Heschl's gyrus is more sensitive to tone level than non-primary auditory cortex.

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Submitted to Hearing Research

Date of submission/revision : 07 March 2002

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Abstract

Previous neuroimaging studies generally demonstrate a growth in the cortical response with an increase in sound level. However, the details of the shape and topographic location of such growth remain largely unknown. One limiting methodological factor has been the relatively sparse sampling of sound intensities. Additionally, most studies have either analysed the entire auditory cortex without differentiating primary and non-primary regions or have limited their analyses to Heschl's gyrus (HG). Here, we characterise the pattern of responses to a 300-Hz tone presented in 6-dB steps from 42 to 96 dB SPL as a function of its sound level, within three anatomically-defined auditory areas; the primary area, on HG, and two non-primary areas, consisting of a small area lateral to the axis of HG (the anterolateral area, ALA) and the posterior part of auditory cortex (the planum temporale, PT). Extent and magnitude of auditory activation increased non-linearly with sound level. In HG, the extent and magnitude were more sensitive to increasing level than in ALA and PT. Thus, HG appears to have a larger involvement in sound level processing than does ALA or PT.

Keywords: fMRI; sound level; cortex.

1. Introduction

1.1 The role of the auditory cortex in the encoding of sound level

Variations in sound level are important in many aspects of audition, such as perception of loudness, estimating the location and movement of a sound source and speech perception. Anatomical and physiological evidence from animals demonstrate that the auditory cortex consists of multiple fields sensitive to a variety of basic acoustic features of sound, such as frequency, sound level, location and variation over time (e.g., Recanzone et al., 1999; Shamma, 2001). Cells in primary and non-primary auditory cortical fields have been shown to be responsive to sound level in many species, including macaque (e.g., Pfingst and O'Connor, 1981), cat (e.g. Heil et al., 1994; Phillips and Irvine, 1981; 1982; Phillips and Orman, 1984) and guinea pig (e.g., Rutkowski et al., 2000).

The human auditory cortex lies mostly on the supratemporal plane (STP) of the temporal lobe and consists of a primary area, situated on the medial two-thirds of Heschl's gyrus (HG) (e.g., Morosan et al., 2001; Rademacher et al., 2001), surrounded by multiple non-primary fields (e.g., Galaburda and Sanides, 1980; Rivier and Clarke, 1997). The number, extent and position of the non-primary fields that have been identified varies but, generally, five to seven non-primary fields are described, lying anterior, posterior and lateral to the primary area. These auditory cortical areas are involved in the analysis of complex sounds which may vary in sound level (e.g., Jäncke et al., 1998; Lockwood et al., 1999; Hall et al., 2001), frequency spectrum (e.g., Lauter et al., 1985; Talavage et al., 2000; Yang et al., 2000), timing (e.g., Binder et al., 2000; Giraud et al., 2000; Zatorre and Belin, 2001) and location (e.g., Baumgart et al., 1999; Weeks et al., 1999).

Neuroimaging studies have reported systematic changes in activation of the auditory cortex with changing sound level (e.g., Millen et al., 1995; Strainer et al., 1997; Jäncke et al., 1998; Lockwood et al., 1999; Mohr et al., 1999; Gutschalk et al., 2001; Hall et al., 2001; Brechmann et al., 2002). There is lack of a clear consensus on the exact pattern of the increase in activation; some studies report a systematic increase in either extent (Jäncke et al., 1998) or magnitude of activation (Mohr et al., 1999), or both (Lockwood et al., 1999; Brechmann et al., 2002). Response saturation at the highest sound levels studied has been reported (Lockwood et al., 1999; Mohr et al., 1999), but others found no such saturation (Jäncke et al., 1998; Hall et al., 2001; Brechmann et al., 2002). At least some of these inconsistencies may be due to the narrow and different ranges of sound levels presented. The response to sound level has generally been measured across only a few tens of decibels (dB) which represents only a fraction of the overall system dynamic range of about 120 dB (Viemeister and Bacon, 1988), and some studies only employed two or three sound levels. These limitations do not allow accurate determination of the shape of the response curve. Mohr et al. (1999) and Hall et al. (2001), however, used five and six sound levels, respectively, and found magnitude to increase linearly as a function of sound level when responses were averaged over all subjects.

1.2 Differences between auditory cortical fields in the processing of sound level

There is some evidence from neurophysiological studies that neurons in different auditory fields vary in their response to sound level and that different auditory fields differ in the proportions of neurons with monotonic or non-monotonic rate-level functions (Phillips and Irvine, 1981; 1982; Phillips and Orman, 1984; Recanzone et

al., 2000; Rutkowski et al., 2000). Cells with monotonic functions show a progressive increase in discharge rate with sound level, until the firing rate reaches a maximum above which further increases in sound level do not affect the discharge rate. Non-monotonic cells show an increase in discharge rate to a maximum value, and further increases in sound level result in a progressive decrease in activity. Pfingst and O'Connor (1981) showed that, for a sample of non-monotonic neurons in monkey primary and non-primary auditory cortex, the sound pressure levels evoking maximal discharge in different neurons were evenly distributed throughout the dynamic range of hearing. Monotonic and non-monotonic neurons may be involved in sound level processing in different ways; monotonic cells showing increasing discharge rates over a wide range of intensities and non-monotonic cells tuned to particular best SPLs. Different proportions of these cell types between the tonotopic fields may reflect a functional segregation in coding and processing of level information. This level of detail is, however, inaccessible with neuroimaging which is sensitive to aggregate differences in the level-dependent response, rather than individual responses from these different cell types.

Most studies of human cortical responses to sound level have not differentiated between regions of the auditory cortex, limiting their investigation to either the primary auditory area (on HG) or the entire STP. A recent fMRI study by Brechmann et al. (2002), however, investigated the representation of changing sound level of frequency-modulated tones in four auditory cortical areas (T1a, T1b, T2 and T3). They found that the sound-level-dependence differed across these areas. The area T1b, which includes primary auditory cortex as well as some lateral non-primary auditory cortex, showed the most robust level-dependence. They used a broad range

of intensities, but only a small number of sound levels were investigated, so the shape of the level-dependent response within T1b could not be determined.

Using magnetoencephalography (MEG), Gutschalk et al. (2001) have shown that, when modelled using two sources, the two dipole sites in auditory cortex differ in their response to level. An anterior source, thought to represent a non-primary area lateral to primary auditory cortex on HG, was not sensitive to stimulus level. In contrast, a posterior source on the border between HG and PT exhibited an increase in response amplitude as the stimulus sound level was increased. Localisation of MEG sources is of limited precision and so these locations are estimates. It is possible that the posterior source could be due to activation of T1b given by Brechmann et al. (2001).

1.3 Spatial organisation of cortical responses to sound level

There is some evidence for iso-intensity bands orthogonal to the tonotopically organised isofrequency bands in mammalian auditory cortex (cat primary area: Phillips et al., 1994; guinea pig anterior/primary and dorsocaudal fields: Taniguichi and Nasu, 1993). Within the primary auditory area, an orderly spatial organisation of a number of parameters related to the encoding of sound level has been demonstrated, including minimum threshold, dynamic range, best SPL and non-monotonicity of sound-level functions (Heil et al., 1992; 1994; Phillips et al., 1994). Convincing single unit evidence for ampliotopic organisation, however, has only been obtained in the mustache bat (Suga, 1977), in which iso-intensity is represented along radii on the cortical surface within the constant frequency part of the primary auditory cortex.

An ampliotopic organisation within human auditory cortex has been suggested on the basis of an early MEG study which reported a shift in the computed location of the dipole source with changing sound level. Pantev et al. (1991) studied the effect of changing the level of a 1-kHz tone on the source of the auditory evoked magnetic field for three subjects. They observed a posterior-to-anterior shift of the source and noted that the locus of cortical excitation became more superficial with increasing sound level. These data were modelled using a single source, which does not rule out the possibility that the field actually arises from several sources that are centimetres apart. Indeed, Lutkenhoner et al. (2000) suggest that MEG data represent a more complex spatio-temporal source structure than has previously been reported, in which case the estimated source location would represent only the "centre of activity" at a point in time and obscure the true organisation. Lockwood et al. (1999) describe an 8 mm shift in activation measured by positron emission tomography (PET) from inferior to superior temporal lobe locations with increasing sound level of 0.5 and 4 kHz tones. To interpret this shift as ampliotopy could be misleading, however, as it may simply reflect inherent variability in the location of the peak of activation, especially given the large amount of data smoothing and averaging that is required for PET. The increased resolution provided by fMRI may be of benefit in the identification of any such spatial organisation.

1.4 The present study

The present study used fMRI to quantify the pattern of the response to monaural sound level in three anatomically-defined regions of the primary and non-primary auditory cortex. We used a relatively small step size and measured the activation over a broader range of sound intensities than has previously been studied, in order to

allow accurate determination of the response function within each region. We also measured the location of the peak response at each sound level in individual subjects to investigate any possible ampliotopic organisation.

2. Methods and Materials

2.1 Subjects

Ten right-handed subjects, aged 21-38, with no history of neurological or hearing impairment, participated in the study. All subjects gave informed written consent and the study was approved by the University of Nottingham Medical School Ethical Committee. Prior to the imaging session, the hearing sensitivity of subjects was measured using pure-tone audiometry, and hearing thresholds of all subjects fell within the normal range (<20 dB HL) at frequencies between 250 and 8000 Hz inclusive. Tympanometry was also performed and measures of acoustic reflexes were obtained to tones of 250, 500, 1000 and 2000 Hz. Tympanograms and acoustic reflex thresholds were within normal limits, bilaterally, for all subjects. Tympanograms were all normal type A, with middle ear pressure above -100 daPa and middle ear compliance above 0.2 ml. Acoustic reflex thresholds were tested at 250 Hz, 500 Hz, 1000 Hz and 2000 Hz. Thresholds were all less than 100 dB HL, with the majority at 90 to 95 dB HL. 90 dB HL is approximately equivalent to 100 dB SPL, as dB HL is a dB measure above the standard audiometric threshold (which is approximately 10 dB SPL at 500 Hz, Dadson and King, 1952). The maximum level of stimuli used in the fMRI study was 96 dB SPL, so acoustic reflexes should not have been activated in the majority of cases.

2.2 Stimuli

300-Hz sinusoids were synthesised with a sampling rate of 48 kHz and presented using a specially engineered, MR-compatible sound system that delivers acoustic stimuli using electrostatic drivers built into industrial ear defenders (Palmer et al., 1998). The current experiment followed from a previous study by the co-authors in which had been measured robust sound level dependent activation by a 300-Hz tone presented between 66 and 91 dB SPL (Hall et al., 2001). A frequency of 300 Hz was chosen as it is distant from the frequency of peak energy of the scanner noise (1.92 kHz, plus higher harmonics) (Hall et al., 2000). Tones were presented monaurally, to the left ear, at ten sound levels; 42, 48, 54, 60, 66, 72, 78, 84, 90 and 96 dB SPL. These presentation levels were calibrated by mounting the sound system used in the fMRI study on KEMAR (Burkhard and Sachs, 1975) equipped with a Brüel and Kjær microphone (Type 4134) connected to a Brüel and Kjær measuring amplifier (Type 2636). The tones were 600 or 1200 ms in duration, and were ramped on and off with 10 ms inverted-cosine ramps.

The experimental paradigm is illustrated in Figure 1. Each condition consisted of a sequence of eight 600-ms tones and one 1200-ms target tone, separated by 100 ms of silence, giving a total stimulus time of 6.8 s. The position of the target tone was randomised and the subjects were instructed to press a button with their right index finger on each occurrence of the target. This task thus required attention to the stimuli. So that the subjects could determine the reference duration of the non-targets in each epoch, the first two tone bursts in a sequence were always non-targets. The order of the stimulus and silent baseline conditions was randomised. Each condition occurred 24 times; giving a total of 264 stimulus epochs and an experimental time of 39.6

minutes. The occurrence of subjects' button presses was logged for off-line analysis of detection performance.

2.3 fMRI scanning

Scanning was performed on a 3 Tesla MR system with head gradient coils and a birdcage radio-frequency coil (Bowtell et al., 1994; Bowtell and Peters, 1999). An MBEST echo-planar sequence (TE = 36 ms) was used to acquire sets of 32 contiguous coronal images in 2144 ms. Voxel resolution was 4 x 4 x 4 mm (matrix size, 128 x 128). A set of images were acquired every 9 s using a clustered-volume-acquisition sequence, as shown in Figure 1. These images were acquired during the 2200-ms silent interval between stimulus epochs (9 – 6.8 s) to avoid masking of the stimuli by the scanner noise produced during image acquisition. A high resolution (1.5 x 1.5 x 2 mm) structural image was acquired for each subject in a separate scanning session using a T1-weighted sequence.

2.4 Image analysis

For each subject, a standard image analysis protocol was performed using SPM99 software (http://www.fil.ion.ucl.ac.uk/spm). Head movement was corrected by a computational algorithm to minimise the sum of squared differences between the mean image and each image in the time series (Friston et al., 1995; 1996). The amount of motion correction applied was generally less than 2 mm in each plane and less than 2° rotation about each axis (i.e., less than 1 voxel). Functional images were then coregistered with the individual’s structural image using the mutual information algorithm as implemented in SPM99 (Maes et al., 1997) and normalised into standard

brain space. Spatial normalisation was achieved by warping the brain outline and major anatomical landmarks of the structural image to those corresponding points in a template image, and using these parameters to write the functional data into the same space. The brain template used was defined by the Montreal Neurological Institute (MNI) (Evans et al., 1993). Normalisation to this template permits point sources within any brain region to be referenced using coordinates in three dimensions and compared with any other brain that has been similarly normalised. Final voxel resolution of the normalised images was 2 x 2 x 2 mm. Images were spatially smoothed using a 4 mm isotropic Gaussian kernel to enhance the signal-to-noise ratio. This smoothing would introduce minimal spatial spread of activation as the kernel width is equal to the acquired resolution. Low-frequency artefacts were removed by high-pass filtering the time series at 0.3 cycles/minute.

Image analysis was conducted for each subject using the general linear model and t statistics were computed to identify voxels that were significantly activated in each of the ten stimulus conditions relative to the silent baseline. Maps of t values were transformed to the unit normal distribution to give maps of Z values. These statistical maps were then thresholded at a probability level of $P<0.001$ (T value = 3.13) to describe regions of significant tone activation relative to the silent baseline.

2.5 Identification of auditory areas

Borders of functional cortical fields are not visible from the cortical structure and their precise locations do not align exactly with topographical landmarks defined by sulci and gyri. However, despite inter-subject variability primary auditory cortex generally includes the medial two-thirds of HG (e.g., Morosan et al., 2001;

Rademacher et al., 2001). The relative locations of the multiple non-primary fields tend to be consistently arranged with respect to the absolute location of HG (Rivier and Clarke, 1997; Wallace et al., 2002). Thus, identification of HG allows the relative location of auditory cortical fields to be estimated. Cortical morphology therefore provides a practical heuristic for defining a tentative, but fairly gross, parcellation of the auditory cortex with which to interpret the functional imaging data. The three auditory cortical regions were defined for the group using a mean of their normalised high-resolution structural brain images. The principle landmarks, including HG, aligned with one another and, despite some blurring of the image as a result of averaging, the Sylvian fissure and the sulci bordering HG were visible in the group mean brain. The mean structural brain was displayed using custom written software MRIcro (Rorden and Brett, 2000) and three templates (Figure 2) were created according to the criteria outlined below.

The region HG is a distinctive gyrus that has an oblique medial to lateral axis and lies on the supratemporal plane. It terminates medially at its border with the insula, anteriorly by the first transverse sulcus and posteriorly by Heschl's sulcus. The region HG closely corresponds with Penhune et al.'s (1996) 50% probability contour of the HG for a different group of subjects, which was defined using similar morphological criteria. HG is likely to include the primary auditory area (e.g., Rademacher et al., 2001), but may also include part of the immediately adjacent non-primary auditory cortex on the lateral third of HG. The volume of left HG was 2656 mm^3 and on the right, it was 2416 mm^3.

The small non-primary anterolateral area, ALA, encompasses the area running from the long axis of HG and extending beyond HG to the convexity of the superior temporal gyrus. ALA is limited medially by the lateral edge of HG. Anteriorly and posteriorly it is bordered by lateral extensions of the anterior and posterior sulci of Heschl. The volume of the ALA template was 1800 mm^3 in both hemispheres. When compared to fields identified using histological methods, ALA coincides with an anatomical field of the same name, which lies lateral to the primary area on HG (Wallace et al., 2002).

The planum temporale, PT, extends posteriorly along the supratemporal plane and is bounded laterally by the convexity of the superior temporal gyrus and medially by the insula. The anterior border is marked by the Heschl's sulcus and the extension of this sulcus to the lateral edge. Due to lack of clear landmarks delimiting the posterior boundary of PT, this border was defined using MNI co-ordinates for the posterior border of the 45% probability contour of PT described by Westbury al. (1999). PT is a fairly large region and probably encompasses multiple functional fields, including LA, STA and PA (Rivier and Clarke, 1997; Wallace et al., 2002). Its volume was 3042 mm^3 on the left and 2986 mm^3 on the right. No attempt was made to further parcellate PT into possible functional fields, due to lack of visible anatomical landmarks for such fields.

2.5 Extent and magnitude analysis

Changes in the pattern of activation in left and right auditory cortices were measured by calculating the extent of the region activated and the magnitude of the response for each tone level condition for anatomically-defined regions. This approach allowed

quantification of activation of specific anatomical areas independent of between-subject variability in location of the peak of activation and therefore enabled direct comparisons to be made between the magnitude of activation of these anatomical areas across subjects.

The absolute values for the extent of activation are somewhat dependent upon the chosen statistical threshold. In the present study, the shape of the growth in extent is more important than the absolute values of extent because this is more resilient to the effect of thresholding. Extent measures based on statistical maps that were corrected for multiple comparisons were often zero at the lower sound levels, and these floor effects make corrected extents less sensitive for characterising the shape of the growth function. Thus we defined extent of activation as the number of voxels in each region whose probability of activation exceeded an uncorrected one-tailed threshold of P=0.001. For extent values to be comparable across HG, ALA and PT regions, the number of activated voxels was transformed by dividing it by the total number of voxels in each template.

The magnitude of the response was represented by the percentage change in the response for each stimulus condition relative to the silent baseline and was calculated separately for HG, ALA and PT regions. Voxels in the unsmoothed, normalised, high-pass filtered, functional data within the three templates (Figure 2) were averaged to produce a mean time course for each region. The mean values were corrected for the size of the region by obtaining a measure of activation per unit volume by dividing by the volume of the template.

2.6 Analysis of shifts in location of activation

Ampliotopic organisation of the peak of activation was evaluated by measuring the shifts in the location of the peak of activation (coordinates of the voxel displaying the local maximum statistic) for each sound level relative to the silent baseline. Three peaks of activation were studied in each hemisphere, corresponding to HG, ALA and PT respectively.

3. Results

3.1 Psychophysical data

Subjects reported being able to hear all ten sound-level conditions and identified the target tone correctly for all conditions (mean % correct = 72.5 %; StDev = 13.0 %). Accuracy of detection was somewhat influenced by sound level [$F(10,19) = 9.46$, $P<0.01$]. However, pairwise comparisons indicated that this difference was largely due to the better performance for the loudest level (mean % correct = 86.7%, StDev = 6.5% for 96 dB SPL), rather than a decline at the quietest level (Figure 3).

3.2 General pattern of functional activation

Auditory activation was observed bilaterally on the STP in primary and non-primary areas of the auditory cortex. Eight of the ten subjects showed auditory activation in at least seven of the listening conditions relative to the silent baseline. The location of this activation varied across subjects, but generally up to three main peaks, or foci, were present on the contralateral (right) STP. One focus on the STP was present in all ten subjects for at least the loudest 96-dB condition, and corresponded to HG. A focus lateral to HG, in the area that we have termed ALA, was present in five subjects. A

third focus posterior to ALA was present in all ten subjects and was located within the boundaries of PT (Westbury et al., 1999). Foci were also identified in ipsilateral (left) auditory cortical areas, although ipsilateral activation was often markedly less than contralateral, especially for higher sound levels. This is unsurprising given that there is auditory representation from both ears in both cortices, but the contralateral pathways are more pronounced than ipsilateral (e.g., reviewed in Pickles, 1981). These ipsilateral foci also occurred in three distinctive areas. Seven subjects showed activation ipsilaterally in HG; eight had activation of ALA and six showed activation in PT.

In three subjects, activation was observed in the left precentral gyrus containing the primary and secondary motor areas. This activation is most likely to be associated with the motor demands of the right finger button press and certainly this activation did not change with sound level.

3.3 Effect of sound level on the extent of auditory activation

In general, increasing sound level generated an increase in the extent of activation (Figure 2). The involvement of HG, ALA and PT in sound processing was consistently found for all tone conditions, as indicated by activation relative to the silent baseline. Overall significant effects of level were present across regions and subjects [$F(1,9) = 23.00$, $P<0.001$] and responses with level were different across the three regions studied [$F(4,36) = 8.99$, $P<0.01$] (Figure 4). Between-subject variations were observed in the size of the activated regions in each hemisphere and in the effect of increasing sound level on these regions. These variations did not correlate with individual subjects' ability to perform the detection task. For example, one subject

scored 93% correct on both the 42 and 96 dB conditions, but their extent of activation in HG was 0% and 12% respectively. Another subject improved their scores from 25% at 42 dB to 83% at 96 dB, and yet their activation in HG extent increased from 0% to only 3%.

Regression analyses for individual subjects indicated that the effect of level on the extent of activation was significant for more subjects in HG, than in ALA or PT. Out of ten subjects, effect of level was significant ($P < 0.01$) for eight in contralateral HG and for three in ipsilateral HG. In ALA, a significant effect of level on extent of activation was observed for one subject contralaterally, and four subjects ipsilaterally. For PT, effect of level was significant for four subjects contralaterally and two ipsilaterally. Thus, the extent of the response appeared to be the most sensitive to increasing sound level in contralateral HG, compared with the other areas. The extent of the activation in non-primary areas, ALA and PT, were less sensitive to changing sound level than HG.

For HG, an analysis of variance with sound level and hemisphere as within-subject factors showed a significant effect of sound level on the extent of activation [$F(9,81) = 12.72$, $P < 0.001$]. The relationship between sound level and extent of activation has a significant quadratic component [$F(1,9) = 14.58$, $P < 0.01$]. Thus it is not linear, as has been previously suggested on the basis of a narrower dynamic range (Hall et al., 2001). Figure 3 indicates that the extent of activation with 300 Hz tones does not materially increase with sound level until approximately 70 dB SPL. The response function increases gradually between 70 and 84 dB SPL, and then increases more rapidly up to 96 dB SPL.

For these monaurally-presented tones, hemispheric asymmetries in the extent of activation were observed. The extent of activation in contralateral HG was greater than in ipsilateral HG [$F\ [1,9]= 16.62$, $P = 0.003$]. At low sound levels, the extent of the activation observed in each hemisphere was similar. Above 72 dB, however, the contralateral extent was greater than the ipsilateral, and this interaction between hemisphere and sound level condition reached significance [$F\ (9,81) = 7.98$, $P = 0.001$] at 90 and 96 dB. The increasing difference between the activation of the hemispheres is illustrated by the separation of the mean estimates and the decreasing overlap of the error bars (Figure 4). No hemispheric asymmetries were observed for the extent of activation in ALA and PT.

3.4 Effect of sound level on magnitude of activation

Figure 5 shows the percentage change in the measured BOLD signal for each stimulus condition relative to the baseline, in HG, ALA and PT. In both hemispheres, significant effects of level were present [$F\ (1,9) = 8.93$, $P < 0.001$] and the increase in the magnitude with sound level followed a different course across the three regions [$F\ (4,36) = 3.08$, $P < 0.05$]. Between-subject variations were observed in the magnitude of the activation reported and in the effect of increasing sound level on these regions. These variations showed no systematic relationship with individual subjects' ability to perform the detection task. The average response function for HG (Figure 5) demonstrates an increase with sound level that differs between the hemispheres. ALA and PT were less sensitive to sound level than HG and the response functions do not show such a consistent overall pattern with changing level.

Regression analyses for individual subjects showed the effect of level on the magnitude of activation to be significant for more subjects in HG, than in ALA or PT. The effect of level was significant ($P < 0.01$) for seven subjects in contralateral HG and four in ipsilateral HG. Level sensitivity was observed in ALA. Three subjects exhibited a significant effect of level on response magnitude in the contralateral hemisphere, and one in the ipsilateral hemisphere. In PT, the effect of level was significant for four subjects contralaterally and one ipsilaterally.

Within-subjects analysis of variance showed a significant effect of sound level on response magnitude in HG [$F(9,81) = 7.00$, $P< 0.001$]. Again, the increase in response magnitude as a function of sound level was nonlinear, as the relationship had a significant quadratic component [$F(1,9) = 7.29$, $P < 0.05$]. No significant effect of hemisphere was observed on the magnitude of activation [$F(1,9)= 0.024$, $P= 0.879$]. The growth with sound level illustrated in Figure 5 appears to be somewhat flatter in the ipsilateral auditory cortex, but the interaction between hemisphere and level did not reach significance [$F(9,81)= 1.94$, $P= 0.058$].

3.5 Effect of sound level on location of activation

To determine whether there were any systematic shifts in peak activation across sound level, the locations of peak activation for each sound level were plotted in three dimensional space for each of the three auditory regions. The three peaks with the highest statistical values were studied in each hemisphere, corresponding to locations within HG, ALA and PT. In no region did the peak locations for each sound level show a systematic shift with sound level. The points at similar sound levels from different subjects appeared to be randomly distributed throughout each anatomical

region. No systematic pattern of changes was observed when such 3-D scatter plots were generated for each individual subject (data not shown). The lack of an observable systematic shift with sound level can be seen for HG in Figure 6. If a clear ampliotopic arrangement was present then a grouping of the different grey levels should be observed in this figure.

4. Discussion

4.1 Nature of the increase in activation with sound level

A rise in the extent and magnitude of activation as a function of sound level was present in both hemispheres, but contralateral auditory cortical areas often exhibited greater activation than ipsilateral areas for high sound levels. The magnitude of the response in HG was the most sensitive to increasing sound level of the three anatomically-defined regions studied. HG putatively corresponds to the primary auditory cortex in humans (e.g., Morosan et al., 2001; Rademacher et al., 2001). Extent and magnitude increased nonlinearly as a function of sound level, having a significant quadratic component present in the relationship. In some subjects, there was evidence for level sensitivity in adjacent non-primary auditory areas, ALA and PT, but across the group of ten subjects this pattern was less consistent than it was for HG. Thus, the primary area on HG may have a larger involvement in sound level processing than the non-primary areas. This result is consistent with that of Brechmann et al. (2002) who reported that the region T1b showed more robust level dependence than non-primary areas T1a (anterior to HG), T2 (centred on Heschl's sulcus) and T3 (corresponding to PT). However, T1b incorporates two regions, HG and ALA, that are segregated in our study.

The present study and that of Brechmann et al. (2002) investigated the response to sound level in these auditory areas by using pure tones and frequency-modulated pure tones, respectively. Some auditory cortex, including non-primary regions, has been shown to be more responsive to complex stimuli, such as complex tones (Hall et al., 2002) and speech (Binder et al., 2000). It is thus possible that, whilst the primary area (HG) was shown to be the most sensitive of the three areas to increasing level of 300-Hz tones, some auditory cortical regions may be extremely sensitive to sound level for more complex sounds. A further issue in interpreting the results of the present study is that the sensitivity of the response magnitude in ALA and PT to increases in sound level may be reduced by the way in which these responses were measured. For example, the maximum proportion of voxels activated by the tone relative to the silent condition in these two regions was only 10-15 %. By contrast, in contralateral HG almost 30% of voxels were activated. Since the response magnitude reflects an averaged value for all voxels within each template region, it will be more diluted by the response from non-activated voxels in ALA and PT than in HG.

Differences between response functions of primary and non-primary auditory areas could represent functional specialisation of different auditory cortical fields. One interpretation is that the primary area is involved in processing basic aspects of sound, such as sound level, and then feeds this information to surrounding cortical areas involved in sound perception. This idea is certainly somewhat simplistic, since it is unlikely that any single area is functionally specialised only for the encoding of sound level, but that all three areas contribute to varying degrees.

There was no correlation between the mean performance and extent of activation indicating that these auditory areas are unlikely to be involved in sound intensity *discrimination*. The mean behavioural performance was always well above threshold and only increased for the 96 dB condition, yet the extent of activation measure remained just above zero until 72 dB SPL at which point it increased steadily. The lack of correlation is perhaps unsurprising given that Belin et al. (1998) found no significant positive correlation between the discriminability of sound level changes and rCBF in a PET activation study. A negative correlation was reported, but this was located in the right heteromodal parietal cortex and was marginally significant ($P<0.01$ uncorrected).

4.2 Evidence for response saturation

We found that the extent and magnitude measures remained sensitive to sound level at the top of the range studied. Direct comparisons between studies are made difficult by the use of different criteria for sound level measurement, but our result agrees with Hall et al. (2001), who also used 300-Hz tones up to 95 dB SPL, and Jäncke et al. (1998), whose stimuli were tones of different frequency (200, 400, 600, 800, 1000 and 2000 Hz) and speech stimuli up to 91 dB SPL. These studies also found no evidence for saturation. In contrast, Mohr et al. (1999) reported fMRI response saturation to speech stimuli at levels of around 90 to 95 dB SPL and Lockwood et al. (1999) also suggest that the PET response to a 500-Hz tone approaches saturation between 70 and 90 dB HL. These levels are approximately equivalent to 80 to 100 dB SPL, as dB HL takes as reference the standard audiometric threshold (which is approximately 10 dB SPL at 500 Hz, Dadson and King, 1952). The neurophysiological data of Phillips et al. (1994) support our findings. For a 160-Hz frequency tone, they found no evidence

of saturation in the accumulated activity of the population of neurons, although the highest sound level tested was 80 dB.

4.3 Ampliotopic organisation of the auditory cortex

In general, for all subjects, areas encompassing HG, ALA and PT were activated for all intensities of the 300-Hz tone. There was no systematic shift in location of activation, as quantified by the location of the local maximum statistic indicating a lack of an ampliotopic arrangement in the fMRI data. Shifts in the peak of activation varied across subjects and across regions; some showing no change at all in the location of the peak of activation and others varying with level. Thus, no clear pattern emerged from this analysis. This does not rule out the possibility that ampliotopy does exist; it may still be obscured by the relatively low spatial resolution of the technique.

Tentative proposals for ampliotopy in human auditory cortex have been put forward. Pantev et al. (1991) observed a posterior-to-anterior shift of the source of the evoked potential with increasing sound level, although this result varied across the three subjects. Methodological difficulties in precise source localisation of electroencephalogram data (e.g., Mondt, 1989) also effect the credibility of the interpretation of this result. Lockwood et al. (1999) observed an inferior-to-superior shift with increasing sound levels. The tones were presented to the right ear, but a shift in the peak of the PET activation was found only in the ipsilateral temporal cortex. The interpretation of this shift as ampliotopy is problematic given the inconsistency across hemispheres. The peak shifts observed in ipsilateral cortex may simply reflect the greater variability of a weaker ipsilateral response. Weaker fMRI

response increases are more greatly affected by random fluctuations in the data and so foci with low statistical significance are less likely to be reliable in their location.

Neurophysiological recordings have not provided convincing evidence for ampliotopy in the auditory cortex of any mammal, apart from the echo-locating bat (Suga, 1977), so it is possible that no such organisation is present. It is, of course, extremely probable, even if the auditory cortex is ampliotopically arranged, that the 4 mm^3 voxel resolution afforded by the present study is not sufficient to show it. A further possibility is that the location of the peak of activation is an unreliable measure of functional localisation. Hunton et al. (1996) addressed the issue of functional-anatomical variation using PET data and found the peak locations of changes in blood flow for individual subjects (based on the local maximum statistic) to vary up to 11.5mm from the averaged peak location across subjects, which would explain why no systematic change is observed when data is pooled across subjects. The peak of activation may also be an inappropriate measure of functional localisation. For example, fMRI responses are based on changes in blood flow and oxygenation and so can be dominated by the underlying veins (e.g., Lai et al., 1993). Arterial artefacts are also present for PET activation (Johnsrude et al., 2002). Thus, shifts in the peak of the greatest statistical effect may reflect changes within the neurovasculature, rather than in neuronal populations.

4.4 Comparison with neurophysiological rate-level functions

The neurophysiological basis of the fMRI response is not yet fully understood. One model suggests that the activation signal in fMRI is proportional to the average neural firing rate caused by post-synaptic spiking activity (Heeger et al., 1999; Rees et al.,

2000), while another indicates that it reflects synaptic metabolism (Logothetis et al., 2001). Although we cannot judge which model is the more appropriate, we speculate on the neurophysiological basis of the sound-level dependent fMRI activation.

Response differences between the three auditory cortical regions may arise due to the existence of different proportions of cells with different rate-level functions. Phillips and Irvine (1981) showed that 55% of the sample of units from which they recorded in cat primary auditory cortex possessed monotonic rate-level functions. Such units progressively increase their discharge rate with sound level. If the neuronal population was sensitive to a range of sound level thresholds, then the relatively high proportion of monotonic responses in the primary area could account for the monotonic pattern of level dependence observed in HG in the present study. In contrast, recordings by Phillips and Orman (1984) indicate a large proportion (86%) of non-monotonic neurons in the non-primary posterior field. Non-monotonic cells maximally discharge at a particular sound level, and therefore at different dB SPLs different populations of such cells would respond. Non-monotonicity could arise in two ways. First, non-monotonicity can be due to inhibitory synaptic input within the cortical layers. Thus, at high sound levels, spiking activity will be reduced, despite there being a high metabolic cost. Second, non-monotonicity can arise prior to the cortical input and so, at high sound levels, spiking activity will be low and so will be the synaptic energy cost. Therefore, if the fMRI response reflects synaptic metabolism then, for a population of non-monotonically responding neurons, increasing sound level may or may not lead to an increase in the fMRI response, depending on the origin of that non-monotonicity. Certainly, in the present study we did not observe any consistent sound-level dependence in non-primary auditory areas.

There is little directly comparable neurophysiological data on how the population response varies with sound level as most studies record responses from single units (but see Heil et al., 1994; Phillips et al., 1994). Phillips et al. (1994) have reported the proportion of activated neurons in their sample of primary auditory cortical neurons as a function of SPL in four cats that were each tested at a different tone frequency. At low SPLs, activated neurons showed sharp frequency tuning close to the stimulating frequency, but at higher intensities of the same tone frequency there was a spread of excitation to neurons with characteristic frequencies both higher and lower than the test frequency. For a 160-Hz tone, which was the test frequency used by Philips et al. that was closest in frequency to the 300-Hz tone used in the present study, the change in the proportion of responding neurons with increasing sound level was initially small. However, a rapid increase began at around 40 to 60 dB SPL and continued up to 80 dB SPL, which was the highest level studied. This slow initial and subsequent rapid increase may be comparable to the function observed to 300-Hz tones in the present study.

The sharp increase in the fMRI response observed at around 70 dB SPL in the present study and in the neurophysiological data at 40 to 60 dB SPL (Phillips et al., 1994) is somewhat reminiscent of the rapid increase in the number of activated auditory nerve fibres at around 70 dB SPL in the “recruitment” models of Evans (1975) and Ozdamar and Dallos (1976). In these models, the sharp tips of tuning curves limits the spread of activity until at about 70 dB SPL the sound encroaches upon the much shallower low-frequency tails of higher frequency fibres. These models are supported by neurophysiological data recorded from cat auditory nerve fibres by Kim and Molnar

(1976), which demonstrates a dramatic increase in the number of active fibres at about 70 dB SPL for a 1 kHz (relatively low frequency) tone. There are numerous transformations between the auditory nerve and the cortex, but it seems not unreasonable that the spread that occurs in the periphery should be manifested in some way more centrally and the shape of the extent/sound level functions measured in the present study may reflect this recruitment.

4.5 Summary

Extent and magnitude of auditory cortical activation increased non-linearly with sound level in both hemispheres. Contralateral auditory cortex was more responsive than ipsilateral cortex to the monaurally presented tone, especially at higher levels. Activation along HG was more sensitive to increasing sound level than adjacent non-primary areas. We suggest that the primary auditory area may have a larger involvement in sound level processing.

5. Acknowledgements

MR scanning facilities were provided by the Magnetic Resonance Centre, University of Nottingham. We thank John Foster for operating the 3T MR scanner, Miguel Gonçalves for help with statistical analyses and Elizabeth Lovell and Diana Harbour for conducting the audiometry, tympanometry and acoustic reflex thresholds.

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Figure legends

Figure 1. Schematic diagram illustrating the experimental protocol. (i) Each stimulus epoch comprises a sequence of 9 tone bursts. The “target” tone burst is twice the length of the others and occurs at an unpredictable point in the sequence. (ii) In the part of the sequence shown, randomly-presented stimulus epochs are represented by shaded blocks labelled with a sound level value (in dB SPL), with a silent baseline epoch as the "empty" block. The solid black arrows represent the occurrence of the image acquisition, repeated every 9 s, in the brief interval between stimulus epochs.

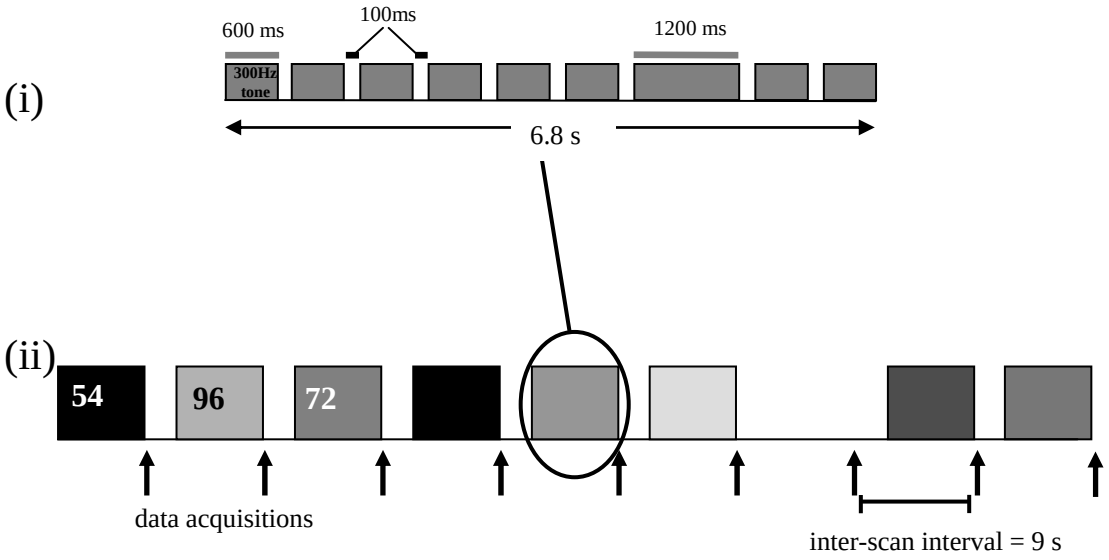
Figure 2. Group activation for five different sound levels (indicated at bottom left of each panel in dB SPL), analysed relative to the silent baseline. Activations, shown in yellow, are overlaid onto a slice of the group mean normalised structural image, oriented along the supratemporal plane. A general trend of an increase in auditory activation as a function of sound level is seen. The borders of the three templates for HG (red), ALA (green) and PT (blue) on which further analyses were based are shown on the 42 dB SPL image.

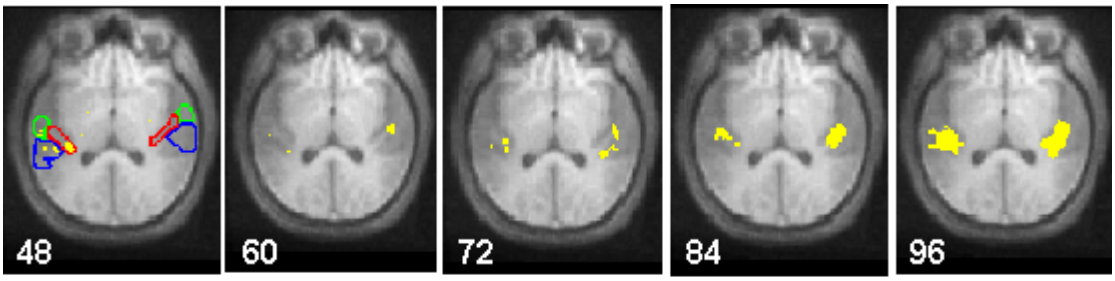
Figure 3. The average percentage of target tones correctly identified by the ten subjects, plotted as a function of sound level.

Figure 4. The mean extent of activation for each of the three anatomically-defined auditory regions (HG, ALA and PT) as a function of sound level. Extent of activation is expressed as a percentage of the total number of voxels in the region. Solid black lines represent data for the hemisphere contralateral to the stimulated ear and dashed grey lines data for the ipsilateral hemisphere. Error bars represent 95% confidence intervals.

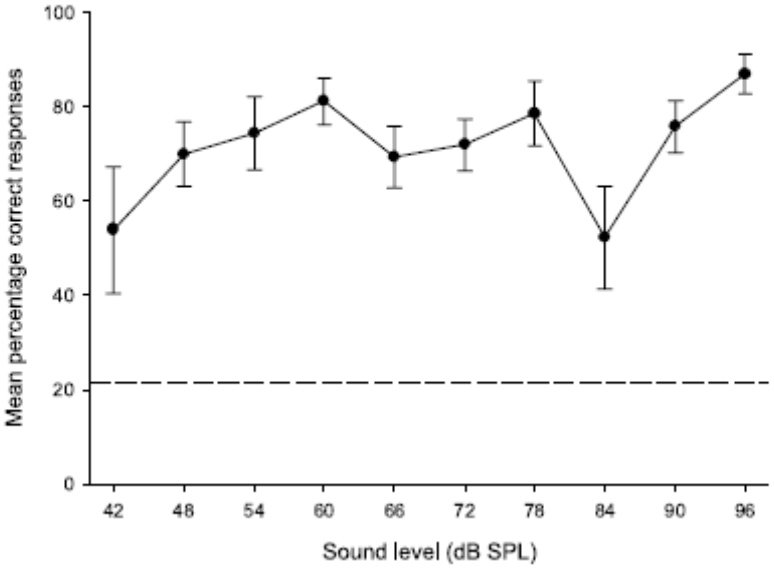
Figure 5. The mean percentage change in the response to each stimulus condition relative to the baseline for the regions HG, ALA and PT in each hemisphere. Again, as in Figure 3, solid black lines represent data for the hemisphere contralateral to the stimulated ear and dashed grey lines data for the ipsilateral hemisphere. Error bars represent 95% confidence intervals.

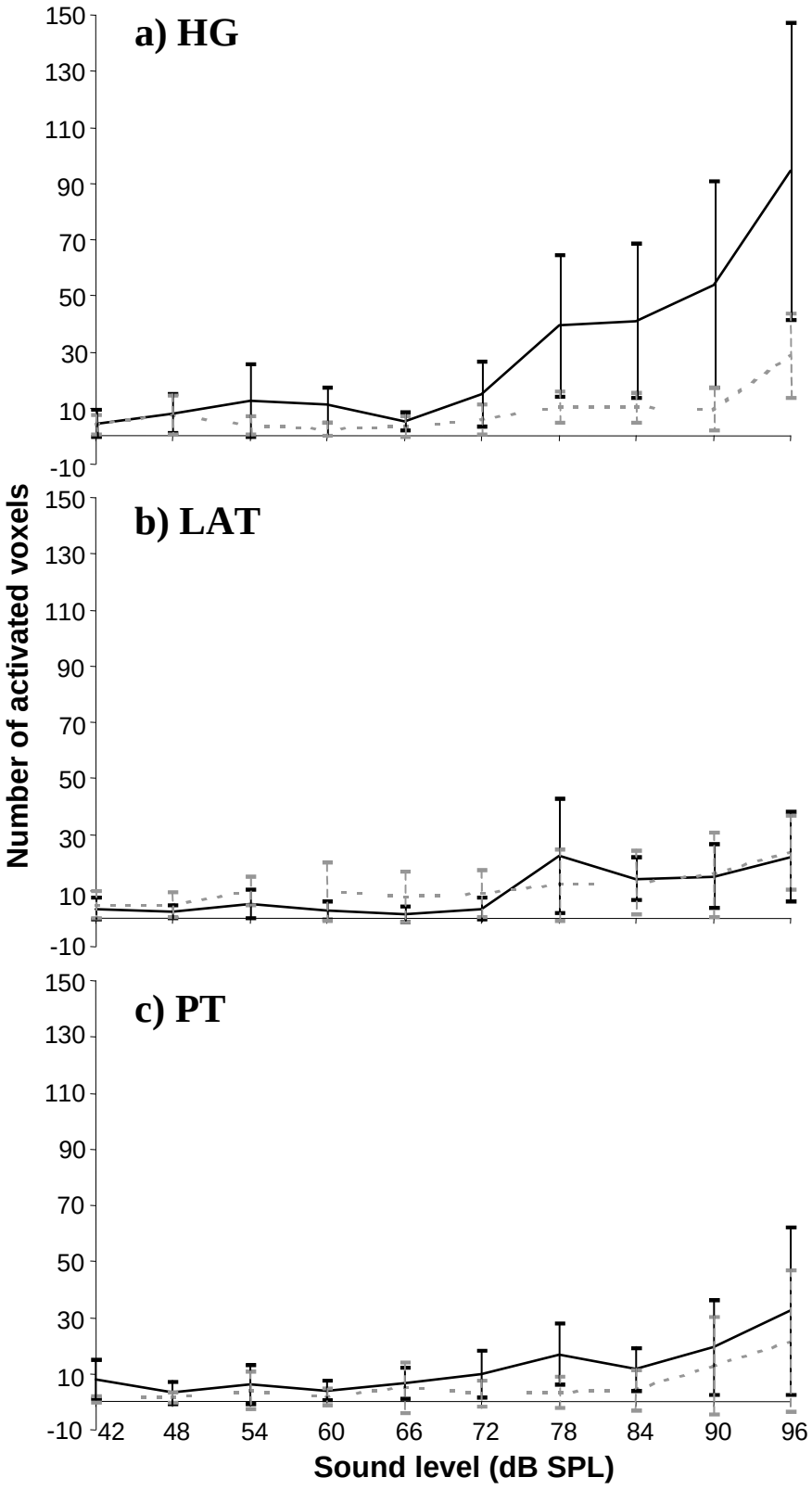
Figure 6. The locations of the statistical peak of activation in HG at each of the sound levels are plotted separately for each of the subjects. The two graphs show data for the right hemisphere contralateral to the stimulated ear, and for the left ipsilateral hemisphere respectively. The grey scale shading of the circles represents the different sound levels, from a white for the highest level to black for the lowest level.

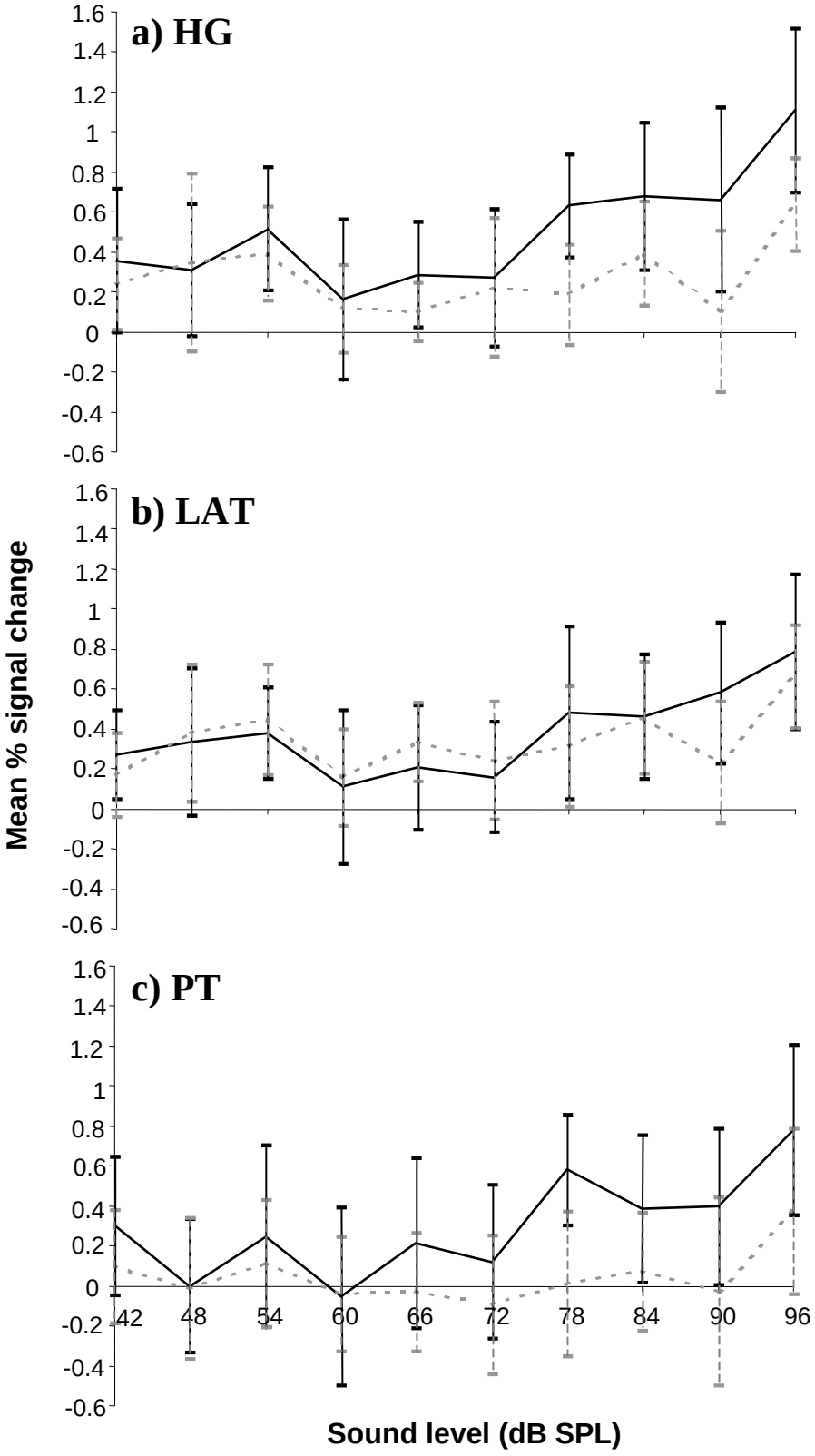

(i)
600 ms
100ms
1200 ms
300Hz tone
6.8 s
(ii)
54
96
72
data acquisitions
inter-scan interval = 9 s

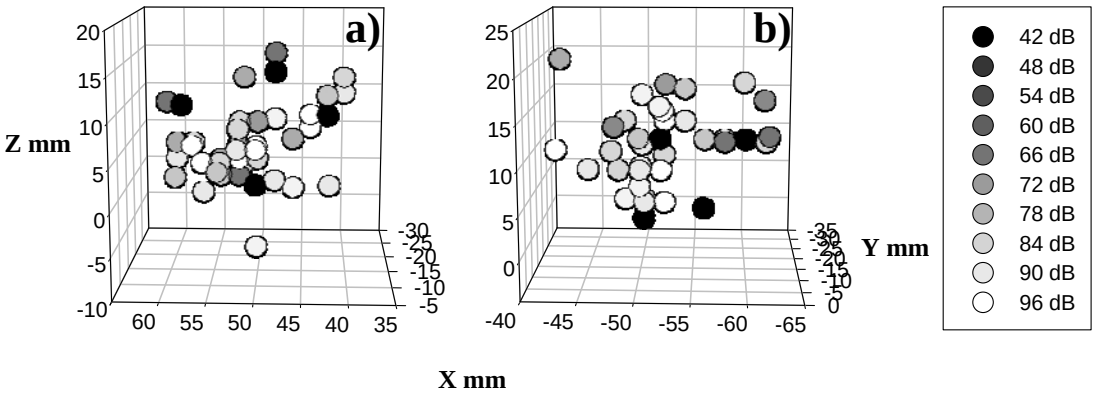


Sound Level (dB SPL)


Mean percentage correct responses
100
80
60
40
20
0
42
48
54
60
66
72
78
84
90
96
Sound level (dB SPL)


a) HG
b) LAT
c) PT
Number of activated voxels
150
130
110
90
70
50
30
10
-10
42
48
54
60
66
72
78
84
90
96
Sound level (dB SPL)


a) HG
b) LAT
c) PT
Mean % signal change
Sound level (dB SPL)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
42
48
54
60
66
72
78
84
90
96


a)
b)
Z mm
Y mm
X mm
20
15
10
5
0
-5
-10
60
55
50
45
40
35
-30
-25
-20
-15
-10
-5
25
-40
-45
-50
-55
-60
-65
42 dB
48 dB
54 dB
60 dB
66 dB
72 dB
78 dB
84 dB
90 dB
96 dB