Cerebral Responses to Change in Spatial Location of Unattended Sounds

Leon Y. Deouell,[1,2,*] Aaron S. Heller,[2] Rafael Malach,[3] Mark D'Esposito,[2] and Robert T. Knight[2]

[1]Department of Psychology and the Interdisciplinary Center for Neural Computation, The Hebrew University of Jerusalem, Jerusalem 91905, Israel

[2]Department of Psychology and Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, CA 94720, USA

[3]Department of Neurobiology, Weizmann Institute of Science, Rehovot 76100, Israel

*Correspondence: msleon@huji.ac.il

DOI 10.1016/j.neuron.2007.08.019

SUMMARY

The neural basis of spatial processing in the auditory cortex has been controversial. Human fMRI studies suggest that a part of the planum temporale (PT) is involved in auditory spatial processing, but it was recently argued that this region is active only when the task requires voluntary spatial localization. If this is the case, then this region cannot harbor an ongoing spatial representation of the acoustic environment. In contrast, we show in three fMRI experiments that a region in the human medial PT is sensitive to background auditory spatial changes, even when subjects are not engaged in a spatial localization task, and in fact attend the visual modality. During such times, this area responded to rare location shifts, and even more so when spatial variation increased, consistent with spatially selective adaptation. Thus, acoustic space is represented in the human PT even when sound processing is not required by the ongoing task.

INTRODUCTION

Audition has crucial importance for both basic survival and higher cognitive functions. Yet an understanding of the functional organization of the auditory system at the cortical level lags behind that of the visual system. Similar to vision, it has been suggested that auditory information is processed along two separate streams: a nonspatial ("object") rostro-ventral stream involving the anterior temporal and inferior frontal cortex and a spatial caudo-dorsal stream involving the posterior temporal, parietal, and more dorsal prefrontal cortex (Alain et al., 2001; Clarke et al., 2002; Rauschecker and Tian, 2000; Romanski et al., 1999), but this distinction is still debatable (Adriani et al., 2003; Arnott et al., 2004; Belin and Zatorre, 2000; Griffiths et al., 2004; Middlebrooks, 2002; Zatorre et al., 2002). Especially elusive has been the search for clear spatial processing in the unimodal auditory cortex. In the cat,

neurons with spatial tuning were found in both anterior and posterior supratemporal areas, although with some predilection for posterior nonprimary regions (Middlebrooks et al., 2002; Stecker et al., 2003). Several human fMRI studies found the planum temporale, a nonprimary auditory cortex region on the posterior supratemporal plane, to be involved in spatial processing, but critically, almost all of these studies required subjects to attend to, and make judgments regarding, the spatial location of the sound source (e.g., Bushara et al., 1999; Griffiths and Green, 1999; Zatorre et al., 2002). Thus, it is not clear whether the active regions reflect automatic representation of auditory spatial information or reflect top-down processes related to discriminating or attending to spatial locations (cf. Brechmann and Scheich, 2005, on task-dependent specificity). While it has been conjectured that PT activation reflects preattentive processing of sound location (Krumbholz et al., 2005), this has never been directly shown. In fact, a recent study argued specifically that the planum temporale is involved only when the task requires overt sound localization (Zimmer and Macaluso, 2005).

A few previous studies have examined subjects listening attentively to sounds with varying locations without the requirement to make active judgments ("passive attention" or "passive listening"). In a PET study, Zatorre et al. (2002) (experiment 1) found no selective activation to stimuli shifting between different locations relative to stationary sounds in a passive listening paradigm. Rather, the posterior auditory regions activated only when the sources differed in their spectral content or when subjects made spatial judgments. Thus, Middlebrooks (2002) commented that the posterior areas of the superior temporal gyrus (STG) are not particularly involved in spatial processing. Notwithstanding, a few studies using fMRI did report posterior STG activation related to spatial variation (smooth motion or discrete) during nominally "passive listening" (Baumgart et al., 1999; Brunetti et al., 2005; Maeder et al., 2001; Pavani et al., 2002; Smith et al., 2004; Warren and Griffiths, 2003). Yet, while these studies did not require any specific type of processing, all instructed the subjects to pay close attention to the stimuli (in some cases, even to pay attention to their spatial aspect). Because subjects had no task other than to attend

to the stimuli, and because the stimuli were constructed to induce perception of either smooth motion or variable spatial sources, it is quite possible that the subject engaged in tracking the spatial location of the shifting sounds. Thus, it is still unknown whether the posterior STG activity depends on deliberate processing of the spatial attributes of attended sounds or reflects task-independent intrinsic spatial sensitivity of neuronal elements. Here, we used an fMRI version of the auditory "mismatch" paradigm and examined nonintentional auditory spatial processing elicited when subjects ignore sounds.

In the mismatch paradigm, low-probability deviant sounds are embedded in streams of repetitive sounds that are played in the background, while subjects are instructed to ignore the sounds. The rare changes in the acoustic environment elicit a neuronal response with a peak latency of 100–250 ms, evident on the scalp as the mismatch negativity event-related potential (MMN) (Näätänen, 1990). Several features of the mismatch response make it suitable for addressing the automatic processing of distinctive features of sound. First, MMN can be elicited by changes of simple physical (acoustic) properties such as frequency, intensity, duration, and location of the sounds, as well as by more complex features (see Näätänen, 1992; Näätänen et al., 2001, for reviews). Second, the response to change along a given feature is largely independent of change in other features (e.g., Csepe et al., 2001; Deacon et al., 1998; Deouell et al., 2000; Giard et al., 1995; Ilvonen et al., 2001; Ritter et al., 1995; Rosburg, 2003; Schröger, 1995). Finally, elicitation of MMN does not require attention or response from the subject. Major attenuation of the MMN is seen only under very specific and highly demanding situations (Näätänen, 1991; Shalgi and Deouell, 2007; Sussman et al., 2003; Woldorff et al., 1991; Woldorff et al., 1998). Thus, the MMN is considered an automatic, preattentive index of change detection.

Several groups have used hemodynamic measures (PET and fMRI) to examine the mismatch response, defined here as the nonintentional response to infrequent acoustic change in an unattended stream of sounds (e.g., for pitch change: Doeller et al., 2003; Molholm et al., 2005; Opitz et al., 1999; for duration changes: Dittmann-Balcar et al., 2001; Molholm et al., 2005; Rinne et al., 2005; for phonetic changes: Celsis et al., 1999; Tervaniemi et al., 2000). All studies found activation to occur along different parts of the superior temporal gyrus, and few have also found less robust activation in the inferior frontal gyrus (see Deouell, 2007, for review). Only one group attempted to measure the fMRI blood-oxygen-level-dependent (BOLD) response to unattended *spatial* mismatch. Doeller et al. (2003) tested 18 subjects in an event-related fMRI study including unattended pitch changes as well as sound location changes. Virtual locations were produced by manipulating the sounds' interaural time and level differences. Doeller et al. found clear bilateral STG responses to pitch changes, but no significant BOLD activity was found in the comparison between

spatial deviants and standards, even when the statistical threshold for significance was lowered to quite "liberal" levels. Note that the magnitude of spatial change used (from 30° to 90°) elicited robust MMN electrical potentials both in Doeller et al.'s subjects and in other studies (cf. Deouell and Bentin, 1998; Deouell et al., 2003, 2006; Schröger, 1995, 1996; Schröger and Wolff, 1996). Moreover, our recent ERP study using low-resolution tomographic analysis (LORETA) for localizing the electrical MMN response showed that spatial changes of 30° activate the planum temporale bilaterally (Deouell et al., 2006; see also Sonnadara et al., 2006). Thus, a discrepancy remains between the electrical measurements, suggesting nonintentional spatial sensitivity in the PT, and the hemodynamic responses, which do not show such a response (Doeller et al., 2003; Zimmer and Macaluso, 2005).

Here, we measured the hemodynamic response of healthy subjects to changes in the spatial location of sounds in three experiments during tasks requiring the subjects to ignore the sounds. The response to pitch change was measured as well in one experiment. Several methodological steps were taken to optimize the perception of sound space in the scanner, and a sparse (clustered volume acquisition) (Hall et al., 1999) design was used to eliminate the masking noise of the scanner during sound presentation. Contrary to previous null results, we show that the PT is reliably activated by spatial change when subjects are not required to process such a change or even to listen to the sounds at all.

RESULTS AND DISCUSSION

Experiment 1

In experiment 1, we contrasted homogeneous blocks of spectrally rich stimuli, all emanating from the same location in the right hemispace (standard ["S"] blocks), with blocks in which infrequent location deviants replaced some of the sounds in the block (standard-deviant ["SD"] blocks). The deviants were 45° medial or 45° lateral to the standard locations, but still within the right hemispace. We also contrasted homogeneous blocks of harmonic tones with repeating pitch, with blocks that included rare pitch deviants. The details are described in the Experimental Procedures section below. The subjects were instructed to ignore all sounds and concentrate on a silent video movie of their choice.

Sounds versus Silence

As expected, blocks with repeating spectrally rich sounds (S blocks) contrasted with completely silent blocks activated wide regions across the superior temporal gyrus bilaterally, including the transverse temporal gyri, planum polare, and planum temporale (Figure 1). This result is congruent with many studies showing activation of the core (primary) and belt (secondary) auditory areas by broadband sounds (Rauschecker, 1997; Wessinger et al., 2001). The left inferior colliculus (IC) was also conspicuously activated by the right lateralized sounds. This
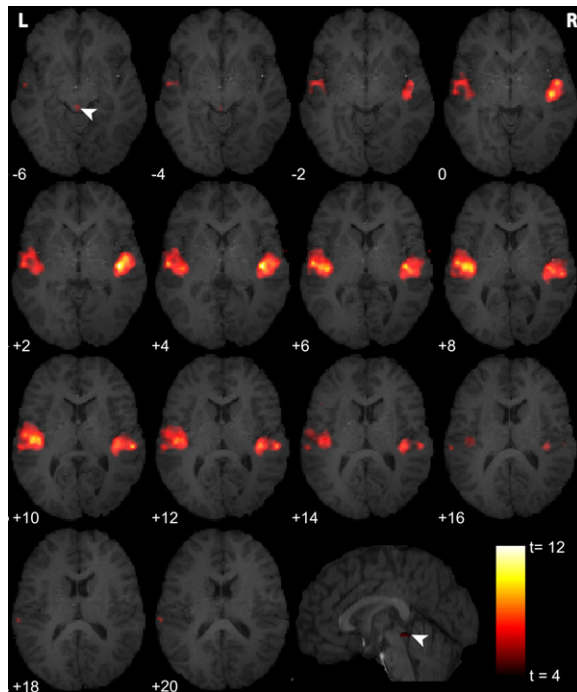
Figure 1. Regions More Active during Sound Presentation than during Silence

The threshold for this statistical parametric t map was set at $p < 0.001$ (uncorrected), with a minimum cluster of ten voxels. Bright colors ($t > 9.3$) are significant at a (corrected) family-wise error level of $p < 0.05$. The activation in the left inferior colliculus (white arrowhead) is seen in the top left axial sections and in the parasagittal slice on the bottom right. Here and elsewhere, the left side of the axial or coronal slices is presented on the left.

is in agreement with the contralateral preference of IC neurons in the cat (Semple et al., 1983; cf. Thompson et al., 2006). It is noteworthy that almost no other brain region was significantly active in this passive hearing condition (cf. Wessinger et al., 2001), incongruent with the report that in the monkey extensive areas outside the superior temporal gyrus are sound responsive (Poremba et al., 2003). This could be the result of lower sensitivity of fMRI relative to the autoradiographic method used in the monkey, to the more restrictive set of sounds used here, or to the diversion of attention away from the sounds.

Superior Temporal Activation by Spatial Change

Our main question was the nature of activation in STG in response to spatial change in an unattended sound stream. A superior temporal gyrus anatomical ROI was used to analyze the contrast between blocks containing standards and rare deviants combined (SD blocks) and the blocks with only standards (S blocks) separately for Location and Pitch conditions. Within this ROI, bilateral regions of the medial planum temporale were significantly more active ($p < 0.05$, corrected) for SD blocks containing spatial deviants than for blocks containing only standards

(MNI coordinates, left maximum: $x = -48$, $y = -32$, $z = 16$; right: $x = 60$, $y = -30$, $z = 10$) (Figure 2). This location is congruent with previous fMRI studies implicating the medial PT in spatial processing of sounds (Warren and Griffiths, 2003; Warren et al., 2002). It is also consistent with recent source reconstructions of the electrical MMN (Deouell et al., 2006; Sonnadara et al., 2006; Tata and Ward, 2005). Importantly, the localization of spatial processing to the medial PT suggests that this region automatically processes discrete spatial changes even when attention is not allocated to either the detection of such a change or to sounds in general.

Regions Outside the STG Active during Spatial Change Detection

A whole-brain analysis comparing the spatial S and SD blocks with a less conservative statistical threshold ($p < 0.001$, uncorrected, minimum cluster of 10), revealed additional regions in bilateral inferior frontal gyrus, right middle frontal gyrus, right superior frontal sulcus, right anterior cingulate, left supramarginal gyrus, and left occipitotemporal border (Figure 3). This confirms previous observations suggesting that nonintentional auditory change detection involves a network of brain regions, in which the STG and the lateral prefrontal cortex are most consistently found (Deouell, 2007; Doeller et al., 2003; Rinne et al., 2007).

Superior Temporal Activation by Pitch Change

Frequency change, as opposed to spatial change, yielded a statistically weak (subthreshold) response in more anterior STG regions, overlapping the left transverse temporal gyri (see Figure S1 in the Supplemental Data available with this article online). These anterior regions, which are distinct from the areas activated by spatial change, replicate previous results in this domain (Opitz et al., 2005). The weak response is not surprising considering the level of activation reported by previous studies that examined nonintentional detection of pitch changes of similar or even larger magnitudes (e.g., Doeller et al., 2003; Molholm et al., 2005; Opitz et al., 2002). A possible reason for the nonsignificant pitch effects is that the stimuli in the pitch conditions were harmonic tones, which are much weaker stimulators of the auditory cortex than the broader-band noise used in the spatial conditions (cf. Wessinger et al., 2001). Finally, we specifically examined whether pitch deviation elicited significant activation within the region activated by spatial change. To that end, we formed a region of interest defined as the STG voxels activated by the spatial deviation at a significance level of $p < 0.001$ and examined whether the mean regression coefficients ("β values") in this ROI for the contrast Pitch-SD > S were significantly different from zero. The mean values for pitch change were in fact very low within this ROI (0.085 and 0.021 for the right and left side ROIs, respectively) and far from significant across subjects [$t(12) = 1.25$, $p = 0.23$; $t(12) = 0.23$, $p = 0.82$, for right and left hemisphere, respectively]. The spatial deviation effect was also significantly larger than
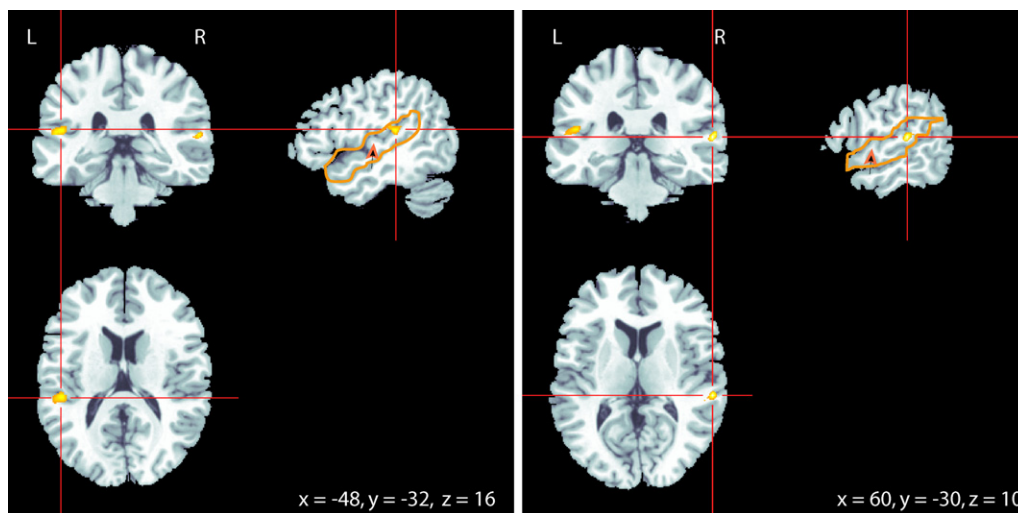
Figure 2. Regions within the Superior Temporal Gyrus Active for Spatial Change
The masked statistical parametric t map show the regions within the superior temporal gyrus ROI that were more active for spatial change (SD) blocks than for standard location (S) blocks (p < 0.05, corrected). The left and right panels point to the left and right PT activation, respectively. The orange line on the sagittal view denotes the ROI. Voxels outside the STG were not included in this analysis. For orientation, the orange arrows on the sagittal sections point to the cross section of the transverse temporal gyri, harboring the primary auditory cortex.

the effect of pitch change in these ROIs in a within-subject two-way analysis with factors Deviant Type (Location, Pitch) and Side (Left, Right hemisphere) [F(1,12) = 20.2, p < 0.01] with no main effect of side or an interaction.

To summarize, the main result of experiment 1 was that the presence of spatial change results in increased activation in a medial PT region bilaterally, in a condition in which the subjects are not requested to detect such changes and in fact are asked to ignore the sounds altogether.

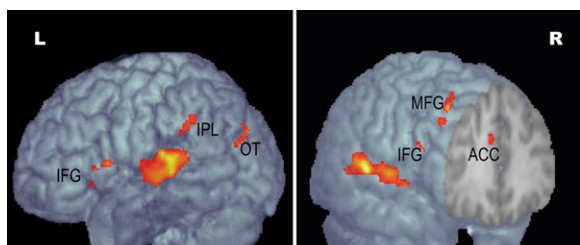What is the mechanism responsible for the activation of the medial PT in response to the spatial change? Because

Figure 3. Whole-Brain Analysis: Spatial Change
The unmasked statistical parametric t maps show regions significantly more active in blocks containing spatial deviants than in blocks containing standards only. No mask was applied. The map is superimposed on a semitransparent rendition of the normalized brain of a representative subject. The threshold for significance was set at p < 0.001, with a minimum cluster of ten voxels. Left panel: left lateral view. Right panel: right frontal view with the anterior pole of the brain (showing no effects) removed to reveal the right anterior cingulate focus. IFG, inferior frontal gyrus; MFG\SFS, middle frontal gyrus\superior frontal sulcus; IPL, inferior parietal lobule; OT, occipitotemporal junction; ACC, anterior cingulate cortex.

we contrasted mixed blocks of standard and deviant locations with blocks including only standard locations, it could be argued that the active regions are simply more responsive (tuned) to the physical location of the deviant (present only in the SD blocks) than to the location of the standard, rather then responsive to spatial *change*. This cannot be the case, however, because deviant and standard locations were reversed between the two runs, which were collapsed for the analysis, and so an effect in one direction in one run would have been offset by the opposite effect in the other run. Thus, the higher activation in the SD blocks relative to the S blocks is genuinely the response to the spatial *change* present in the SD blocks. However, change can elicit a response due to at least two mechanisms. According to the adaptation model, the activated PT locus may harbor a mixture of neurons with distinct spatial receptive fields (SRF). Quite likely, each neuron gets adapted by sounds appearing in its SRF, and more so with more frequent stimulation (see Ulanovsky et al., 2003, 2004, for the case of pitch). Mixing two locations in one block, as in the SD blocks, entails less frequent stimulation of each population of neurons, less adaptation, and consequently a stronger overall neural response in the SD than in the S blocks (cf. Grill-Spector et al., 1999; Grill-Spector and Malach, 2001). If so, then introducing even more spatial locations in one block should *increase* the response. Alternatively, according to the memory trace model, the stronger response in the SD blocks is due to active detection of a rare change from an established regularity, as in the memory trace model for the MMN electrical response (see Näätänen et al., 2005). If so, then mixing even more locations in one block should *reduce* the effect by interfering with the establishment of
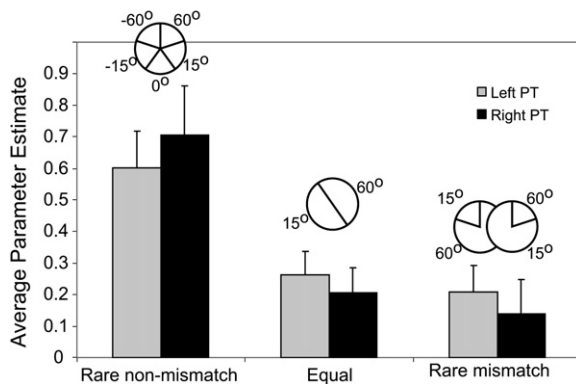
Figure 4. Activation of PT with Different Degrees of Spatial Variation

The bars represent the mean regression coefficient values (and standard errors of the mean) within the PT ROI elicited by the 3 conditions of experiment 2. The pie charts above the bars indicate the probability of the sound locations (indicated by the azimuths, in degrees), among the stimuli in each sequence.

regularity and thus with the establishment of a memory trace for the standard (see Jacobsen and Schröger, 2001). These contrasting predictions were examined in experiment 2.

Experiment 2

Experiment 2 concentrated on the response to unattended spatial change. Three types of SD blocks were used (see pie charts in Figure 4). In one, 20% location deviants were mixed with 80% standards (Rare mismatch [RM] condition, identical to the Location condition of experiment 1). In another, the same 20% location "deviants" were mixed with four other sound locations, each comprising 20% of the stimuli (Rare non-mismatch [RNM] condition), presented in random order. In the third condition, there were equal proportions of "standards" and "deviants" (Equal condition). Under the memory trace account, if the "deviant" location would be presented alongside several other locations each with equal probabilities (as in the RNM condition), instead of in a stream of repetitive locations (as in the RM condition), no standard representation would be formed, and thus the response should be diminished in the RNM condition relative to the RM condition (Jacobsen and Schröger, 2001). In distinct contrast, under the adaptation account, the overall response should be increased in the RNM condition relative to the RM condition because less adaptation occurs in the former than in the latter.

We used the regions of significant activation found in experiment 1 within the STG as predetermined ROIs in which the above predictions would be measured. Figure 4 shows the average parameter estimates (contrast regression coefficients) obtained in the PT locus on the right and on the left for the three contrasts tested. These values can

be taken as an index for the sensitivity to the SD relative to S blocks in each condition, within the ROI. The pie charts above the bars show, for each condition, the proportion of different locations in the SD blocks.

All three conditions elicited a statistically significant activation in the PT ROIs ($p < 0.05$). Two-way ANOVA with factors Condition (Rare nonmismatch [RNM], Equal, Rare mismatch [RM]), and Side (left, right), revealed a main effect of condition [$F(2,12) = 11.52$, $p < 0.01$] with no main effect of side or an interaction. Post hoc contrasts showed that the RNM condition elicited a significantly stronger response than either the equal or the RM conditions ($p < 0.05$, two-tailed). The equal and the RM conditions did not differ significantly. Whereas this analysis was based on an ROI defined by the uncorrected $p < 0.001$ threshold in experiment 1 (to allow for some intersubject variability), similar results were obtained when the ROI was defined based on the restricted PT regions in which the activation in experiment 1 was elicited with a family-wise type-I error of 0.05 (i.e., "corrected" threshold).

This result is congruent with the predictions of the adaptation model described above. That is, when more locations were presented within the block, less adaptation occurred, and thus overall activity was larger. The fact that the Equal condition yielded a similar response to the RM condition is explained by the fact that, relative to the RM block, the neurons sensitive to the location that was deviant in the RM block were more adapted in the Equal block, but at the same time the neurons sensitive to the other location were less adapted. In summary, the results of experiment 2 clearly show that the medial PT region is sensitive to spatial variation, and not particularly to rare unexpected changes of the mismatch type.

The subjects in experiments 1 and 2 were repeatedly instructed to watch the movie and ignore the sounds, and post-scan debriefing confirmed that they complied. However, the design provided no online indication that they were indeed continuously on-task. Experiment 3 was designed to replicate the findings of the first two experiments while employing an active visual task that provided an online measure of task performance.

Experiment 3

This experiment replicated the RM and RNM conditions of experiment 2 (with some technical changes, see Experimental Procedures). However, while in half of the blocks subjects watched a silent, subtitled movie, as in the previous two experiments, during the other half they performed a go-nogo visual task ("press the button for odd numbers only"). This task required the subjects to continuously monitor the visual stream and provided an ongoing measure of the subjects' involvement with the visual task. Subjects' performance was high (mean hit rate 99%), attesting that they were on-task throughout the blocks. However, all six subjects reported that they had to make a significant effort to continuously attend to the visual task, lest they erred. Indeed, despite the apparent ease of every single trial, each subject performed a few false alarms (mean
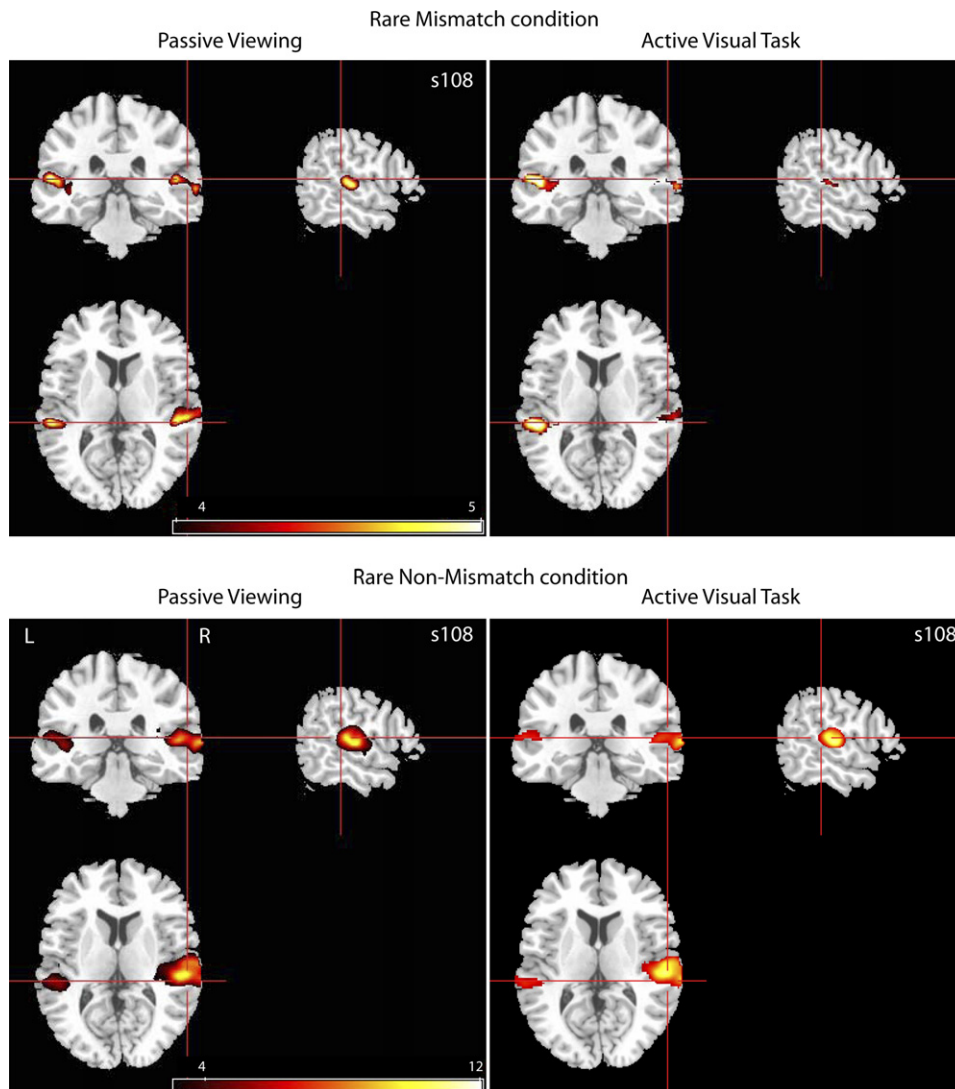
Figure 5. Activation Pattern across Visual Tasks
Statistical parametric map for a representative subject of experiment 3 in the four experimental conditions (p < 0.001, minimum cluster of 10; see Figure S2 for all subjects). For reference, the red crosshair points to the locus of maximal activity on the right hemisphere found in experiment 1. The sagittal sections depict the right hemisphere.

3.5%). Moreover, following the imaging session, outside the scanner, five of the subjects performed the go-nogo visual task while also monitoring for auditory deviants (Supplemental Data C) and unanimously showed a dual-task cost (Figure S4), which makes it unlikely that they chose to attend to the auditory input while performing the visual task in the imaging session.

All subjects showed PT activation at the individual level (p < 0.001, cluster > 10 voxels), especially on the right, regardless of whether they watched a movie or performed the visual task, and in both RNM and RM conditions (Figure 5 and Figure S2). In a direct contrast of the two conditions [(Movie:SD - S) > (Visual task: SD - S)], none of the subjects showed a significant difference in activa-

tion within the STG. There was some effect of task in that in the RM condition the number of suprathreshold voxels within the anatomically defined PT was somewhat larger when the subject watched a movie than when he or she performed the visual task [F(1,5) = 7.03, p = 0.045]. In contrast, there was no significant difference between tasks in the number of suprathreshold voxels in the RNM condition, and in fact there were nominally more active voxels in the visual go-nogo task (mean 675.5, SEM 140.5) than in the movie-watching task (mean 601 ± 64.3) for this condition. Finally, we used the region activated within the PT in experiment 1 as a predefined ROI (as in the analysis of experiment 2) and extracted from it the average parameter estimate obtained in experiment 3 for the contrast

(SD – D) for each condition. As in experiment 2, these values were significantly larger than zero for all conditions (p < 0.05), with no significant effect of tasks (F < 1 in a Task × Side within-subject ANOVA for RM and RNM; Figure S3). Thus, this experiment confirms that the PT becomes active in response to auditory spatial change even when subjects actively attend to the visual modality.

General Discussion

The critical results of the present set of experiments can be summarized as follows. First, changes in sound location, confined to a hemifield, elicit a neural response within the STG, and specifically at the medial PT bilaterally. Moreover, in contrast to previous claims (Zimmer and Macaluso, 2005), we show that deliberate attention to sound location or even to sounds in general is not necessary for this region to respond. Second, the activity in the PT is sensitive to the degree of adaptation of spatially specific neural units. The more locations presented, the greater the activity. Third, nonintentional processing of spatial changes involves regions outside the STG. For sounds presented in the right hemifield, active regions include the left inferior parietal lobule, left middle occipital gyrus, bilateral IFG, and right anterior cingulate.

Planum Temporale Activation

The planum temporale has been implicated in spatial processing using hemodynamic imaging previously, but in most prior research, participants' attention was directed toward the sounds, and in most cases specifically toward their spatial location. A previous attempt to elicit a response to unattended spatial changes in an MMN paradigm with fMRI failed (Doeller et al., 2003), despite using up to two times larger deviations than used herein. Several elements of our methods may have made our study more sensitive in this respect. First, we used a sparse design in which sounds (both standards and deviants) were presented in silence, without the interruption or masking created by scanner noise. In contrast, Doeller et al. presented their sounds on the background of the scanner noise. Second, we used specialized electrodynamic headphones, which by nature do not distort the interaural time and level differences. In contrast, Doeller et al. used pneumatic headsets, which are less optimal for maintaining accurate interaural timing and level differences. Note that in their accompanying ERP study, Doeller et al. used a different experimental setup with electrostatic headphones. Third, we used unrecognizable spectrally rich sounds. Spectrally rich sounds have been shown to provide more localization cues, and auditory cortex neurons of primates are more sensitive to the spatial location of sounds with broader spectral content (Recanzone et al., 2000). Last, the sounds were individually matched to the subject by using prior recording obtained from his or her ear canals (see Experimental Procedures; cf. Pavani et al., 2002). This procedure has been shown to produce better localization performance than application of generalized head-related transfer functions or fixed interaural time and intensity

differences (Hammershoi and Möller, 2002; Möller et al., 1996). Indeed, we made sure that our subjects could accurately determine the relative positions of the sounds (see Experimental Procedures).

The site of activation in the medial PT matches closely the location described by Warren and Griffiths (2003) as well as Warren et al. (2002). Their task required the subjects to listen to sounds that rotated around the head and indicate when the rotation stops. Likewise, this general region was activated in several other experiments in which subjects attended to moving sounds (e.g., Baumgart et al., 1999; Bremmer et al., 2001; Lewis et al., 2000). A recent study congruently showed MEG sources in the vicinity of the PT that are adapted by spatially identical stimuli but not by phonetically identical stimuli (Ahveninen et al., 2006). The similar findings in these studies, under different paradigms, indicate that this area in the medial PT is reliably involved in spatial processing. The present study adds critical information on the parameters of activation in this area. (1) The space-related activity is not dependent on attentive listening to spatial change or on active localization of sound. Rather, it is automatically generated by changes in spatial location, even when sound processing is not required by the ongoing task. (2) The region is sensitive to *within-hemispace* changes of 45°. Previous studies have used a larger range of changes throughout blocks. In our three experiments, occasional shifts of 45° were enough to cause activation. (3) Rare, discrete shifts in space are sufficient to elicit responses in this area. In most previous experiments, sounds shifted in a predictable direction, creating either a sense of a smoothly moving target or, at least, allowing the next location to be roughly predicted. Thus, the PT response could have been related to tracking rather than to basic spatial encoding.

A recent fMRI study using a different design came to the opposite conclusion as ours regarding the automaticity of the PT response (Zimmer and Macaluso, 2005). This study manipulated the interaural coherence of noise bursts delivered binaurally. While coherence was directly correlated with localization performance and with posterior STG activation during active sound localization, coherence did not affect this region during passive listening. Thus, Zimmer and Macaluso concluded that active localization is required for eliciting posterior STG activation related to spatial processing. There are several differences between the design of this study and ours. One in particular could be critical for explaining the conflicting results. While we show that PT activation depends on the presence of variation in sound source location, Zimmer and Macaluso used a block design in their passive experiment (experiment 2), in which all sounds had the same virtual sound location (center) within block. Our results show that the PT neurons are in fact sensitive to spatial positions when the location of sounds or even the sounds themselves are not relevant to the task. We suggest that this can be shown in fMRI in passive attention situations or even when attention is actively directed to another modality,

provided that variable sound sources are compared with nonvarying sound sources. This may be due to the non-topographic representation of space in this area, on which we elaborate below. The fact that the PT is sensitive by default to spatial change does not imply that it is encapsulated from any effects of attentional top-down influences. Although our experiment 3 shows that PT is active similarly when subjects passively watch a movie or when they perform a test requiring sustained visual attention, a systematic manipulation of attentional load is required to assess the degree to which this activity depends on available resources (Shalgi and Deouell, 2007).

A suggested model of PT computation hypothesizes that template matching is a critical mechanism by which neurons in this area perform the task of disambiguation of incoming stimuli (Griffiths and Warren, 2002). These templates may be of varying timescales, including online templates underlying the MMN, as well as longer-term stored templates. Considering the individualized stimuli used in the present study, our findings are in line with Warren et al.'s (2005) recent conjecture that, regarding spatial processing, the relevant stored templates may be based on the individual's own head-related transfer functions, including the pinnae-related spectral cues.

The medial PT may not be exclusively dedicated to spatial processing per se. It has been shown to be activated also by conditions in which spatial information was not manipulated (see Warren et al., 2005, for a recent review). One recent suggestion is that this region, a part of the so-called "dorsal" auditory pathway, is generally responsible for auditory-motor transformations (Warren et al., 2005). If this is true, then the spatial resolution within this region may limit the accuracy of motion toward objects as determined solely by sound. Thus, it is important to determine this resolution. Our study suggests that within-hemispace discrimination exists in the human PT and sets its minimal resolution (or just noticeable difference) at 45°. This may be too conservative though, and further parametric fMRI studies will need to challenge this limit. In a recent parametric EEG study with free-field stimuli, we have found MMN responses for changes as small as 10° within hemispace, and the response was correlated significantly with the degree of change, in steps of 10° (Deouell et al., 2006). Moreover, source reconstruction of these EEG data using the LORETA method localized this mismatch response to the medial planum temporale bilaterally, with peak coordinates of x: ± 59, y: −32, z: 8/15 on the left and right side, respectively, compatible with the locations found in the current fMRI study.

The claim that relatively fine resolution of spatial representation exists in human PT may seem inconsistent with a few previous imaging studies that did not find spatiotopic mapping in the auditory cortex (e.g., Woldorff et al., 1999; Zatorre et al., 2002; Zimmer and Macaluso, 2005; Zimmer et al., 2006). How do these negative findings fit with the differential spatial responses within the PT found here? One plausible explanation is that neurons in the medial PT do have distinct spatial tuning curves,

which are steep enough to discriminate intrahemispace locations, but these neurons are mixed within the voxels captured by fMRI. Indeed, single-unit measurements in monkeys consistently find only minimal clustering of neurons with close spatial receptive fields (Recanzone et al., 2000). Thus, one fMRI voxel would not show a predilection to be activated more than others in response to stimuli in a particular location in space. This limitation of the spatial resolution of the fMRI technique (not to be mixed with the spatial resolution of neurons) has been addressed before by Grill-Spector and her colleagues who suggested the "fMRI adaptation" method to deduce the characteristics of neurons at the subvoxel level (Grill-Spector et al., 1999; Grill-Spector and Malach, 2001). The underlying premise of this method is that if all neurons within a voxel respond similarly to a group of stimuli, they will adapt more than if separate groups of neurons respond only to one or to a subset of stimuli and not to the others. Our design, especially experiments 2 and 3, fits well into this framework. The PT region of interest was more active when two stimuli of different locations were presented alternatively than when only one was presented, and even more so when stimuli from five different locations were presented within a block. Thus, different neuronal populations must have been present within each voxel, each with its own tuning curve or stimulus-specific adaptation characteristics (cf. Ulanovsky et al., 2003, 2004).

Conclusions

We show here that spatial variation in an unattended stream of sounds elicits a response in a region of the planum temporale previously shown to be active during attentive listening. Together with our previous EEG study (Deouell et al., 2006), the results of the three experiments suggest that neurons in this region represent, in a nonintentional or preattentive fashion, the location of sound sources in the environment. The medial PT region may parallel the monkey caudal belt fields (CM and CL), which were found to harbor spatially sensitive neurons, correlated with localization behavior (Recanzone et al., 2000; Tian et al., 2001). Space representation in this region may provide the neural substrate needed for an orientation response to critical auditory events and for linking auditory information with information acquired through other modalities.

EXPERIMENTAL PROCEDURES

Subjects
Thirteen subjects (nine women and four men) from the UC Berkeley community participated in experiment 1 (mean age 23, range 19–43; 11 right handed, one left handed, and one ambidextrous). They all had normal, symmetrical hearing, by their report. The recording of one more subject was aborted due to the subject's discomfort. Nine subjects (eight women, one man, eight right handed, one left handed, mean age 23, range 19–27) participated in experiment 2. One more subject was scanned, but data had to be discarded due to a technical error. Six subjects (two women and four men), students at the Hebrew University of Jerusalem, participated in experiment 3 (ages 25–35, mean 29.3, one right handed, four left handed, and one ambidextrous). All subjects gave informed consents prior to participation. The

procedures were approved by the institutional review board at the University of California, Berkeley (experiments 1 and 2) and the Tel Aviv Medical Center, Israel (experiment 3).

Stimuli

In the pitch mismatch condition, stimuli were complex tones consisting of a fundamental of 500 or 600 Hz and three harmonics (integer multiples of the fundamental) with decreasing amplitudes. The stimuli used in the spatial mismatch conditions of all three experiments were created by randomly mixing (by time series summation) 20 recordings of environmental sounds (e.g., water running, engine noise, animal vocalizations) downloaded from the internet. A segment of 200 ms of the mixed sound (with 10 ms rise and fall time) was used for this experiment. In pilot studies, we found that this stimulus robustly activates the auditory cortex. It was impossible to recognize any of the constituents of the sound in this short noise burst (Figure S6). To create maximally externalized and localizable sounds, each subject went through the following procedure of binaural recording (Figure S5). Prior to the fMRI experiment, the subject was seated in a sound-attenuated and echo-reduced chamber, in the center of a semicircular array of five loudspeakers positioned at approximately ear height, in the frontal plain, 90 cm from the center of the head at ±60°, ±15°, and 0° relative to the midsagittal plane (negative numbers are to the left). Each subject was equipped with two miniature electret microphones (Sennheiser KE4-211-2) embedded in-ear plugs placed in the external auditory canal, pointing outward, with their front end aligned with the external auditory meatus. The sounds were played from each loudspeaker in turn and recorded by the intra-aural microphones to disk via a stereophonic preamplifier (Audio Buddy, M-Audio, USA) which fed into a sound card (Mia 24, Echo, USA, for experiments 1 and 2, Audigy 2 ZS for experiment 3) recording at 24 bits with a 44.1 Kb/s sampling rate. Residual low-frequency noise ("humm"), under 30 Hz, was digitally filtered out. The frequency spectrum of the mixed sounds thus recorded had its main power between 30 and 7300 Hz. Recorded this way, the stereophonic sounds genuinely reflected the sound pressure at the external auditory meati of the subjects, with all individual binaural and pinnae related spatial cues embedded (Hammershoi and Möller, 2002; Möller et al., 1996). These individual binaural recordings were later used as subject-specific stimuli in the fMRI session. For the experiment, the recorded sounds were trimmed to 250 ms segments, including 10 ms prior to the played stimulus onset and 40 ms after the stimulus offset, including room reverberations extending after the offset of the played sound.

Sound Delivery

To achieve good localization, the timing, level, and spectral information had to be preserved. We used fMRI-compatible electrodynamic headphones (MR-Confon, Germany) to deliver the sounds. To compensate for both the particular frequency response of the microphones used for the recordings and that of the headphones, the two were calibrated in closed loop. This was done by playing white noise through the headphones, in the MRI scanner, to a pilot subject wearing the electret microphones in his ear canals and adjusting the playback using a 1/3 octave graphical equalizer so as to get as flat as possible frequency response in the resultant recording. These equalization settings, which need to be established only once, were used to play the sounds to the subjects. This method of using individual binaural recordings has been shown to allow superior localization of sound over other methods of virtual space production, such as general head-related transfer functions, and in fact were found equal to real-life localization (Möller et al., 1996). Finally, to validate the effectivity of the method, each subject was tested in the scanner before starting any actual scanning. Eighty-four pairs of stimuli recorded as described above were presented, and subjects indicated, with button presses, whether the second sound was more to the left, to the right, or in the same position as the first sound. All subjects performed the task with an accuracy of over 90%.

Experiment 1 Procedure

Subjects were tested across five functional runs, each run consisting of 40 blocks. Two types of blocks alternated in each run, lasting 10 s and followed by acquisition of one EPI brain volume lasting 2 s. No scanning was done during the block. With the exception of silent blocks in the first run, each block consisted of 25 sounds, at a constant rate of 2.5 per second (SOA = 400 ms). On-Off, Location, and Pitch conditions were tested in separate runs. The first, an On-Off run, contrasted sound blocks filled with the mixed noise bursts recorded at 60° to the right, and blocks of silence. Following this run, Location and Pitch runs alternated, with the order counterbalanced across subjects. For each run in both Location and Pitch conditions, all the stimuli were standard in one-half of the blocks (S blocks), whereas in the other half of the blocks (SD blocks), 20% of the stimuli were deviants and 80% were standards. Deviants and standards were mixed in SD blocks in a quasirandom order, with the constraint that at least three standards preceded each deviant and that at least two deviants occurred during the last 4 s of the block. This was done to ensure that the scan following the block captured the response to the deviant somewhere around its peak. In one Location run, the standards were mixed noise bursts recorded at 60°, whereas the deviants were bursts recorded at 15° to the right. In the other run, the standard was at 15° and the deviant at 60°. The two runs were then analyzed together. In the two Pitch runs, 500 Hz harmonic tones at 60° were standards and 600 Hz tones at the same position were deviants in one run, and vice versa in the other run.

Experiment 2 Procedure

All stimuli in this experiment were the subject-specific, spatially localizable mixed noise recordings described above. Three conditions (two runs each) were tested: "Rare mismatch (RM)," "Rare nonmismatch (RNM)," and "Equal." In each, half of the blocks included only one type of stimulus (S blocks), and the other half of the blocks included two or more different stimuli (for consistency with experiment 1, we continue to call these SD blocks). These blocks alternated within each run. The *RM* condition was identical to the Location condition in experiment 1 (with 20% deviant/80% standard trials). In the *RNM* condition, S blocks consisted of sounds at 60°, whereas SD blocks consisted of a mixture of sounds at −60°, −15°, 0°, 15°, and 60°, with equal 20% probabilities. The order of the sounds in this block was quasirandom, with the constraints that two consecutive sounds were always from different locations and the difference in location between two consecutive sounds was between 30° and 60°. The latter constraint prevented highly salient jumps of sound from one side to the other (e.g., from far left to far right) that might orient the subjects toward the sounds and create a "novelty" effect. The constraint also kept the changes in the range of that experienced in the SD blocks of the RM condition. In the "*Equal*" condition, SD blocks consisted of equal portions of sounds at 60° and 15°, which alternated regularly. The S blocks in one run consisted of stimuli at 15° and in the other run the stimuli of the S blocks were at 60°. The order of the conditions was counterbalanced between subjects.

Experiment 3 Procedure

The auditory conditions replicated those of the RM and RNM of experiment 2, with the exception that each run consisted of 20 blocks rather than 40, which was deemed too long for an active task. Based on the signal-to-noise ratio found in experiment 2 and the need to keep the experiment within reasonable length, the RM condition was tested for eight runs, and the RNM for only four runs. One of the subjects was tested only with the RM condition. In alternating runs (order counterbalanced across subjects), the subjects' task was to ignore the sounds and watch a silent subtitled movie (replicating experiments 1 and 2) or to perform a go-nogo visual task. The visual trials consisted of 200 ms presentation of a digit (1–9 ; black on an 80 × 80 pixels white background, font Arial), followed by 800 ms response interval. The digits were presented in one of five randomly allocated font sizes to enhance the demands for processing the numerical value rather than

some peripheral feature of the nonresponse targets (Robertson et al., 1997). The subjects were instructed to fixate a cross in the middle of the screen and to push a fiber-optic response button as fast as possible upon seeing an odd number while refraining from pressing for even numbers. False alarms were followed by a red asterisk for the duration of the remaining interstimulus interval, alerting the subjects of their error. At the end of each run, a feedback screen informed the subjects of their hit and false alarm rate as well as the mean reaction time.

MRI Acquisition

For experiments 1 and 2, scanning was performed on a 4 Tesla INOVA scanner (Varian, Inc., USA) at the Brain Imaging Center at the University of California at Berkeley, using a quadrature transmit-receive coil (MR Instruments, Inc., Minneapolis, MN). Subject were positioned in the scanner with the headphones in place and supported by a cushion. First- and second-order shimming were used to correct for inhomogeneity of the field. Eighteen axial slices, with voxel size of 3.5 × 3.5 × 3.5 mm, covering the whole cerebrum were aligned with the AC-PC line. Subjects were first scanned with a T1 weighted sequence to generate anatomical images coregistered with the functional data. Functional data were acquired using a gradient echo EPI sparse sequence with TE = 28 ms, TR = 12 s, and TA (time of acquisition) = 2 s. Last, a high-resolution T1 weighted MPFLASH image was taken with resolution of 1 × 1 × 1 mm. Experiment 3 was conducted on a 3 Tesla Siemens Magnetom Trio at the Asher Center for Human Brain Imaging at the Weizmann Institute, Rehovot, Israel. Twenty-two axial slices with resolution of 3.5 × 3.5 × 3.5 were acquired. Parameters of the EPI sequence were TE = 30 ms, TR = 12 s, TA = 2 s. As for experiments 1 and 2, the functional scans were preceded by a T1 coplanar anatomical scan and followed by a high-resolution 3D MPRAGE T1 weighted image.

fMRI Analysis

fMRI analysis was performed using the SPM2 package (http://www.fil.ion.ucl.ac.uk/spm/software/spm2). Scans were motion corrected by realigning to the first EPI image, normalized to the MNI space, and smoothed with an 8 × 8 × 8 Gaussian kernel. Stimulation-related activation was mapped using the general linear model approach. Each block was modeled as an event of 10 s duration, convolved with a canonical HRF. Linear trends were removed from each run, and low-frequency noise was reduced using a high-pass filter with a cutoff of 0.008 Hz. For each subject, contrasts were performed between the Silence and Sound blocks in the first On-Off run and between the S and SD blocks in the Location and Pitch runs of the first experiment, as well as between S and SD runs of the RM, RNM, and Equal conditions of the second and third experiment. For experiment 1, a second-level random-effect group analysis was then performed to yield statistical parametric maps of the resulting t values for each contrast at the group level. A region of interest of the full extent of the superior temporal gyrus was predefined using the Automated Anatomical Labeling system (AAL) (Tzourio-Mazoyer et al., 2002), combining bilaterally the areas labeled superior temporal gyrus, Heschl gyrus and temporal pole. A random-effect contrast was deemed significant if it passed a significance level of p < 0.05, corrected for multiple comparisons within the ROI, using random field theory as implemented in SPM2. A more liberal criterion of p < 0.001, uncorrected, and a minimal cluster of ten voxels was used to look for activation across the whole brain in experiments 1 and 3. For the second and third experiments, designed to test contrasting accounts of the results of experiment 1, we used the areas found active within the STG in experiment 1 (using the uncorrected 0.001 threshold) as predefined ROIs. The average β values (regression coefficients) within these ROIs were used as the dependent variable in the analysis of experiments 2 and 3.

Supplemental Data

The Supplemental Data for this article can be found online at http://www.neuron.org/cgi/content/full/55/6/985/DC1/.

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