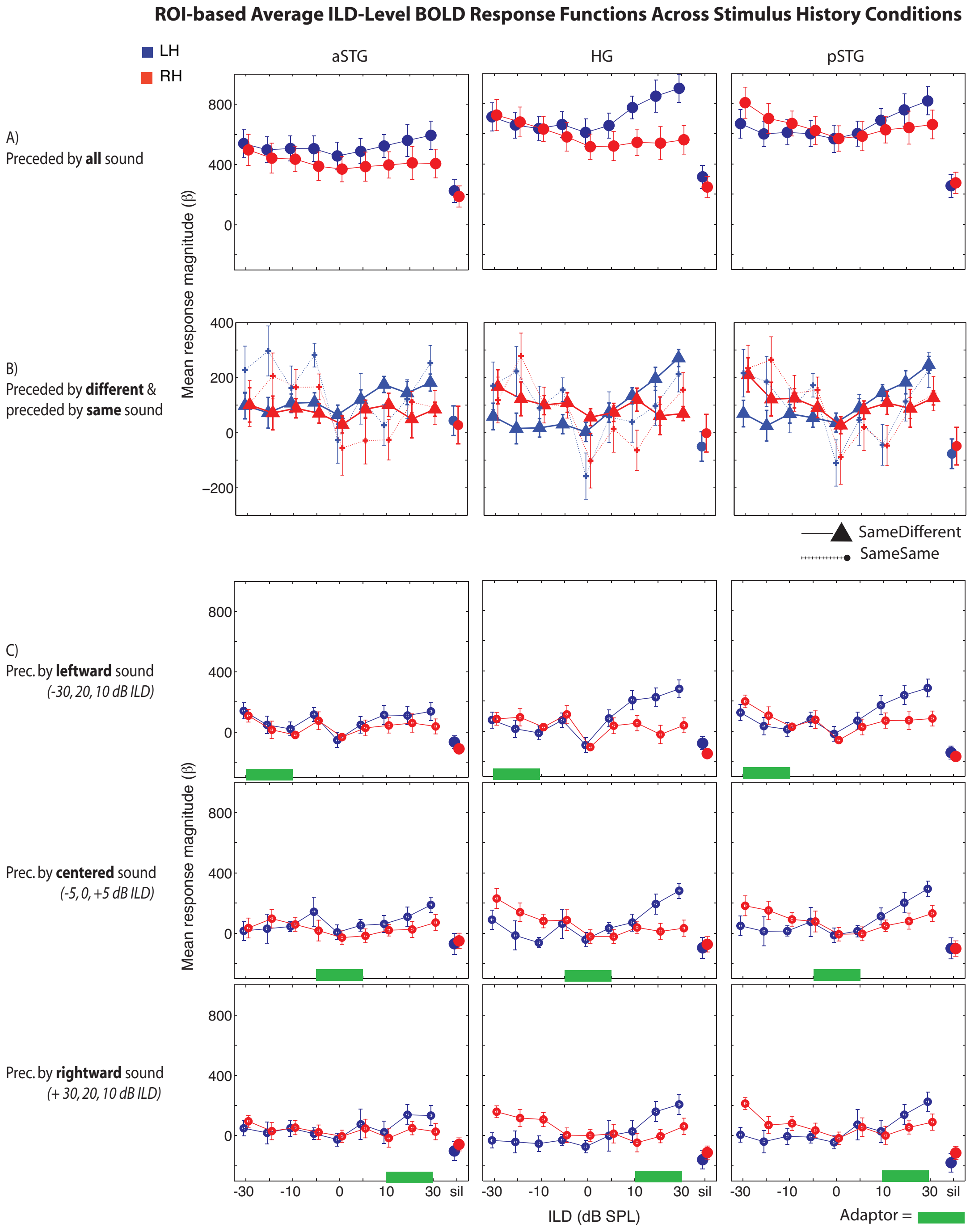

Figure 4.1: Caption on following page.

Figure 4.1: Caption continued from previous page. ILD$_{GCT}$ level-response functions in aSTG, HG, and pSTG ROIs plotted for A) all sound stimuli (balanced across stimulus history), B) same/different and same/same stimulation, and C) across stimulus history conditions. Mean beta-weights in each condition calculated for each subject across sound-responsive voxels ($z > 2.3$, uncorr) in each ROI, as defined individually on each subject's cortical surface. Data points plotted are group averages, and error bars are standard error of the mean (S.E.M.) across subjects. Sounds coming from the left side of auditory space are by convention represented as negative values, and sounds from the right as positive values. Triangles = SameDifferent; small circles = SameSame. Blue = LH responses; red = RH responses. Green bars indicate ILD values of adaptor stimuli for each stimulus history condition.

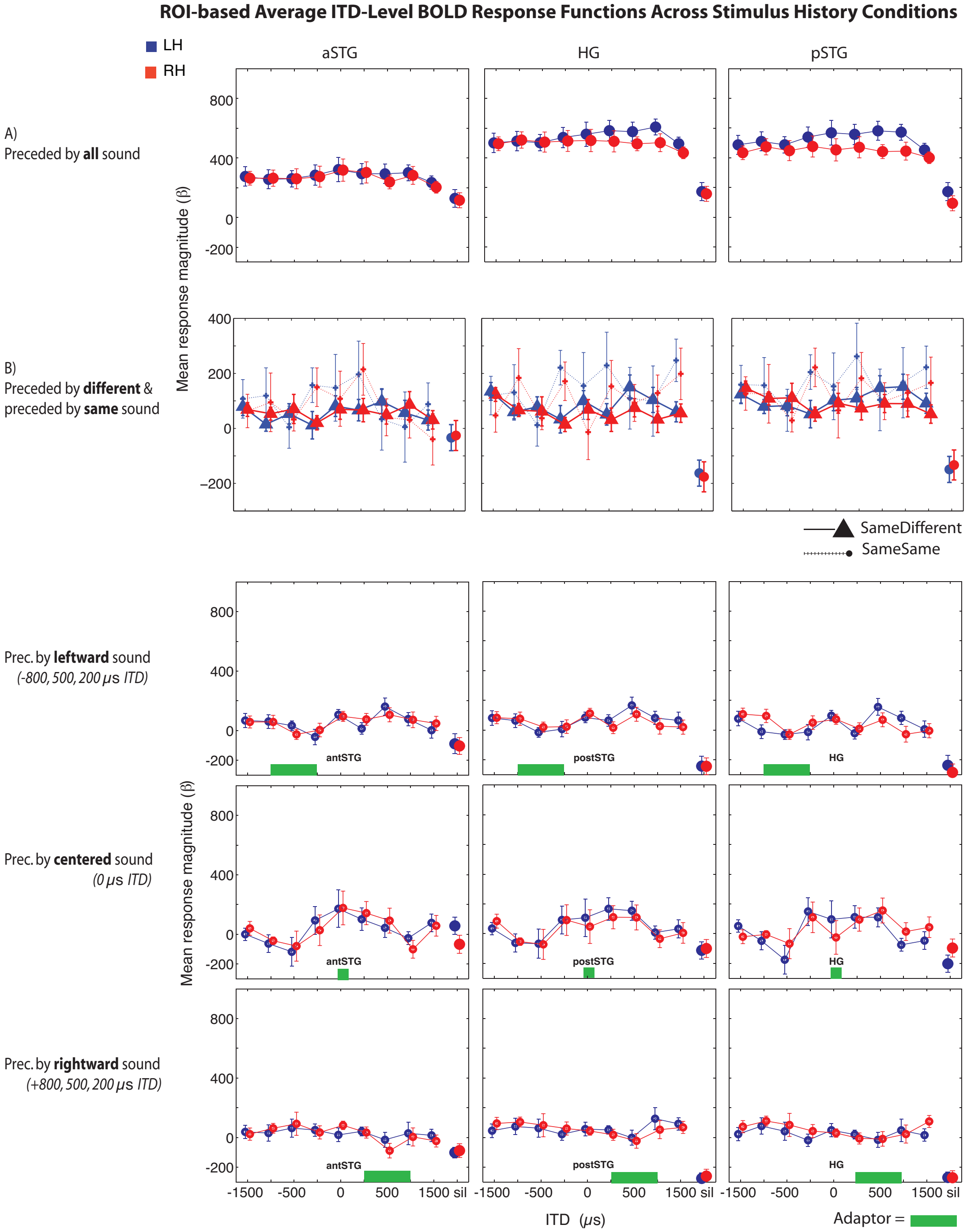

Figure 4.2: Caption on following page.

Figure 4.2: Caption continued from previous page. ITD$_{NBT}$ level-response functions in aSTG, HG, and pSTG ROIs plotted for A) all sound stimuli (balanced across stimulus history), B) same/different and same/same stimulation, and C) across stimulus history conditions. Mean beta-weights in each condition calculated for each subject across sound-responsive voxels ($z > 2.3$, uncorr) in each ROI, as defined individually on each subject's cortical surface. Data points plotted are group averages, and error bars are standard error of the mean (S.E.M.) across subjects. Sounds coming from the left side of auditory space are by convention represented as negative values, and sounds from the right as positive values. Triangles = SameDifferent; small circles = SameSame. Blue = LH responses; red = RH responses. Green bars indicate ILD values of adaptor stimuli for each stimulus history condition.

level-response functions, average values across sound-responsive voxels in each ROI were computed for ILD and ITD probe responses to the three leftward (“L3) and three rightward (“R3”) stimulus values (±30, 20, and 10 dB ILD, and ±800, 500, and $200\mu s$ ITD) when preceded by adaptors that were leftward (“PBL,” same cue values as L3), centered (“PBC,” -5, 0, and 5 dB ILD, or $0\mu s$ ITD), or rightward (“PBR,” same cue values as R3). (See Figure 4.3.) As in the direct-effects ROI-based average analyses in Chapter 3, t-tests were used to test the significance of differences 1) between RH versus LH responses for PBL, PBC, and PBR stimulus history conditions (“inter-hemispheric contrasts”), and 2) between responses to PBL versus PBR conditions for each hemisphere (“intra-hemispheric contrasts”).

For ILD_{GCT}, the only intra-hemispheric contrast that reached significance indicated that the RH response in HG to L3 sound was greater when preceded by rightward than by leftward adaptors ($p = .0316$). In pSTG, the LH response to both L3 ($p = .0815$) and R3 ($p = .0901$) probes showed a significant trend to be greater when preceded by leftward as opposed to rightward adaptors. Inter-hemispheric contrasts comparing the LH and RH response to a probe in a given stimulus history condition were significant in pSTG for the response to both L3 and R3 across all stimulus history conditions (L3PBL: $p = .0048$, L3PBC: $p = .0006$, L3PBR: $p = .00004$, R3PBL: $p = .00009$, R3PBC: $p = .0021$, R3PBR: $p = .0163$), reflecting the robust contralateral tuning to ILD seen in pSTG in the Chapter 3 direct-effects analyses. Likewise, nearly all of the inter-hemispheric contrasts in HG for both L3 and R3 probes were significant across stimulus history conditions (L3PBC: $p = .0221$, L3PBR: $p = .0244$, R3PBL: $p = .0358$, R3PBC: $p = .0445$, R3PBR: $p = .0451$), except for the response to L3 when preceded by leftward adaptor sounds, apparently reflecting the effect of stimulus history on the RH response to leftward stimuli (attenuated when preceded by leftward adaptors, enhanced when preceded by centered or rightward adaptors) previously seen in the ILD level-response functions plotted across stimulus history. Descriptively — looking at the bar plot values for ILD across stimulus history conditions — it is notable that the RH response to both L3 and R3 probe stimuli appears to change very little across stimulus history conditions, except in the HG response to L3 sound. In contrast, the LH response in pSTG and HG to both L3 and R3 probe sounds is consistently greater for probes preceded by leftward than by rightward adaptor sounds (though these comparisons only trend toward significance in pSTG).

For ITD_{NBT}, the mean response magnitudes in this hemifield-level ROI-based average analysis were again much smaller in magnitude than those for ILD. The only intra-hemispheric contrast that trended toward significance suggests that the RH response in pSTG to L3 probes is greater when preceded by rightward as opposed to leftward sound ($p = .0986$). Inter-hemispheric contrasts show that LH responded more than RH in pSTG to R3 probes across stimulus history conditions (R3PBL: $p =$ *.0147*, R3PBC: $p =$ *.0148*, R3PBR: $p =$ *.0125*), reflecting the tuning asymmetry previously seen in the direct-effects analysis in which LH shows more contralaterally biased tuning to ITD than does RH. RH also exhibits some contralateral bias, showing a greater response to L3 probe sound than does LH, but only when preceded by rightward sound (L3PBR: $p =$ *.0177*). However, again looking descriptively at the pattern of bar plot values for ITD across stimulus history conditions, it appears likely that stimulus history plays a role in shaping tuning in pSTG and HG to ITD; RH responses to L3 probes were consistently greater when preceded by rightward as opposed to leftward adaptors, and vice versa for the LH responses to R3 sound, which were slightly (but consistently) greater when preceded by leftward as opposed to rightward adaptors.

To create voxel-wise maps of the above analyses, significant BOLD responses in AC voxels ($p < .05$, FDR corrected across voxels in AC ROI) to leftward and rightward "hemifield-level" probe stimuli across stimulus history conditions were plotted on the Freesurfer's template 2-D surface (FSaverage). (See Figure 4.4.) For ILD_{GCT}, modulation of the BOLD response to probe stimuli by stimulus history condition can

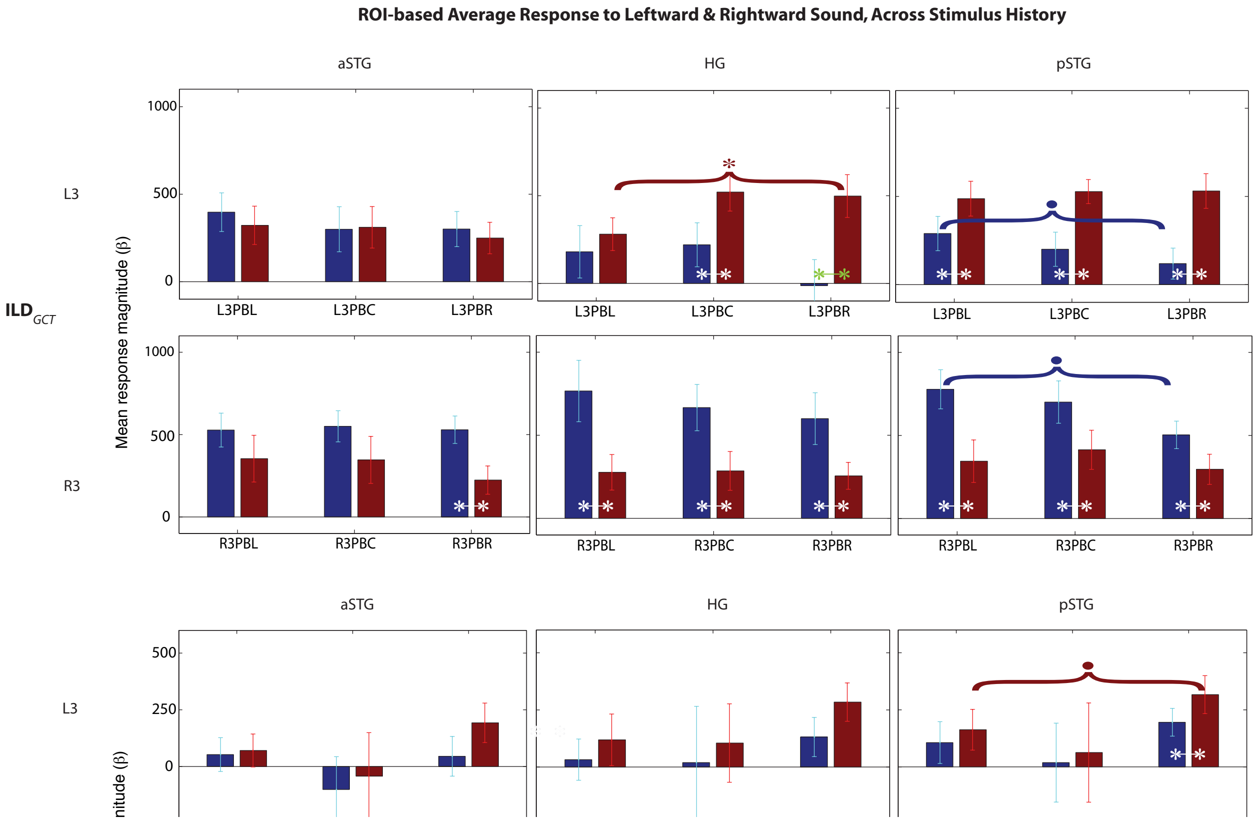

Figure 4.3: Average response values in sound-responsive voxels in each ROI to the three leftward (L3) and rightward (R3) probe stimuli when preceded by left (PBL), center (PBC), or right (PBR) adaptor sounds. L3/PBL are defined as -30, -20, & -10 dB for ILD$_{GCT}$ stimuli, and -800, -500, & -200μs for all ITD stimuli; C3/PBC as -5, 0, & 5 dB for ILD, and 0μs for ITD; and R3/PBR as 10, 20, & 30 dB for ILD, and 200, 500, & 800μs for ITD. Error bars represent standard error of the mean (S.E.M.) across subjects. Blue bars = LH responses; red bars = RH responses. White lines extending across LH and RH bars = significant differences (or those showing a trend toward significance) between RH vs. LH responses for each spatial condition (inter-hemispheric contrast). Horizontal braces ⏞ extending across grouped binaural cue values = significant differences (or those showing a trend toward significance) between responses to L3 vs. R3 stimulation for each hemisphere (intra-hemispheric contrast). Significance levels shown at $p < .05$ (*) and $p < .1$ (•).

be seen, especially in the LH response to R3 sound, which was greatest when preceded by leftward adaptors, became diminished when preceded by centered adaptors, and showed no significant response in any voxels when preceded by rightward adaptors. The RH response to L3 sound did not exhibit a consistent effect of stimulus history in this mapping analysis, with voxel-wise responses to L3 sound significant only when preceded by centered adaptor sounds. Intra-hemispheric comparisons of LH response to contralateral R3 sound when preceded by leftward versus rightward adaptors yielded no significant voxels at $p < .05$ when corrected for multiple comparisons using FDR, but at a threshold of .01 uncorrected there was greater LH response to R3 when preceded by leftward versus rightward adaptors in voxels posterior to the medial portion of HG. Only a very small area on the medial tip of HG can be seen associated ($p < .01$, uncorrected) with the opposite contrast — RH response to contralateral L3 sound when preceded by rightward versus leftward adaptors. For ITD_{NBT}, only isolated voxels can be seen to respond ($p < .01$, uncorrected) to L3 or R3 in either hemisphere, across nearly all stimulus history conditions. Notably, however, the RH response to L3 when preceded by rightward adaptor sounds was significant ($p < .05$, FDR corrected in AC) in a small area of voxels in the extreme posterior of AC.

4.3.2 Evidence regarding AC code for auditory space gleaned from stimulus history data

Magezi and Krumbholz (2010) and Salminen *et al.* (2009) put forth three different predictions about the EEG/MEG response in AC to change in sound location, each associated with a different model of neural encoding of auditory space. Jeffress' (1948) place code hypothesis, predicated on the presence of neurons narrowly tuned to locations throughout azimuthal space, predicts that the degree of attenuation in the response to a probe stimulus should solely reflect the difference in location between adaptor and probe sounds (the closer together the two sounds are, the more

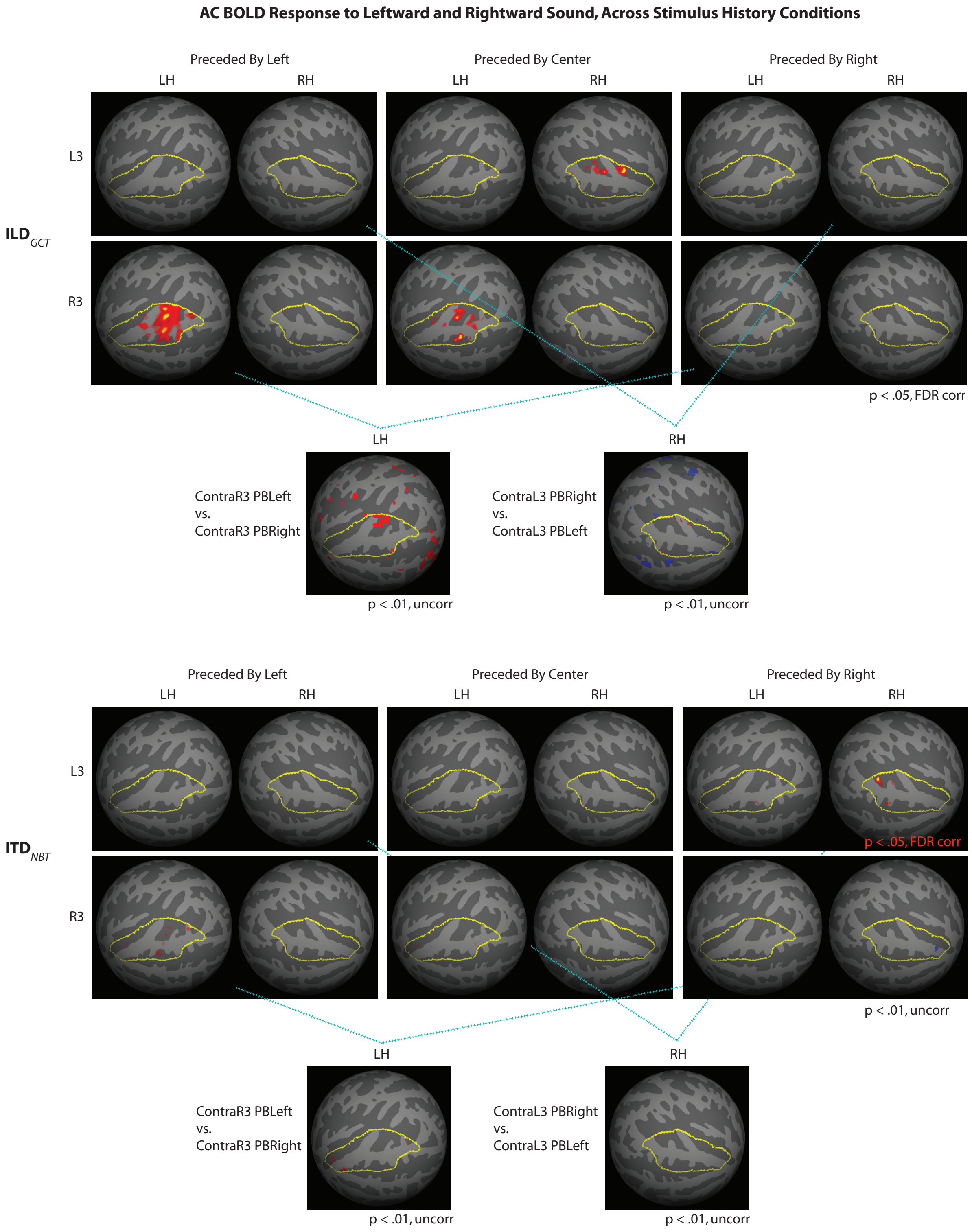

Figure 4.4: Caption on following page.

Figure 4.4: Caption continued from previous page. Group AC BOLD response for ILD and ITD to the three leftward (L3) and three rightward (R3) binaural cues, when preceded by left, center, or right adaptor sounds. L3/Left are defined as -30, -20, & -10 dB for ILD$_{GCT}$ stimuli, and -800, -500, & -200μs for all ITD$_{NBT}$ stimuli; C3/Center as -5, 0, & 5 dB for ILD, and 0μs for ITD; and R3 as 10, 20, & 30 dB for ILD, and 200, 500, & 800μs for ITD. and also to the difference in response to the Contralateral 3 vs. Ipsilateral 3 cues. Voxel-wise responses displayed on Freesurfer's template 2-D surface (FSaverage) at $p < .05$, corrected for multiple comparisons (FDR) in AC (outlined in yellow), except where noted.

attenuated the signal), regardless of the absolute location of the two sound sources. Alternatively, "centrality weighted" versions of the place code hypothesis in which more accurate auditory spatial coding at midline is driven by a greater density of midline-tuned neurons (Stern and Colburn 1978) predict that the response to adaptor/probe combinations should be greater for probes that are more centered than the adaptor ("inward" sound location change) as opposed to probes that are more lateralized than the adaptor ("outward" change). Lastly, the opponent-channel hypothesis — in which auditory space is encoded by the balance of activation between a larger group of neurons broadly tuned to contralateral sounds (with peaks deep inside contralateral space) and a smaller group broadly tuned to ipsilateral space — predicts that the response should instead be greater for outward than inward change.

To test the prediction associated with the place code hypothesis, a difference magnitude predictor was created with a quadratic shape ("quadratic magnitude difference" model) in which the smallest response was assumed for SS adaptor/probe combinations, with increasing responses (decreasing adaptation) occurring as differences between adaptor and probe binaural values increased in either direction, negative or positive. The voxel-wise fit of the data to this predictor was tested using a GLM analysis as described in Section 4.2.3, and voxels showing a significant response ($p < .05$, FDR corrected in AC ROI) were plotted on the FS average template brain. (See Figure 4.5.)

For ILD_{GCT}, no voxels in either hemisphere exhibited a significant fit with the quadratic difference magnitude response model. For ITD_{NBT}, both hemispheres showed large areas of voxels exhibiting a negative fit to the quadratic model, indicating that in these voxels there was increased sensitivity to adaptor/probe combinations with identical (same/same) or close-to-identical ITD values, and that this sensitivity diminished the greater the absolute magnitude difference between adaptor and probe ITD values became. This result is consistent with the ITD level-response functions plotted for SS and SD adaptor/probe combinations, which showed that responses were enhanced in the SS condition, particularly at centered and moderate (-200, 0, and 200μs) and extreme rightward (1500μs) ITD values.

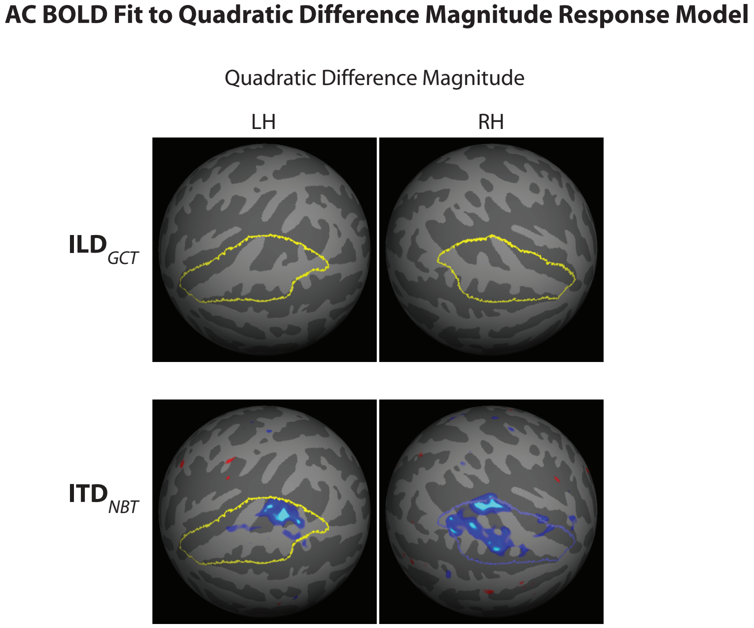

Figure 4.5: Voxel-wise fit of group average BOLD response to quadratic difference magnitude response model, $p < .05$, FDR corrected within AC ROI (outlined in yellow). Red = significant positive voxel-wise response to model. Blue = significant negative voxel-wise response to model.

To test the predictions about outward and inward sound location change associated with the "centrality-weighted" versions of the place code hypothesis and opponent-channel model, predictors were created for ILD$_{GCT}$ and ITD$_{NBT}$ adaptor/probe combinations simulating outward sound location change ("Out," regardless of absolute location), inward change ("In," regardless of absolute location), outward change only for adaptor/probe combinations left of midline ("OutLeft"), outward change only for adaptor/probe combinations right of midline ("OutRight"), inward change only for adaptor/probe combinations left of midline (“InLeft”), and inward change only for adaptor/probe combinations right of midline (“InRight”). The voxel-wise fit of the data to these predictors was tested using a GLM analysis as described in Section 4.2.3, and voxels to contrasts of Out versus In, OutLeft versus InLeft, and OutRight versus InRight were plotted on the Freesurfer’s template 2-D surface (FSaverage) for ILD_{GCT} and ITD_{NBT}. (See Figure 4.6.) No voxels rose above a significance threshold of $p < .05$ (FDR corrected in AC) for any contrast, so voxels responding at $p < .01$ (uncorrected) were plotted to explore subthreshold patterns in the data. It is notable that all subthreshold responses in AC were positive, reflecting a consistently greater response to outward as opposed to inward sound location change. Additionally, the response to OutRight versus InRight ILD was primarily in LH, while the response to OutLeft versus InLeft was in RH, as would be expected given the contralateral bias previously observed in the ILD response. The consistency and physiological plausibility of the contralaleral dominance and AC loci of these responses suggest they represent meaningful neural responses rather than just noise. Patterns in the subthreshold response to ITD_{NBT} were less clear.

Because the voxel-wise maps suggest that, at least for ILD, the contrast between outward versus inward sound location change is strongest when comparing between sound sources in the same hemifield, the responses to OutLeft, InLeft, OutRight, and InRight were submitted to an ROI-based averaging analysis to more closely explore predictions regarding outward and inward sound location change. Average values across sound-responsive voxels in each ROI in response to each of these predictors were computed for ILD and ITD data. T-tests were used to test the significance of differences for intra-hemispheric contrasts between response to outward versus inward sound within each hemisphere, and for inter-hemispheric contrasts between LH versus RH responses to each condition. (See Figure 4.7.)

For ILD_{GCT}, the LH response in HG to outward sound change in the contralateral right hemifield was significantly greater than to inward sound change (p = *.0162*),

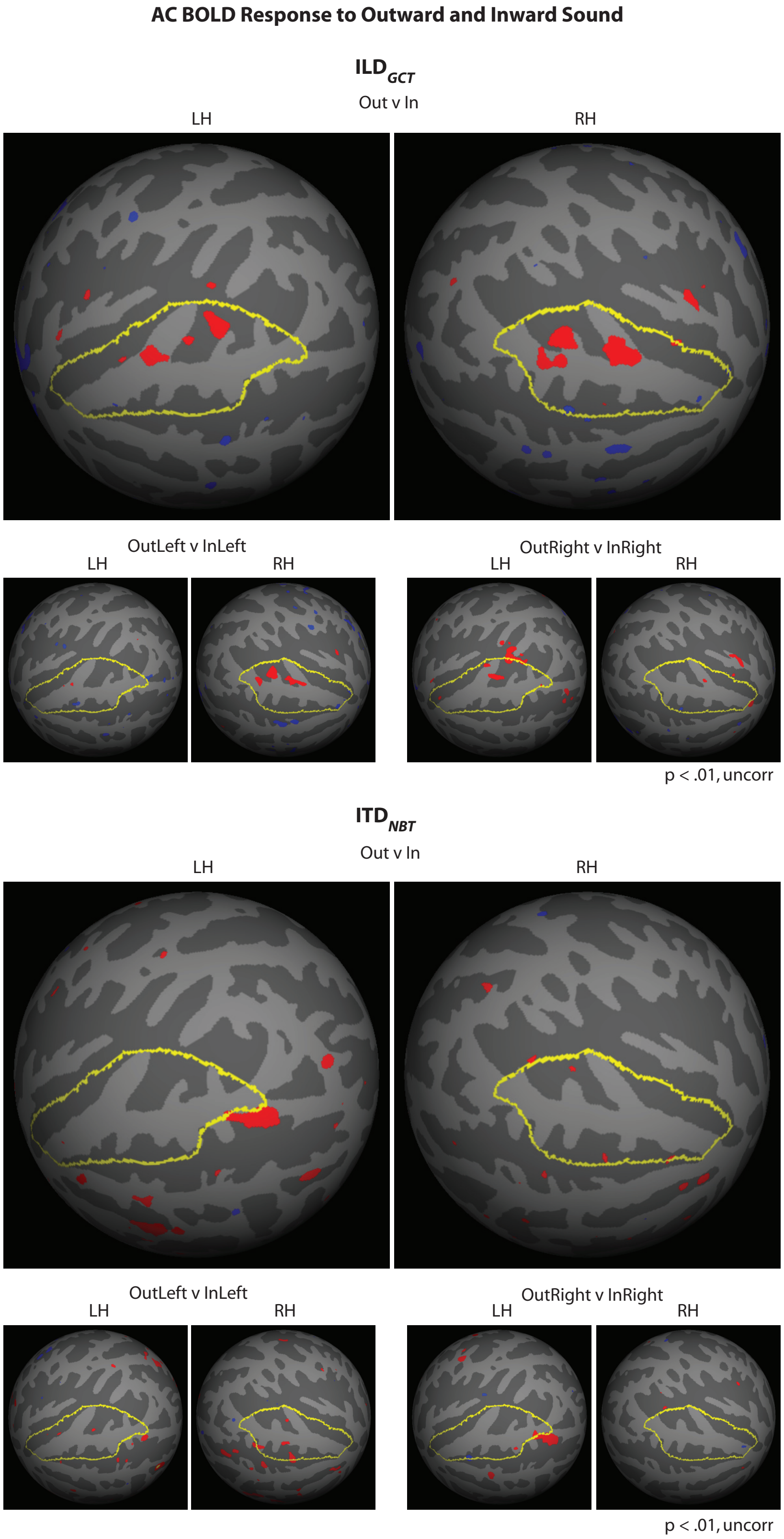

Figure 4.6: Caption on following page.

Figure 4.6: Caption continued from previous page. Group AC BOLD maps plotted on Freesurfer's template 2-D surface (FSaverage) for ILD$_{GCT}$ and ITD$_{NBT}$ for voxels responding differently ($p < .01$, uncorrected) to Out (probe stimulus more lateralized than adaptor) vs. In (adaptor more lateralized than probe stimulus) OutLeft vs. InLeft, and OutRight vs. InRight sound location changes. OutLeft and InLeft = relevant sound location changes restricted to the left hemifield. OutRight and InRight = relevant sound location changes restricted to the right hemifield. Red indicates greater response to outward sound; blue indicates greater response to inward sound. AC outlined in yellow.

and showed the same relationship in pSTG, although the difference did not reach significance ($p = .1015$). However, the magnitude of the RH response to ipsilateral right hemifield outward sound was nearly identical to that for inward sound. In contrast, the RH response to sound change in the contralateral left hemifield showed a consistent pattern of being greater for outward versus inward sound in both HG and pSTG, though the differences did not reach significance. Inter-hemispheric comparisons show that the RH was greater than the LH response to left hemifield outward sound in pSTG ($p =$ *.0008*) and HG ($p =$ *.0126*), and is also greater for left hemifield inward sound in HG ($p =$ *.0289*). LH responded more than RH to outward sound change in the right hemifield in both pSTG ($p =$ *.00007*) and HG ($p =$ *.0008*). Additionally, LH responded more than RH to right hemifield inward sound change in pSTG ($p =$ *.0253*) and aSTG ($p =$ *.0141*).

For ITD_{NBT} stimulation, intra-hemispheric contrasts show that RH responded more to outward than inward ITD sound change in the contralateral left hemifield in aSTG ($p =$ *.032*), and that there was a similar trend in pSTG ($p = .054$). However, there was also a trend in aSTG ($p = .0715$) and pSTG ($p = .0545$) for LH to respond more to ipsilateral left hemifield outward as opposed to inward sound. In pSTG RH responded more than LH to both outward ($p =$ *.0442*) and inward ($p = .0512$) sound change in the left hemifield. No intra-hemispheric contrasts were significantly different in response to ITD-mediated sound location change in the right hemifield, but LH did respond significantly more than RH to outward right hemifield sound in pSTG ($p =$ *.0114*) and showed a trend for the same relationship in aSTG ($p = .0563$). LH also trends toward responding more that RH in pSTG to inward right hemifield sound ($p = .0733$).

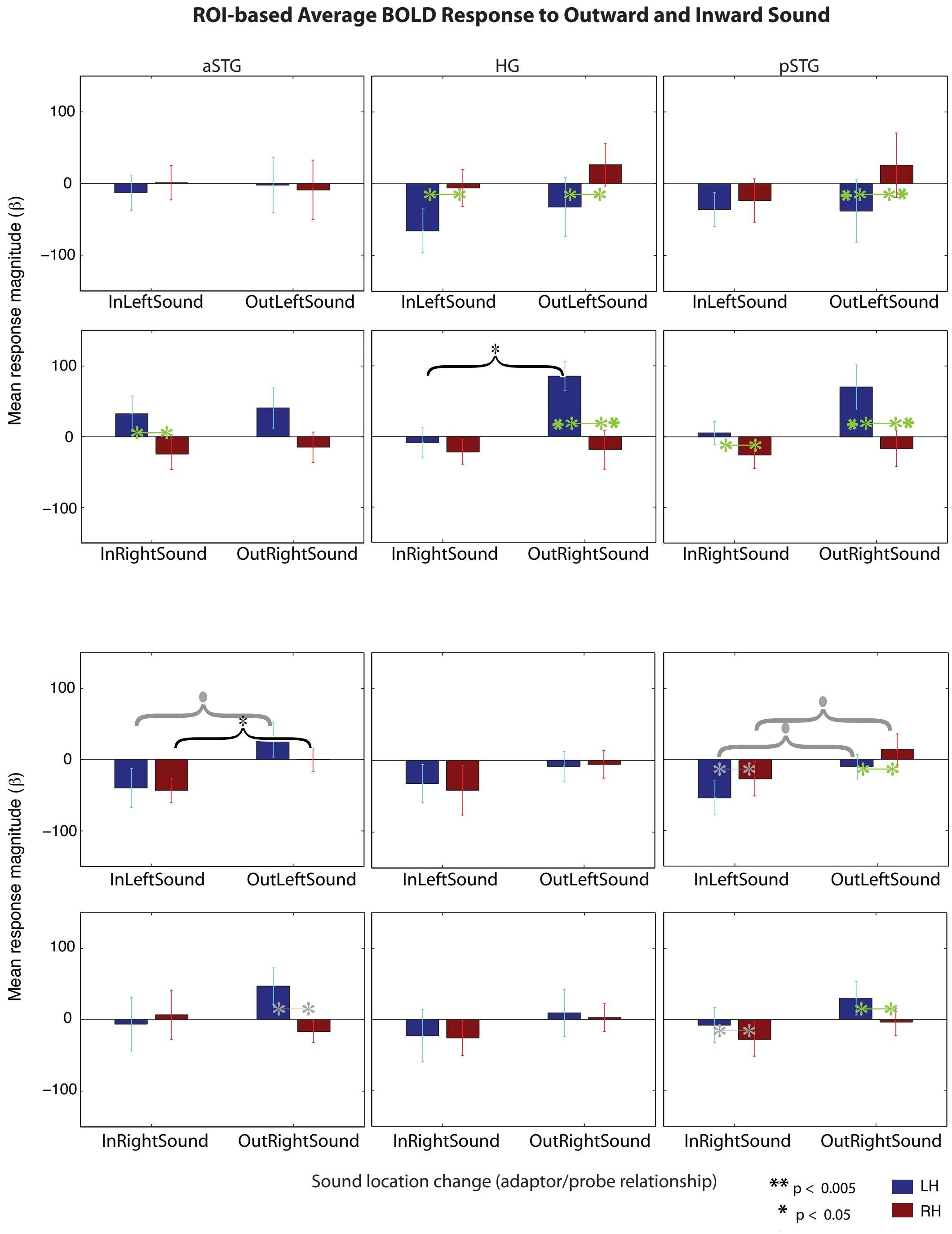

Figure 4.7: Caption on following page.

Figure 4.7: Caption continued from previous page. Average response values in sound-responsive voxels in each ROI to sound "location change" conditions: InLeft (adaptor more lateralized than probe, for stimulus pairs in left hemifield), OutLeft (probe more lateralized than adaptor, for stimulus pairs in left hemifield), InRight (adaptor more lateralized than probe, for stimulus pairs in right hemifield), and OutRight (probe more lateralized than adaptor, for stimulus pairs in right hemifield). Error bars represent standard error of the mean (S.E.M.) across subjects. Blue bars = LH responses; red bars = RH responses. White/green lines extending across LH and RH bars = significant differences (or those showing a trend toward significance) between RH vs. LH responses for each condition (inter-hemispheric contrast). Horizontal braces ⏞ extending across In and Out conditions = significant differences (or those showing a trend toward significance) between responses to In vs. Out stimulation for each hemisphere (intra-hemispheric contrast). Significance levels shown at $p < .005$ (**), $p < .05$ (*) and $p < .1$ ($\bullet$).

4.4 Discussion

4.4.1 AC BOLD response to ILD_{GCT} and ITD_{NBT} exhibits stimulus history effects

An effect of binaural adaptor sound on AC BOLD tuning to ILD_{GCT} and ITD_{NBT} probe stimuli is seen in the ROI-based average binaural level-response functions plotted across various stimulus history conditions. (See Figures 4.1, B and 4.2, B.) Comparisons of the tuning curves plotted for SS adaptor/probe combinations to those plotted for SD combinations suggest that the response to SS stimulation differs from the SD response. Although for ILD, the SS response was not significantly different than that for SD at each cue value (due partly to the high variability associated with the SS responses, for which there were relatively few trials), those cue values at which there are significant differences reveal a consistent pattern in which the response to SS stimulation is attenuated/adapted relative to the SD response for ILD cues in right hemispace, but are enhanced relative to the SD response for cues in left hemispace. This relationship can be seen in the SS/SD tuning curves across ROIs and across hemispheres. In contrast, the SS/SD tuning curves for ITD_{NBT} stimulation suggest that the SS response is enhanced compared to the SD response at ITD values near midline in both hemispheres.

At present, we do not have a clear explanation for these observations, particularly the results for ILD, which suggest that together LH and RH process left hemifield sound differently than right hemifield sound, at least in the context of sound that is changing or repeating. With respect to enhancement of midline ITD responses for SS stimulation, however, it is easier to speculate that such an effect could play some role in shaping ITD tuning, and could potentially involve channels tuned to midline, the existence of which has been hypothesized by Dingle *et al.* (2010). The lack of a consistently adapted/attenuated response for SS ILD stimulation in the current data appears to be at odds with the response attenuation observed at higher ILD stimulus presentation rates observed in Exp. 1 of the present series of studies (see

Section 3.4.4). This may be due, at least in part, to the different time course of stimulus history across experiments; Exp. 1 presented stimuli which repeated for 12 s blocks, while Exp. 2 and 4 presented 1 s stimuli followed in 3 – 5 s by the next 1 s (same or different) stimulus, a difference possibly resulting in different effects of stimulus history. The fact that the relationship between SS and SD tuning functions differs for ILD and ITD does suggest that these cues may be processed differently in AC, a hypothesis which has received some support from other neuroimaging studies (Schröger 1996; Ungan *et al.* 2001; Tardif *et al.* 2006; Johnson and Hautus 2010), but for which no compelling evidence was found in our previous analysis of the direct effects of binaural cue modulation on the AC BOLD response (see Section 2.3.5).

Visual comparison of the SD tuning functions with the all sound tuning functions appears to suggest that sound change may sharpen tuning. The LH and RH SD responses in HG to leftward ILD sound are more differentiated than they are in the all sound function. The SD functions in HG and pSTG for ITD sound look as if they may be more tuned, in each hemisphere, for contralateral sound than are the all sound ITD functions, however the differences are subtle. Because the SD functions are collapsed across all stimulus history conditions, combining across probe responses preceded by ipsilateral, contralateral, and centered adaptors, breaking the SD responses down into more detailed adaptor/probe relationships (as seen in the binaural level-response functions for stimulation preceded by leftward, centered sound, and rightward sound [Figures 4.1, C and 4.2, C]), is likely to yield more meaningful information regarding how ILD and ITD tuning functions are affected by hearing preceding binaural sounds. For ILD, visual comparisons of these stimulus history functions to the tuning curves derived from the responses to all sound stimuli (Figure 4.1, A) — which is carefully balanced to control for stimulus history conditions — indicate that the shapes of the functions and relationships across hemispheres are not materially changed in the stimulus history functions. There does appear to be an effect in HG, however, in which the presence of a rightward (or centered) adaptor attenuates the LH response in HG to left hemifield sound (and potentially enhances the RH response) relative to the all sound function, accounting for the greater differentiation between the LH and RH response to leftward sound observed previously for the SD tuning function compared to the all sound function. Comparing the stimulus history level-response functions for ITD to the all sound level-response function for ITD (Figure 4.2, A) indicate that in pSTG and HG both the shape of LH response function for stimuli preceded by a leftward adaptor and the shape of the RH function for stimuli preceded by rightward stimuli appear more contralaterally biased than the all sound ITD tuning function, particularly if responses to $\pm 1500\mu s$ stimuli are excluded from consideration.

4.4.2 Responses to probe sound in contralateral hemifield are enhanced when preceded by adaptor sound in ipsilateral hemispace

ROI-based averaging analyses for the responses to binaural sounds in left and right hemispace when preceded by leftward, centered, and rightward adaptors yield more detailed findings about the effect of stimulus history on binaural tuning, and whether these effects differ across hemispheres and cue types. For ILD, the bar plots show that the RH response in HG to contralateral leftward ILD sound was greater when preceded by ipsilateral rightward adaptor sound than when preceded by a leftward adaptor sound. Conversely, the LH response in pSTG to contralateral rightward sound showed a trend toward being significantly greater when preceded by a leftward as opposed to a rightward adaptor. This is consistent with the findings of Schadwinkel and Gutschalk (2010) for ITD-modulated sounds in which BOLD responses to leftward probe ITDs were greater when preceded by a rightward adaptor stimulus.

Consistent with the robust contralateral bias for AC BOLD responses to ILD in HG and pSTG previously observed in the direct-effects analyses, LH and RH both responded significantly more in pSTG and HG to ILD sound in the contralateral hemifield for all stimulus history conditions, excepting the HG response to leftward sound when preceded by a leftward adaptor. In this condition, the RH response was attenuated so that it no longer is significantly greater than the LH response.

Also consistent with the previous direct-effects analysis, LH appeared to show stronger contralateral tuning to ITD than did RH, responding significantly more than did RH to rightward sound, across stimulus history conditions. However, stimulus history appeared to have more of an effect on RH processing of ITD. The RH response to leftward sound was enhanced when preceded by rightward as opposed to leftward adaptors, and the enhanced RH response to leftward sound was significantly greater than was the LH response. A visual assessment of the ITD tuning curves suggests that the primary stimulus history effect described above (enhancement of contralaterally biased response when preceded by sound in ipsilateral space) is a relationship that holds true (though at a subthreshold level of significance) for the ITD data, across ROIs, in both hemispheres (though perhaps more so for the RH response). For the ILD data, the bar plot relationships suggests that this enhancement of contralateral bias with prior ipsilateral stimulation is stronger in LH, with the RH response generally not exhibiting much modulation by stimulus history. However, the one exception to this, the single significant intra-hemispheric contrast, was the RH response in HG to leftward sound, which was highly modulated by stimulus history.

The voxel-wise maps of responses to the above stimulus history conditions capture the modulation of the LH response to rightward ILD sound by stimulus history, showing the greatest response to rightward sound preceded by a leftward adaptor, diminishing response when the adaptor is centered, and no response when the adaptor is leftward. The modulation of the RH response to leftward ILD by stimulus history that was seen in the ROI-based averaged plots is not reflected in the voxel-wise map. With respect to ITD, the responses are so minimal and tuning perhaps so subtle that very few voxels show a response in any of the stimulus history conditions, even at $p < .01$, uncorrected. Notably, however, the effect of modulation by preceding rightward sound on the RH response to leftward sound is powerful enough that there is a significant voxel-wise response.

4.4.3 Greater response to "outward" adaptor/probe combinations, supporting an opponent-channel model of binaural processing

The present stimulus history data was submitted to two different analyses to test the predictions about responses to sound location change posited by the Magezi and the Salminen groups in association with different hypotheses about the neural AC code for auditory space. Maps of voxels fit to a predictor representing the absolute change magnitude in binaural value between adaptor and stimulus ("Quadratic Difference Magnitude") showed that no voxels in either LH or RH fit the model for ILD. This suggests that ILD is not coded, at least as reflected in the BOLD response, by a place code mechanism. The ITD response in both LH and RH, however, showed a significant negative fit with the Quadratic Difference Magnitude model. The implication of this result is not clear. It is unlikely to reflect the action of place coding mechanisms, but may be related to the binaural level-response functions plotted for SS and SD adaptor/probe combinations, which showed an enhanced response for repeated stimulation, particularly at ITD values close to midline.

To test predictions associated with the centrality-weighted place code and opponent-channel hypotheses, predictors for adaptor/probe combinations representing outward and inward sound location change conditions were submitted to voxel-wise mapping and ROI-based averaging analyses. No voxels rose above significance for Out v In, OutLeft v InLeft, or OutRight v InRight for either ILD or ITD, suggesting that if an effect exists, it is subtle. Subthreshold voxel responses ($p < .01$, uncorrected) were examined, and the most consistent finding was that there were no voxels in which the response to inward sound change exceeded that of outward. Voxels that showed more response to outward as opposed to inward sound change were located in or near AC, and for ILD at least, showed the expected contralateral bias with areas of greater sensitivity to OutLeft vs. InLeft sound in RH, and areas of greater sensitivity to OutRight vs. InRight sound in LH.

More sensitive ROI-based average analyses of these conditions yield bar plots that visually indicate that response to outward sound was greater than that to inward for both ILD and ITD, in all conditions, across all ROIs, confirming the results of Salminen *et al.* (2009) and Magezi and Krumbholz (2010). This supports an opponent-channel model of binaural coding in human AC. The current data further allow for comparisons of the outward sound effect for ILD and ITD, and for adaptor/probe combinations in both left and right hemifields. For ILD, the predominance of the outward location change response was strongly contralaterally biased; that is, the effect was seen most clearly for ILD in the LH response to rightward sound, and in the RH response to leftward sound. Although this pattern is clear in the relationships between the responses, the only significant effect was seen in the intra-hemispheric comparison for the LH response in HG to outward sound versus inward sound. Presumably the reason that some of the comparisons failed to reach significance is related to relatively impoverished data set which was not created to maximize trials for outward or inward sound change, but rather to balance across stimulus history conditions. The response for outward sound additionally was stronger in LH than in RH, which suggests a stronger opponent code in LH than RH for ILD. This is at odds with the speculation made by the Magezi group that RH may contain both contralateral and ipsilateral channels, but LH only a contralateral channel, at least for ITD-modulated sound (see Section 1.4.1).

For ITD, the stronger response to outward change was not as obviously contralaterally biased as it was for ILD. Significantly (or trending toward significantly) greater responses for outward as opposed to inward sound were seen for both LH and RH in response to leftward sound in pSTG and aSTG. This contrast was strongest for the RH response in aSTG, and may reflect the effect observed by the Salminen and the Magezi groups, who presented sound stimuli in the left hemifield. The aSTG locus of this response is interesting, as most of the other effects observed throughout these experiments have been in HG or pSTG. The bias toward outward sound is also seen in the LH and RH responses to rightward sound, but no intra-hemispheric contrasts reach significance and the magnitude of the responses are generally smaller. The relative lack of contralateral bias in the ITD response may, like the results in the direct-effects analysis, reflect a genuine difference between ILD and ITD processing or it may be an artifact of the diminished AC tuning for ITD, relative to ILD, observed throughout this study.

Chapter 5

GENERAL CONCLUSIONS AND FUTURE DIRECTIONS

The goal of the experiments described in the preceding chapters was to systematically characterize tuning in the human AC BOLD response to binaural stimulation. Experiment 1 investigated the relationship between spatial tuning to ILD and sensitivity to monaural level by comparing responses to monotic stimulation with those to dichotic ILD or diotic (equal intensities at each ear) stimulation. Consistent with neurophysiological data, a contralaterally-tuned ILD response function was observed, with maximal responses at extreme contralateral ILDs. The ILD tuning curve was non-monotonic, however, with responses declining at moderate contralateral and ipsilateral values but increasing again at extreme ipsilateral ILDs. Responses to monotic sound were contralaterally biased with greater responses in the AC contralateral to ear of presentation, also consistent with previous data. A comparison of the tuning to monotic gain and to ILD show that the degree of contralaterality in response to the two types of stimuli was only weakly related, suggesting that ILD is processed at least partially independently of monotic gain statistics, presumably by active spatial tuning mechanisms. The Experiment 1 data also show binaural suppression for both diotic and dichotic ILD sound in posterolateral regions, particularly at moderate ipsilateral ILD values, potentially reflecting a mechanism that could serve to actively shape the AC response to ILD.

Experiments 2 – 5 measured the BOLD response to parametrically modulated ILD and ITD to characterize AC binaural tuning across cue values, cue types, cortical regions, and stimulus history conditions. The aim was to assess whether: 1) AC tuning to ILD and ITD is contralaterally biased, 2) there is a hemispheric asymmetry in the bias, 3) particular AC regions are specialized for processing binaural cues, and 4) processing patterns are similar or different across ILD and ITD. Consistent with the findings from Experiment 1, robust contralateral tuning to ILD was observed in posterior STG and Heschl's gyrus regions. Again, the tuning curves were non-monotonic with increased responses not only to extreme contralateral ILD values, but also extreme ipsilateral values. In contrast, modest yet monotonically increasing contralateral ITD tuning was observed, only in LH, with RH showing little to no modulation by ITD. This increased sensitivity to ITD in left relative to right hemisphere has been seen in previous neuroimaging (Krumbholz *et al.* 2005a; 2007; Johnson and Hautus 2010) and clinical lesion (Clarke et al. 2000; Spierer et al. 2009) studies, but opposite patterns of contralateral bias in which the right hemisphere is more highly modulated by auditory space have also been observed (Palomäki *et al.* 2002; 2005; Tiitinen *et al.* 2006; Salminen *et al.* 2010a). In the present study, ROI-based average comparisons of responses to stimulation in left versus right hemispace at each cue level also revealed a hemispheric asymmetry for ILD, with greater differences in the response to contralateral versus ipsilateral sound in LH than RH. It is not clear whether the hemispheric asymmetries for ITD and ILD arise from the same mechanisms. Relative to ITD processing asymmetries, Krumbholz *et al.* (2007) hypothesize that RH may receive direct contralateral and ipsilateral ascending projections, while LH receives contralateral projections directly and ipsilateral projections from RH via the corpus callosum. Magezi and Krumbholz (2010) similarly propose that RH may contain both contralaterally- and ipsilaterally-tuned populations of neurons, while LH may host only contralaterally-tuned populations. Similar mechanisms may be involved in the more modest hemispheric asymmetry observed for ILD tuning; however, because ILD modulation cannot be entirely separated from monaural level gain, the asymmetry could alternatively be related to monaural rather than binaural processes.

Results from Experiments 2 and 4 indicate that tuning to ILD and ITD cues was strongest in posterior regions, but that anterior regions also showed weak sensitivity to binaural cue modulation. This is consistent with the point made by Stecker and Gallun (2012) that specialization for auditory spatial processing in posterior relative to anterior AC may involve quantitative rather than qualitative areal differences, as suggested by neurophysiological results indicating that neurons throughout AC display sensitivity to sound-souce location, though response characteristics in more caudal regions render them uniquely suited for processing auditory space (Furukawa and Middlebrooks 2002; Stecker *et al.* 2003; 2005a; Harrington *et al.* 2008).

Analyses of the stimulus history data from Experiments 2 and 4 indicate that BOLD AC responses to ILD and ITD are modulated by exposure to preceding adaptor sounds, although the effect of stimulus repetition includes both response attenuation and enhancement, which is inconsistent with previous reports of stimulus-specific adaptation, both at the level of the individual neuron (Malone *et al.* 2002; Ulanovsky *et al.* 2003; 2004; Pienkowski and Eggermont 2009) and the population response (Ahveninen *et al.* 2006; Deouell *et al.* 2007; Altmann *et al.* 2008; Schadwinkel and Gutschalk 2010). The unusual pattern of modulation by stimulus history is also inconsistent with findings from Experiment 1 showing response attenuation to fast relative to slow presentation rates, which presumably reflected response adaptation. However, regardless of the mechanism, ROI-based average analyses of stimulus history effects at the hemifield level revealed that sensitivity to contralateral stimulation was consistently enhanced by adaptor sounds in the ipsilateral hemispace. This enhancement of contralateral tuning may particularly sharpen RH sensitivity to ITD-modulated sound, serving to minimize the hemispheric asymmetry for preferential LH processing of ITD observed in the direct-effects analyses and in other neuroimaging and clinicial lesion studies. The stimulus history data were also found to replicate previous results (Salminen *et al.* 2009; Magezi and Krumbholz 2010) showing greater sensitivity to adaptor/probe combinations in which the probe was more lateralized than the adaptor ("outward" location change) than to combinations in which the adaptor was more lateralized ("inward" location change), a result that Salminen and colleagues and Magezi and colleagues interpreted as supporting opponent-channel models of binaural processing. Although the present data yielded few statistically significant differences in the response to outward versus inward sound, the pattern of responses in the ROI-based average analysis consistently showed greater response to outward than inward sound location change for both ILD and ITD. There were subtle differences across cue types, however. As expected, the outward versus inward difference for ILD was greater in RH for adaptor/probe combinations in left hemispace and greater in LH for adaptor/probe combinations in right hemispace. For ITD, however, both LH and RH appear to respond more to outward adaptor/probe combinations in both left and right hemispace.

Although there are differences between the BOLD responses to ILD and ITD in degree of contralateral tuning and hemispheric asymmetry, the present results do not yield clear evidence that ILD and ITD are represented separately in AC. Most of the disparities observed could be an artifact of the reduced BOLD sensitivity to ITD, rather than a reflection of distinct AC processing mechanisms for the two cues. However, some of the more subtle differences observed in BOLD tuning to ILD and ITD — specifically the different hemispheric processing patterns for outward/inward sound location change along with the consistent finding that ITD tuning in LH was monotonic while ILD tuning was non-monotonic — suggest that there may be differences between the cues in the relative sizes of contralaterally- and ipsialterally-tuned neural populations within each hemisphere. This would be consistent with previous EEG/MEG evidence indicating, on the basis of differing field topographies and/or interhemispheric dominance patterns, that the two cues are processed separately (Schröger 1996; Ungan *et al.* 2001; Tardif *et al.* 2006; Johnson and Hautus 2010).

Moreover, it remains unclear why contralateral AC tuning to ITD is so much weaker than it is for ILD. Mammalian neurophysiology data, though scant for ITD, would suggest that there is contralateral AC tuning to both ILD and ITD and that there is a similar degree of contralateral bias in both hemispheres. Limited sensitivity to ITD and hemispheric asymmetries may reflect a categorical difference in the way in which human AC is organized to process auditory space and potentially other sound, possibly due to functional demands placed by human processing of oral speech and language. Alternatively, the population level responses captured by fMRI measures may reflect a potentially limited number of ITD- relative to ILD-tuned neurons, which may not have been accurately captured by single neuron recording methods in non-human animals.

Other explanations of the relative lack of tuning to ITD observed are that the BOLD signal may fail to capture important aspects of the cortical representation of ITD, which could involve coding by temporal spike patterns (Furukawa and Middlebrooks 2002), coding by excitatory/inhibitory relationships between "opponent" neural subpopulations (McAlpine *et al.* 2001; Stecker *et al.* 2005), highly local codes (Imig and Adrin 1977), or distributed codes across populations of panoramic neurons (Stecker et al. 2003; Werner-Reiss & Groh 2008) that would not be revealed by the univariate analysis methods employed herein. Additionally, because response to ILD modulation cannot be completely separated from response to monaural gain, it cannot be ruled out that contralateral tuning to ILD may partly reflect response to monaural sound level, and that the actual binaural component of ILD tuning may be as modest as the observed tuning to ITD. This explanation is unlikely, however, given the results observed in Experiment 1, which showed that the degree of contralaterality in response to ILD and monaural stimulation was only weakly related, suggesting that ILD is processed partially independently of monotic gain statistics. And finally, it is possible that cortical sensitivity to ITD — more than to ILD — is driven by top-down, task-dependent influences.

Future directions for continuing to investigate human AC processing of binaural cues could include further analyzing the data from the present set of experiments to explore subcortical tuning, particularly in the IC, and to assess other analytical methods (e.g. population receptive fields) by which to fit the voxel response to binaural tuning. Additionally, experiments which require subjects to perform auditory spatial tasks should be explored, as should alternative imaging methods (e.g., MEG and EEG) that better capture important temporal aspects of the neural response. Finally, neuroimaging (and psychophysical) investigations of binaural processing should be applied to various patient populations with disordered cortical processing, such as aphasia.

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