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Modulation of response patterns in human auditory cortex during a target detection task: An intracranial electrophysiology study

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Abstract

Selective attention enhances cortical activity representing an attended sound stream in human posterolateral superior temporal gyrus (PLST). It is unclear, however, what mechanisms are associated with a target detection task that necessitates sustained attention (vigilance) to a sound stream. We compared responses elicited by target and non-target sounds, and to sounds presented in a passive-listening paradigm. Subjects were neurosurgical patients undergoing invasive monitoring for medically refractory epilepsy. Stimuli were complex tones, band-limited noise bursts and speech syllables. High gamma cortical activity (70–150 Hz) was examined in all subjects using subdural grid electrodes implanted over PLST. Additionally, responses were measured from depth electrodes implanted within Heschl's gyrus (HG) in one subject. Responses to target sounds recorded from PLST were increased when compared to responses elicited by the same sounds when they were not-targets, and when they were presented during passive listening. Increases in high gamma activity to target sounds occurred during later portions (after 250 ms) of the response. These increases were related to the task and not to detailed stimulus characteristics. In contrast, earlier activity that did not vary across conditions did represent stimulus acoustic characteristics. Effects observed on PLST were not noted in HG. No consistent effects were noted in the averaged evoked potentials in either cortical region. We conclude that task dependence modulates later activity in PLST during vigilance. Later activity may represent feedback from higher cortical areas. Study of concurrently recorded activity from frontoparietal areas is necessary to further clarify task-related modulation of activity on PLST.

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Keywords

Attention; Averaged evoked potential; Electrocorticography; Heschl's gyrus; High gamma; Superior temporal gyrus

1. Introduction

Attention strongly modulates neural activity in human auditory cortex (e.g., Petkov et al., 2004; Elhilai et al., 2009). Attention-related modulation can be detected using multiple non-invasive methodologies that include scalp-recorded averaged evoked potentials (AEPs), event-related neuromagnetic fields (ERFs), and functional magnetic resonance imaging (fMRI) (e.g., Näätänen, 1990; Novak et al., 1990; Ding and Simon, 2012; Alho et al., 2013). These methodologies have been especially fruitful in delineating neural mechanisms subserving selective attention by permitting the simultaneous comparison of neural activity elicited by attended and unattended sound streams. A classic example of a selective attention task utilizes a dichotic listening paradigm, wherein subjects respond to target stimuli embedded in a sequence of non-targets delivered to one ear, while ignoring simultaneously presented sounds delivered to the opposite ear. It has been shown using this paradigm or its methodological variants that both target and non-target attended stimuli elicit larger amplitude AEPs and ERFs than their non-attended counterparts (e.g., Giard et al., 2000). This enhancement of responses is noted at the earliest stages of auditory cortical processing, and extends to later stimulus-evoked AEP components such as the N100 (N1) and its analogous ERF response (e.g., Woldorff and Hillyard, 1991; Woldorff et al., 1993). In parallel to the gain enhancement of neural activity elicited by attended streams of sounds, neural activity elicited by non-attended sounds is actively suppressed (Giard et al., 2000; Chait et al., 2010).

Sustained attentional tasks (vigilance) also modulate neural activity in auditory cortex (e.g., Näätänen, 1990). Relevant to the current study, subjects may be required to detect a target sound embedded within a single acoustic stream. Here, the subject must attend to all stimuli in order to correctly identify the target. These “one-channel” tasks represent, in part, processes related to the performance necessary to detect targets within an attended sound stream during a selective attention task. Typically, the N1 component of the AEP (approximate latency 100 ms) and its ERF counterpart evoked in a target-detection task are larger compared to responses elicited by the same sounds when subjects ignore the stimuli (Näätänen and Picton, 1987). These task-related increases are present in responses to both target and non-target stimuli. Processing-contingent potentials are also generated when subjects perform a target detection task. These potentials are termed endogenous because they are not automatically generated by acoustic attributes of sounds, but instead represent neural indices of active sound processing. Both targets and non-targets elicit processing negativities that overlap in time with later exogenous potentials (e.g., Novak et al., 1990). Targets also elicit another processing negativity termed N2 for its approximate latency of 200 ms (e.g., Gamble and Luck, 2011; Rimmele et al., 2011).

While non-invasive studies provide invaluable insights into the neural mechanisms subserving attention, they also suffer from significant limitations. AEPs and ERFs are

limited in their spatial resolution. fMRI studies provide results with superior spatial resolution, but are limited in their temporal resolution and also represent an indirect measure of tissue activation. In contrast, invasive electrophysiologic studies obtained during the clinical evaluation of neurosurgical patients provide direct measures of tissue activation with both high temporal and spatial resolution. These advantages are exemplified by data acquired while subjects perform selective attention tasks. Enhanced transient and sustained AEP components are generated in core auditory cortex located on the posteromedial portion of Heschl's gyrus (HG) and in the surrounding auditory cortex on the superior temporal plane (Bidet-Caulet et al., 2007). Similar enhancements are seen in non-core auditory cortex located on the posterolateral portion of the superior temporal gyrus (PLST) (Neelon et al., 2006). In a dramatic demonstration of the neural mechanisms underlying selective attention, high gamma components of the electrocorticogram (ECoG) recorded from PLST and representing the speech of an attended talker were enhanced, while high gamma components representing the unattended speech of a second simultaneously presented talker were suppressed (Mesgarani and Chang, 2012). The latter findings are especially noteworthy because high gamma activity has been shown to be a reasonable surrogate measure of action potential firing in neuronal ensembles (e.g., Nir et al., 2007; Steinschneider et al., 2008; Mukamel et al., 2011).

It remains unclear, however, what mechanisms are engaged in PLST when subjects perform a target detection task. This region of cortex is difficult to analyze using scalp-recorded EEG because field potentials are potentially contaminated by larger-amplitude responses volume-conducted from sources located on the superior temporal plane. Further, neuromagnetic responses are less sensitive to activity located on PLST because portions of this region have a radial orientation that leads to non-optimal detection of ERFs (Hillebrand and Barnes, 2002). These limitations can be ameliorated by performing target detection tasks in neurosurgical patients implanted with high density electrodes overlying the perisylvian region.

Thus, the goal of this study was to identify task-related contributions of auditory cortical activity on PLST when subjects performed a target detection task. Both event-related band power (ERBP) in the high gamma range and lower frequency AEPs were examined. We were also able in one subject to simultaneously examine activity emanating from PLST while concurrently examining activity from depth electrodes placed within HG. This allowed comparisons of task-related effects within core auditory cortex located in posteromedial portion of HG with non-core areas located on anterolateral HG and PLST. Transformations in sound processing from HG to PLST are important steps in the progressive encoding of sound objects along the ventral auditory cortical pathway stream (e.g., Rauschecker and Scott, 2009; Chang et al., 2010). We hypothesized that attention during a target-detection task would more strongly modulate high gamma activity in PLST than at sites within HG, and that this modulation would be evident throughout the response of this non-core cortex. We further hypothesized that the AEP would contain both larger exogenous-based potentials to targets and non-target sounds when compared to activity in the passive state, and that endogenous processing negativities would be identified. Instead, we found that attention most strongly modulated high gamma responses to target stimuli, and that this modulation occurred within later portions of the induced activity. Further, we

found no evidence of enhanced exogenous AEPs or the generation of endogenous potentials on PLST. As predicted, attention-based modulations were more prominent on PLST than in the activity within HG.

2. Methods

2.1 Subjects

Experimental subjects were three neurosurgical patients diagnosed with medically refractory epilepsy and undergoing chronic invasive ECoG monitoring to identify potentially resectable seizure foci. The subjects were 27 (L237), 23 (R198) and 38 (L258) years old. All subjects were male, right-handed and left hemisphere language-dominant, as determined by intracarotid amytal (Wada) test results. The hemisphere of recording was left in subjects L237 and L258, and right in R198. Research protocols were approved by the University of Iowa Institutional Review Board and by the National Institutes of Health. Written informed consent was obtained from all subjects. Participation in the research protocol did not interfere with acquisition of clinically required data. The subjects could rescind consent at any time without interrupting their clinical evaluation.

The subjects underwent audiometric and neuropsychological evaluation before the study, and none was found to have hearing or cognitive deficits that should impact the findings presented in this study. All were native English speakers. Intracranial recordings revealed that the auditory cortical areas on the superior temporal gyrus were not epileptic foci in any subject.

Experiments were carried out in a dedicated electrically-shielded suite in The University of Iowa General Clinical Research Center. The room was quiet, with lights dimmed. Subjects were awake and reclining in an armchair.

2.2. Stimuli

Experimental stimuli were complex tones, band-pass noise bursts (BPN) and consonant-vowel-consonant (CVC) syllables. More simple, non-speech sounds were included as test stimuli because we were interested in identifying neural patterns associated with target detection on PLST without adding potential confounding factors related to phonetic processing, as well as determining whether these neural patterns would generalize to speech. Further, previous studies from this laboratory have demonstrated that PLST responds robustly to non-speech stimuli (e.g., Nourski et al., 2013, 2014). All stimuli were 300 ms long, had a 5 ms rise-fall time, and were presented with an inter-stimulus interval chosen randomly within a Gaussian distribution (mean interval 2 s; SD = 10 ms) to reduce stimulus predictability. Stimuli were delivered via insert earphones (ER4B, Etymotic Research, Elk Grove Village, IL) that were integrated into custom-fit earmolds. Stimulus delivery and data acquisition were controlled by a TDT RZ2 real-time processor (Tucker-Davis Technologies, Alachua, FL) with a sampling rate of 24414 Hz.

Experimental paradigms were varied to further test the generality of effects occurring during target detection tasks. Prior to the initiation of data collection, each subject was presented with a preview of experimental stimuli to ensure that the sounds were presented at a

comfortable listening level. In subject L237, stimuli were complex tones with fundamental frequencies ranging from 0.25 to 8 kHz in 1 octave steps. The stimuli were presented at 61 dB SPL. The stimuli were presented in four experimental blocks. In each block, an interleaved presentation paradigm was used, where the six tones were presented 40 times each in a random order. Blocks 1 (first) and 4 (last) did not require an overt response. The subject was told that he would hear a sequence of tones without additional instruction. For blocks 2 and 3, the subject was instructed to respond to the 0.5 and 4 kHz tones, respectively, by pressing a button on a response box using his left hand (ipsilateral to the recording side). Prior to the initiation of data collection during these blocks, the subject was presented with a preview of the target stimulus, followed by a practice run, with verbal feedback on correct and incorrect responses provided by a member of the research team.

Subject R198 was first instructed to press a button with his right (ipsilateral) hand whenever he heard a noise burst (BPN, 0.25 kHz center frequency, 1 octave bandwidth), randomly presented within a sequence of tonal stimuli (0.25–8 kHz fundamental, 1 octave steps). The second task was to respond to a 0.25 kHz complex tone target presented within a sequence of octave-wide BPN stimuli with matching center frequencies. The stimuli were presented 50 times each in a random order at 66 dB SPL. Prior to data collection, the subject was presented with a random-sequence preview of all stimuli to ensure that the sounds were presented at a comfortable level and that he understood the task requirements.

Finally, subject L258 participated in a target-detection experiment wherein complex tone stimuli (fundamental frequencies 0.125 or 0.25 kHz) were randomly presented within a sequence of CVC syllables spoken by different male and female speakers. The first task was to respond to complex tone stimuli, and the second task was to respond to speech stimuli uttered by female speakers. Once again, the subject previewed the sounds to ensure he was comfortable with the task.

2.3. Recordings

Recordings were made from perisylvian cortex using subdural grid electrodes, and, in subject L258, recordings were simultaneously made from HG and perisylvian cortex using multicontact depth and subdural grid electrodes, respectively. Details of electrode implantation have been described previously (Nourski and Howard, in press). In brief, hybrid depth electrode arrays were implanted stereotactically into HG, along its anterolateral to posteromedial axis. The electrodes contained 4 contacts cylindrical platinum macro-contacts, spaced 10 mm apart, and fourteen platinum micro-contacts, distributed at 2–4 mm intervals between the macro contacts. Subdural grid arrays implanted over perisylvian cortex consisted of platinum-iridium disc electrodes (2.3 mm exposed diameter, 5 mm center-to-center inter-electrode distance) embedded in a silicon membrane. The electrodes were arranged in an 8×12 grid, yielding a 3.5×5.5 cm array of 96 contacts. A subgaleal contact was used as a reference. Electrode arrays were placed solely on the basis of clinical requirements, and were part of a more extensive set of recording arrays meant to identify seizure foci. Recording electrodes remained in place under the direction of the patients' treating neurologists. Collected ECoG data were amplified, filtered (0.7–800 Hz bandpass,

12 dB/octave rolloff), digitized at a sampling rate of 2034.5 Hz, and stored for subsequent offline analysis.

Subjects underwent whole-brain high-resolution T1-weighted structural magnetic resonance imaging (MRI) scans (resolution 0.78×0.78 mm, slice thickness 1.0 mm) before electrode implantation to locate recording contacts. Two volumes were averaged to improve the signal-to-noise ratio of the MRI data sets and minimize the effects of movement artifact on image quality. Pre-implantation MRIs and post-implantation thin-sliced volumetric CT scans (resolution 0.51×0.51 mm, slice thickness 1.0 mm) were co-registered using a linear coregistration algorithm with six degrees of freedom (Jenkinson et al., 2002). Locations of recording sites were confirmed by co-registration of pre- and post-implantation structural imaging and aided by intraoperative photographs.

Behavioral responses to the target stimuli were recorded using a response box. The timing of the button-press events was recorded and stored along with ECoG data for subsequent offline analysis.

2.4. Data analysis

ECoG data obtained from each recording site were downsampled to a rate of 1000 Hz and analyzed in the time domain as AEPs and in the time-frequency domain as ERBP. Prior to extraction of AEPs and calculation of ERBP, individual trials were screened for possible contamination from electrical interference, epileptiform spikes, high amplitude slow wave activity, or movement artifacts. To that end, individual trial waveforms with voltage exceeding 2.5 standard deviations from the mean were rejected from further analysis. To minimize contamination with power line noise, ECoG waveforms were de-noised using an adaptive notch filtering procedure (Nourski et al., 2013). Data analysis was performed using custom software written in MATLAB Version 7.14 programming environment (MathWorks, Natick, MA, USA).

Time-frequency analysis of the ECoG was performed using wavelet transforms based on complex Morlet wavelets following the approach of Oya et al. (2002). Center frequencies ranged from 20 to 200 Hz in 5 Hz increments. ERBP was calculated for each center frequency on a trial-by-trial basis, log-transformed, normalized to mean baseline power measured using wavelets centered between 200 and 100 ms prior to stimulus onset, and then averaged across trials.

To ensure that changes in the prestimulus baseline across recording blocks did not significantly affect the main findings of this report, we first calculated average baseline high gamma power over trials and recording sites for each recording block. Baseline high gamma power was slightly lower in the active blocks when compared to the passive conditions. However, recording sites that contributed to this difference were outside the region of STG that displayed the main effects. Thus, these baseline differences did not qualitatively confound the task-related results.

Quantitative analysis of the ERBP focused on the high gamma ECoG frequency band, which has been shown to be a sensitive and specific indicator of auditory cortical activation (Crone

et al. 2001; Edwards et al. 2009; Steinschneider et al. 2008, 2011; Mesgarani and Chang 2012; Pasley et al. 2012; Nourski et al., 2014). High gamma band was defined in the present study as the range of center frequencies between 70 and 150 Hz. The wavelet constant ratio used for time-frequency analysis was defined as $f_0/\sigma_f = 9$, where f_0 is the center frequency of the wavelet and σ_f is its standard deviation in frequency. Average high gamma ERBP values were calculated for each recording site within 50 ms time windows with a 50% overlap. Statistical significance of measured ERBP was determined via paired *t*-tests comparing average ERBP values within each time window versus that within an equal duration reference interval spanning 175 to 125 ms before stimulus onset. Correction for multiple comparisons was done by controlling false discovery rate (Benjamini and Hochberg, 1995; Benjamini et al., 2001) at $q < 0.01$.

Activation across all acoustically responsive sites on the lateral surface of the temporal lobe was measured by averaging the ERBP values across all recording sites and all 50 ms windows within 1 s following stimulus onset. Modulation of cortical activity under different stimulus conditions (first and second passive listening block, non-target or target stimulus in a target-detection task) was assessed by measuring corresponding changes in across-grid average ERBP values in each 50 ms time bin.

Activation patterns across the entire recording grid in subject L237 were examined using multivariate pattern analysis to determine whether sufficient information was available in the neural responses to accurately differentiate the six complex tones. The classifier was trained to discriminate the fundamental frequency of each tone stimulus based on the brain responses recorded simultaneously from all contacts (for methodological details, see Nourski et al., 2014).

3. Results

Target detection tasks modulate auditory cortical activity located on PLST. These effects are exemplified by a comparison of response patterns elicited by complex tones during passive listening and a target detection task in subject L237 (Fig. 1). Electrode grid and the location of a responsive recording site on PLST of the left hemisphere (black star) are depicted in Figure 1a. The four panels in Figure 1b correspond to the four experimental blocks. In the first and the last block (Passive 1 and Passive 2, respectively) the subject was not required to either attend or respond to the sounds. The panel labeled “Active (target)” denotes activity elicited by the 0.5 kHz tone when it was the target stimulus. The panel labeled “Active (non-target)” represents activity by the same 0.5 kHz tone, but the target in this acquisition block was a 4 kHz tone. AEP waveforms are superimposed on the time-frequency plots depicting ERBP for a range of ECoG frequencies between 20 and 200 Hz.

High gamma activity at the exemplary PLST recording site was strongly modulated by task demands. When the subject was not required to perform a target detection task (i.e., blocks Passive 1 and Passive 2), the ERBP response was primarily restricted to a relatively short interval rapidly following stimulus onset. The 0.5 kHz tone elicited a similar pattern of activity when the target sound was a 4 kHz tone [Active (non-target)]. However, there was a markedly enhanced ERBP response both in magnitude and duration when the 0.5 kHz tone

was the target stimulus. Surprisingly, there was no significant increase in the AEP amplitude when the 0.5 kHz tone was the target as suggested by previous studies (Kiehl et al., 2001; Neelon et al., 2006, 2011).

Target-detection tasks increased stimulus-induced high gamma activity within PLST, and these increases were further augmented when the stimulus was a target. Findings are illustrated in Figure 2, which quantifies high gamma activity collapsed across all recording channels within the time interval spanning from 0 to 1000 ms after stimulus onset (i.e., including 700 ms after stimulus offset). A univariate ANOVA of single-trial data revealed main effects of order (first vs. second passive or active block, $p < 0.001$), attention (active vs. passive experimental blocks, $p < 0.001$), target (vs. non-target, $p < 0.001$), and an interaction of order and attention ($p < 0.001$). The order of presentation modulated high gamma activity on PLST: the first of the passive and active conditions were larger than the second repetition of the passive and active pairs, suggesting decreased attention over time or habituation to the stimuli or the behavioral paradigm. Also, responses to all tones were larger in the attended conditions than in the two passive conditions. Finally, the 0.5 kHz and 4.0 kHz tones elicited larger responses when they were targets relative to when they were non-targets. Overall, smaller increases noted for the 4 kHz tone relative to the 0.5 kHz tone may represent, at least in part, the result of presentation order and, as will be shown in Figure 3, a more restricted activation pattern over PLST.

While there were significant target effects in the overall high gamma activity averaged across the entire electrode grid, response increases to the target sounds were both temporally specific and spatially restricted. This is exemplified in Figure 3a, which depicts the time course of high gamma responses at each recording site elicited by the 0.5 kHz tone. Different colors represent activity recorded during the four experimental blocks. Response profiles depicted in red represent the 0.5 kHz target. Large amplitude increases in high gamma were primarily observed on recording sites located over PLST in this subject (outlined by grey lines). Importantly, early activity over all recording sites was similar despite variations in the experimental conditions. Thus, early activity up to approximately 150 ms after stimulus onset was nearly identical for the condition when the 0.5 kHz tone was the target relative to when responses to the 0.5 kHz tone were recorded without an active behavioral task (Passive 1 and Passive 2, blue and green waveforms, respectively) or when the 4.0 kHz tone was the target (yellow waveform). Increases specific to the 0.5 kHz target occurred later in time and at a subset of those sites which were active in all conditions. For instance, high gamma activity at site X was increased to a similar degree for all conditions. This contrasts with activity at site Y (site also depicted in Fig. 1). Here, there were non-specific increases in early activity and target-specific increases in later activity.

Similar patterns of high gamma activity were observed in responses to the 4.0 kHz tone (Fig. 3b). Waveforms shown in red now depict responses to the 4 kHz tone when it was the target. As can be seen when comparing Figures 3a and 3b, the 4 kHz tone elicited large-amplitude responses over a more restricted portion of PLST compared to responses elicited by the 0.5 kHz tone. Once again, however, early activity was not strongly modulated by the task while later activity was target-specific. Importantly, there was overlap in the distribution of later responses when either tone was the target. For instance, site Y exhibited an enhancement in

later activity when either the 0.5 or 4 kHz tone were targets. This indicates that this later activity is not encoding stimulus frequency-specific information, but instead is related to the target detection task.

Temporal dynamics of task-related high gamma activity across experimental blocks and in relation to the behavioral responses is depicted in Figure 4. Responses now represent differences in high gamma ERBP averaged across the entire recording grid in 50 ms bins. Figure 4a presents pairwise comparisons between responses elicited by the 0.5 kHz tone in the various experimental blocks. Arrowheads below each plot represent the behavioral response times (button-push responses to the target stimuli during the active blocks). In the 0.5 kHz target detection task, the 40 target trials were associated with 32 hits (509.5 ms median response time) and 8 misses. In the 4 kHz target detection task, the subject had 28 hits (721.5 ms median response time) and 12 misses on the 40 target trials. Responses to the 4 kHz target were significantly slower compared to the 0.5 kHz target ($p < 0.005$, Mann-Whitney rank sum test). This finding, along with a higher number of missed target trials, suggests that either the 4 kHz tone was a more difficult target for the subject compared to 0.5 kHz stimulus or the subject was less interested in performing the task. Further, we cannot exclude the possibility that some of the target trials were missed due to the next stimulus being presented at an interstimulus interval of approximately 2 s, resulting in behavioral performance being interrupted by the occurrence of the next stimulus.

Regardless of whether one compares response to the target relative to the two passive blocks or when the 4 kHz tone was the target, increases were maximal approximately 300 ms after stimulus onset (Fig. 4a, top row). Other pairwise comparisons failed to show these large amplitude increases that appeared specific for the target stimuli (Fig. 4a, bottom row). The small increases noted between Non-target and Passive 2 as well as comparisons between the two passive conditions are likely, in part, manifestations of the previously described effect of order on the neural responses. While the quantitative effects of stimulus condition were smaller in responses to 4 kHz tones (Fig. 4b), qualitatively, target-related effects were consistent with those observed when the 0.5 kHz tone was the target. Further, for both targets, the distribution of behavioral response times was, in general, later compared to the timing of the maximal differences in the high gamma responses.

Target-specific late activity could be associated with a number of factors. For instance, it could represent activity associated with the categorization of the stimulus as the target. On the other hand, this activity could be directly associated with the behavioral response (e.g., auditory-motor planning). If this latter idea is the case, then one should expect that the latency of this activity will co-vary with behavioral response time, and be absent on trials when the subject did not respond to the target stimulus. We examined these possibilities by separating activity on PLST based on reaction time (fast hits with reaction times less than the median and slow hits with reaction times greater than the median) and on trials where the subject missed the target. This analysis is depicted in Figure 5, which illustrates the high gamma envelopes at sites designated X and Y in Figure 3. Figure 5a illustrates activity elicited by the 0.5 kHz complex tone when it was the target versus that obtained in the first passive recording block, whereas Figure 5b depicts the high gamma activity elicited by the 4.0 kHz tone when it was the target versus that obtained in the first passive recording block.

Activity at site X was minimally modulated by reaction time or on “missed” trials when compared against activity occurring during passive stimulus presentations. In contrast, activity at site Y was strongly modulated by the behavioral task condition. Most importantly, the enhanced late response observed when the stimulus was the target did not covary in latency with reaction time, and occurred even when the subject failed to behaviorally respond. Early activity was not strongly modulated, and was similar across all conditions when compared to the response obtained in the passive, awake paradigm. Effects were similar for both active conditions. Therefore, these findings are consistent with the late activity being a manifestation of target categorization in PLST and not being tied directly to behavioral performance.

The observation that later activity appears to reflect task-, but not stimulus-related activation of PLST, mandates that earlier activity represents the specific acoustic attributes of the sounds. We examined this issue by applying multivariate pattern analysis to single-trial high gamma activity occurring across the recording grid (Fig. 6). The ability to accurately predict the specific complex tone was examined in 50 ms bins. We found that classification accuracy was considerably above chance (16.7%) in all four blocks and peaked (~40%) at around 200 ms after stimulus onset, in concordance with earlier data obtained under passive listening conditions (Nourski et al., 2014; see also Chang et al., 2011; Steinschneider et al., 2011).

Prior to implementing this experimental paradigm, a similar, albeit more truncated, paradigm was carried out in another subject with recording electrodes located over the perisylvian cortex of the right, non-dominant hemisphere (Fig. 7a). Two experimental blocks were performed. In the first block, six complex tones were presented along with a target stimulus which was a bandpass noise burst (0.25 kHz center frequency, 1 octave bandwidth). The subject responded with 47 hits (median response time = 772 ms) and 3 misses. In the second block, the non-target stimuli were six 1 octave-wide BPN bursts with center frequencies ranging from 0.25 to 8 kHz in 1-octave steps. The target was a 0.25 kHz complex tone. In this task, the subject responded with 49 hits (median response time = 871 ms) and 1 miss. Performance in the tone target detection task was slower compared to the noise detection task ($p < 0.05$, Mann-Whitney rank sum test).

In both blocks, the target stimuli elicited considerably larger responses than any of the non-target stimuli in either block (including the same stimuli presented as non-targets). Fig. 7b represents high gamma ERBP averaged across the entire recording grid for the time interval of 1 s after the stimulus onset for both blocks. The timing of these increases, as measured across the entire grid, was examined and revealed a peak specific for the target, maximal between 250 and 350 ms (Fig. 7c). Additionally, there was an early increase in high gamma ERBP when the 0.25 Hz BPN stimulus was the target relative to the non-target condition. Similar to the previous subject, an order effect appears to be present wherein enhancement of early activity occurred during the first experimental block when compared to the later experimental block.

A third paradigm using a more complex stimulus set was presented to another subject to test the generality of effects when speech stimuli are target stimuli, and also to test whether

results similar to those observed on PLST would occur in Heschl's gyrus. Electrodes were implanted in Heschl's gyrus and over the lateral perisylvian cortex of the left hemisphere (Fig. 8a). In the first experimental block, target stimuli were 40 harmonic tones (28 with fundamental frequency 0.125 kHz and 12 with fundamental frequency 0.25 kHz) randomly presented in sequences of 140 consonant-vowel-consonant words and non-words spoken by male and female speakers. All stimuli were 300 ms in duration. The subject responded with 37 hits (median response time = 698 ms) and 3 misses.

Responses to these targets were compared to responses from the same stimuli in a second recording block where targets were female speakers. Responses to female speaker targets were compared to the same sounds when the complex tones were targets. In this block, the subject had 38 hits (median response time = 762 ms; not significantly different from tone detection task, $p = 0.054$, Mann-Whitney rank sum test), and 10 misses. The relatively low hit rate in the latter task was likely due to the subject's fatigue, as the subject then requested that further data collection be postponed.

Representative responses from the posteromedial and anterolateral Heschl's gyrus, and PLST are shown in Figure 8b. Minimal increases in ERBP or changes in the AEPs occur when the tones or speech syllables were the target within Heschl's gyrus (high gamma waveforms not shown, data upon request). ERBP at 3 representative sites on PLST show varying degrees of enhanced responses to target stimuli. No increases in AEP amplitude were observed when comparing responses elicited by target and non-target stimuli. Task-related high gamma modulation is quantified in Figure 8c, which depicts the average changes in high gamma activity within PLST that occurs when the tones or female voices were the target. As for the previous subjects, target stimuli enhanced later high gamma activity on PLST, peaking between 250–300 ms and 325–375 ms for the tone-targets and female voice targets, respectively. As before, these peak increases occurred prior to the behavioral response.

4. Discussion

The key findings of this study are that target detection tasks increase stimulus-induced high gamma activity within PLST, and that this increase is further enhanced when the sound stimulus is a target. Enhanced high gamma power to target sound stimuli in the ECoG was observed in all three subjects performing three different target detection tasks, indicating the generality of the effect. Current results extend previous findings that have observed induced high gamma power increases in the EEG and MEG when subjects detect sound targets in a single stream of non-target acoustic stimuli (e.g., Sokolov et al., 2004; see Caporello Bluvás and Gentner, 2013 for review). To our knowledge, this is the first study to unequivocally demonstrate target-specific high gamma power increases in this region of non-primary auditory cortex through examination of ECoG recorded directly from PLST. Previous studies have demonstrated high gamma power increases to attended versus non-attended sounds in selective attention tasks (e.g., Green et al., 2011; Doesburg et al., 2012; Mesgarani and Chang, 2012), and we found a similar effect when comparing high gamma activity acquired during attended versus passive listening blocks (subject L237). In contrast to previous studies, however, we identify additional specific effects restricted to target stimuli.

The most striking feature of target-specific activity in the high-gamma range is that increases occur during later portions (> 250 ms post-stimulus onset) of the responses. Thus, early responses (< 150 ms post-stimulus onset) on PLST were similar regardless of whether the stimulus was a target, non-target, or heard during passive listening (see Figs. 3 and 5). In turn, this suggests that early portions of sound-elicited responses on PLST are more automatic, and modulated less by attentional state. This latter premise may not hold during selective attention, when short-latency AEPs and high gamma elicited by attended sounds are enhanced while those of non-attended sounds are suppressed (e.g., Woldorff and Hillyard, 1991; Woldorff et al., 1993; Mesgarani and Chang, 2012). Regardless of this caveat, the enhanced high gamma elicited by target sounds likely represents a mechanism by which salient sounds can be robustly encoded in auditory cortex (Caporello Bluvas and Gentner, 2013).

While early activity was not strongly modulated by task conditions, it was associated with representation of the stimuli as shown by classification analysis (see Fig. 6). This observation parallels those reported in previous studies which did not require behavioral performance (Chang et al., 2010; Steinschneider et al., 2011; Nourski et al., 2014), indicating that early activity on PLST automatically maintains representation of acoustic stimulus attributes.

Interestingly, later activity was not directly tied to behavioral performance (see Fig. 5) nor was it strongly associated with representation of acoustic attributes of the stimuli (see Fig. 6). Specifically, latency of the neural response did not co-vary with reaction time and occurred even when the subject failed to behaviorally respond to the target stimulus. Additionally, classifier performance was not as accurate in this later time period relative to the early activity. These patterns of late activity were observed regardless of whether the 0.5 kHz or the 4 kHz tone was the target. This suggests that later activity is associated with categorization of the stimulus as a target within PLST and is concordant with the idea that different features of sound processing are multiplexed in multiple time windows (e.g., Walker et al., 2011). The fact that similar responses occurred even when the subject failed to respond is consistent with the hypothesis that portions of non-core auditory cortex are engaged in sound categorization whereas other brain regions, especially prefrontal cortex, are directly involved in making behavioral decisions. Observations and tentative conclusions are comparable to those seen in the auditory belt (field AL) of awake, behaving macaque monkeys (Tsunada et al., 2011; see also Steinschneider, 2011). In these animal subjects, categorization of whether a sound was a /ba/ or a /da/ occurred in field AL. Neural responses were not directly tied to behavioral performance of the animals. In contrast, behavioral performance was best predicted by neural activity in ventral prefrontal cortex (Russ et al., 2008; Lee et al., 2009). Further intracranial studies will be needed to determine if a similar pattern within prefrontal cortex occurs in human subjects.

Multiple non-invasive (EEG and MEG) studies have demonstrated that attention strongly modulates neural activity in the time frame that parallels that seen in the present study. For instance, attended sounds embedded in notch-filtered noise elicited a modest increase in the neuromagnetic evoked M1 component, whereas the sustained portion of the response featured a robust increase peaking at 300–400 ms after stimulus onset (Kauramäki et al.,

2012). Attentional effects on AEPs and AEFs that were maximal within this time frame have been also demonstrated in a variety of other experimental paradigms (Hari et al., 1989; Arthur et al., 1991; Nahum et al., 2009). Similar observations have been made for gamma band responses (> 30 Hz) in both EEG and MEG studies and have been noted in the modulation of attended sounds and visual stimuli, indicating the generality of this effect across tasks and modalities (Eulitz et al., 1996; Tallon-Baudry et al., 1997; Hannemann et al., 2007; Lenz et al., 2007).

Target detection tasks did not engage regions of PLST that were not already engaged during passive listening. This observation is consistent with findings obtained from multiple functional neuroimaging studies. In a meta-analysis of relevant studies by Alho and colleagues (2013), areas where activity was modulated by attention to different sound attributes (pitch, location, speech) were spatially inseparable from those areas activated during passive listening to sounds varying in the same attributes (see also Tzourio et al., 1997). The spatial similarity in processing during passive and active listening within PLST contrasts with effects noted in frontal and parietal brain regions, which are preferentially engaged during active tasks (Pugh et al., 1996; Tzourio et al., 1997; Benedict et al., 1998; Alho et al., 1999). These activations in areas beyond auditory cortex, including frontal regions, may serve as “top-down” modulators of auditory cortical activity, and thus contribute to the development of the later, task-related increases in high gamma activity on PLST through feedback loops (Romanski and Averbach, 2009; Fritz et al., 2010).

In the one subject that had simultaneous recordings from HG and PLST (L258), target detection produced significant enhancements of late high gamma activity on PLST, yet failed to have a comparable effect at electrode sites in either posteromedial or anterolateral HG. The absence of a major target-related effect included both high gamma activity as well as lower frequency AEPs. While limited sampling of HG may have been responsible for this negative finding, there have been inconsistent results from studies examining the effects of attention on activity within HG. In the only other examination of responses obtained using intracranial depth electrodes, selective attention enhanced transient as well as sustained components of the AEP within HG, planum temporale and planum polare (Bidet-Caulet et al., 2007). Even in this study, however, effects were noted in only a subset of recording sites. Additionally, functional neuroimaging has also shown that attention has limited effects on activity within HG, while simultaneously observing large increases of activation on PLST (Pugh et al., 1996). Induced gamma activity as recorded by scalp electrodes from putative generators on the superior temporal plane was not enhanced during a sustained attention task (Leicht et al., 2010). Variability in enhancement of activity within HG during attention-related tasks may in part be attributed to differences in experimental paradigms that vary in their task difficulty, memory load and level of arousal (Petkov et al., 2004). Ultimately, a clear understanding of attentional effects on HG will likely require high spatial sampling of activity acquired from multiple subjects performing a series of tasks that vary in their complexity.

A surprising negative finding was the inability to identify consistent changes in the AEP associated with attention that mirror those observed in non-invasive studies (e.g. Woods et al., 1994; Sabri et al., 2006). This failure included examination of AEPs recorded from HG

and PLST. In contrast, selective attention tasks have been shown to modulate AEP components recorded directly from grid electrodes located on PLST (Neelon et al., 2006, 2011). During the performance of behavioral tasks in the auditory modality, enhancements of exogenous AEP components such as N1 and generation of endogenous components such as processing negativities and the target-specific N2 component are routinely observed (e.g. Novak et al., 1990; Woods et al., 1994; Giard et al., 2000). Our inability to replicate these findings may be based in part on our use of a sustained attention paradigm (vigilance) instead of a selective attention task. Generators for the N1 component are diffuse and have at least two generators in the superior temporal plane; one in HG and the other in planum temporale, the latter having a greater contribution to the scalp-recorded N1 (Näätänen & Picton, 1987; Scherg et al., 1989; Näätänen, 1990; Giard et al., 1994). Direct intracortical recordings provide further support for the major role of planum temporale in generating N1 (Liégeois-Chauvel et al., 1994). The absence of a consistent effect on AEP amplitude or morphology currently seen may reflect the lack of sampling of this important region of auditory cortex (e.g., Kiehl et al., 2001).

It should be borne in mind that sample size in the present study was small (three patients), and the study included three different experimental paradigms. Despite this variation, similar task-related results were obtained, providing evidence for the reliability of the fundamental findings. Importantly, human intracranial electrophysiology studies are performed in subjects with epilepsy and a long history of anticonvulsant drug use. Therefore, extrapolation of findings to the general population warrants caution. However, current findings are in general accord with those obtained in subjects without neurological disorders. Further, the rare opportunities to intracranially examine auditory cortical processing generally result in the reporting of data obtained from limited numbers of subjects (Sahin et al., 2009; Chang et al., 2010; Mesgarani and Chang, 2012). Electrode coverage in each subject is also limited and based on clinical requirements. Each new study must therefore build upon findings reported in earlier studies in order to assess the reliability and generality of effects. In the current study, it was shown that early PLST activity represents the processing of sound attributes, consistent with previous intracranial studies (e.g. Chang et al., 2010; Steinschneider et al., 2011; Mesgarani and Chang, 2012; Nourski et al., 2014). We build upon these findings by demonstrating the modulation of later activity by behavioral task requirements. Future studies must corroborate current observations and extend analyses by examining task-related activity in other brain regions known to be important for sound processing (e.g., prefrontal cortex). Finally, understanding the basic mechanisms underlying auditory perception, the role of attention, and sound-related behavior will best be accomplished by integrating data obtained in human studies with those obtained in experimental animals (e.g., Brosch et al., 2011; David et al., 2012; Sutter et al., 2013).

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Abbreviations

AEP	averaged evoked potential
BPN	band-pass noise
CVC	consonant-vowel-consonant
ECoG	electrocorticogram
ERBP	event-related band power
ERF	event-related field
fMRI	functional magnetic resonance imaging
HG	Heschl's gyrus
PLST	posterolateral superior temporal gyrus

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Highlights

- Target-detection tasks increase high gamma activity in human auditory cortex.
- Modulation primarily occurs on posterolateral superior temporal gyrus.
- Target-specific activity occurs during later portions of the response.
- Activity representing acoustic features occurs early in the response.
- There is no consistent modulation of evoked potentials.

Fig. 1.

Responses to 0.5 kHz tones from a representative site on PLST. **a:** Anatomical reconstruction of the subdural grid implanted over perisylvian cortex in subject L237. **b:** Exemplary ECoG data from a representative recording site on PLST (marked with a star in panel a) showing responses to the 0.5 kHz tone presented in four different experimental blocks. AEP waveforms are superimposed on the time-frequency ERBP plots.

Fig. 2.

High gamma responses to the six complex tone stimuli averaged across the entire recording grid and normalized to the response in the first passive condition (Passive 1). Error bars represent across-trial SD.

Fig. 3. High gamma response envelopes to the 0.5 kHz tone (**a**) and 4 kHz tone (**b**) recorded from the subdural grid (placement shown in Fig. 1a). Colors represent different recording blocks. Depicted responses begin at stimulus onset and span 1000 ms. The outline of the STG is shown in grey. Anterior is to the left.

Fig. 4. Temporal dynamics of high gamma modulation. **a:** Responses to the 0.5 kHz tone. **b:** Responses to the 4 kHz tone. Pairwise differences in high gamma ERBP between experimental blocks are plotted in 50 ms bins as functions of time after stimulus onset. Arrowheads indicate the timing of the behavioral responses to the target stimulus.

Fig. 5.

High gamma response envelopes to the 0.5 kHz tone (**a**) and 4 kHz tone (**b**) recorded from two representative contacts on the subdural grid (X and Y, shown in Fig. 3). Depicted responses begin at stimulus onset and span 1600 ms.

Fig. 6.

Tone classification analysis based on cortical high gamma ERBP. Classification accuracy for the six complex tone stimuli is plotted as a function of analysis time window. Colors represent different recording blocks.

Fig. 7.

Confirmatory data from non-dominant (right) hemisphere in subject R198. **a:** Location of subdural grid implanted over perisylvian cortex in subject R198. **b:** High gamma responses to the experimental stimuli averaged across the entire recording grid. **c:** Temporal dynamics of high gamma modulation in a target detection task. Responses to the 0.25 kHz tone and 0.25 kHz BPN are shown in top and bottom panel, respectively. Pairwise differences in high gamma ERBP between experimental blocks corresponding to target and non-target conditions are plotted in 50 ms bins as functions of time after stimulus onset. Arrowheads indicate the timing of the behavioral responses to the target stimulus.

Fig. 8.

Confirmatory data from dominant (left) hemisphere in subject L258. **a**: Anatomical reconstruction of recording electrode locations. HDE implanted in HG and subdural grid implanted over perisylvian cortex are shown in upper and lower panels, respectively. Insets: line drawings of MRI cross-sections showing position of two representative contacts on the HDE (sites A and B). **b**: High gamma responses to complex tones and speech syllables recorded from two representative sites on HG (A, B) and three sites on PLST (C, D, E). **c**: Temporal dynamics of high gamma modulation in a target detection task. Responses to the tones and speech syllables are shown in left and right panel, respectively. Pairwise differences in high gamma ERBP between experimental blocks corresponding to target and non-target conditions are plotted in 50 ms bins as functions of time after stimulus onset. Arrowheads indicate the timing of the behavioral responses to the target stimulus.