Adaptation of high-gamma responses in human auditory association cortex

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Eliades SJ, Crone NE, Anderson WS, Ramadoss D, Lenz FA, Boatman-Reich D. Adaptation of high-gamma responses in human auditory association cortex. J Neurophysiol 112: 2147–2163, 2014.—This study investigates adaptation of high-frequency cortical responses (>60 Hz; high-gamma (HG)) to simple and complex sounds in human nonprimary auditory cortex. We used intracranial electrocorticographic recordings to measure event-related changes in HG power as a function of stimulus probability. Tone and speech stimuli were presented in a series of traditional oddball and control paradigms. We hypothesized that HG power attenuates with stimulus repetition over multiple concurrent time scales in auditory association cortex. Time-frequency analyses were performed to identify auditory-responsive sites. Single-trial analyses and quantitative modeling were then used to measure trial-to-trial changes in HG power for high (frequent), low (infrequent), and equal (control) stimulus probabilities. Results show strong reduction of HG responses to frequently repeated tones and speech, with no differences in responses to infrequent and equal-probability stimuli. Adaptation of the HG frequent response, and not stimulus-acoustic differences or deviance-detection enhancement effects, accounted for the differential responses observed for frequent and infrequent sounds. Adaptation of HG responses showed a rapid onset (less than two trials) with slower adaptation between consecutive, repeated trials (2–10 s) and across trials in a stimulus block (~7 min). The auditory-evoked N100 response also showed repetition-related adaptation, consistent with previous human scalp and animal single-unit recordings. These findings indicate that HG responses are highly sensitive to the regularities of simple and complex auditory events and show adaptation on multiple concurrent time scales in human auditory association cortex.

auditory cortex; adaptation; gamma; oddball; electrocorticography; deviance detection

EVENT-RELATED CHANGES in high-frequency cortical oscillations (>60 Hz; high-gamma (HG)) are used increasingly to measure sensory information processing in the human brain (Hipp et al. 2011; Hoogenboom et al. 2006; Lachaux et al. 2005, 2012; Miyanari et al. 2006). In auditory cortex, increased spectral power in the HG range is thought to reflect local neuronal population- firing activity (Mukamel et al. 2005; Ray et al. 2008) that is not phase locked to the eliciting stimulus, in contrast to evoked responses. Auditory-related increases in HG power (responses) have been used to study perceptual feature-binding (Tallon-Baudry and Bertrand 1999), complex scene analysis (Mesgarani and Chang 2012), and more recently, speech-feature representations (Mesgarani et al. 2014). Electrocorticographic (ECoG) recordings from human auditory cortex yield HG responses to simple and complex sounds (Brugge et al. 2009; Crone et al. 2001; Edwards et al. 2005; Howard et al. 2000; Nourski et al. 2013) that are highly robust and reliable (Cervenka et al. 2013). However, the dynamic properties of HG responses, including their sensitivity to regularities in the auditory environment, have not been established.

In contrast, it is well established that evoked responses recorded from sensory cortex show decreases with stimulus repetition that do not generalize to novel or different stimuli (Herrmann et al. 2013, 2014; Lanting et al. 2013; Todorovic et al. 2011), a phenomenon known as short-term adaptation or repetition suppression (Desimone 1996; Grill-Spector et al. 2006; Ulanovsky et al. 2003). The stimulus-specific properties of adaptation have been used in functional MRI studies to investigate regional specialization (Chong et al. 2008; Dragoi et al. 2000; Grill-Spector et al. 2006; Krekelberg et al. 2006) and are demonstrated using oddball paradigms, in which one stimulus is presented infrequently among a frequently repeated second stimulus (Escera et al. 1998; Näätänen et al. 2007; Sams et al. 1985). Short-term adaptation is thought to contribute to neuronal population-coding accuracy (Ahissar et al. 2000; Carandini and Ferster 1997; Gutnisky and Dragoi 2008; Ulanovsky et al. 2004) and in turn, may improve auditory perception in complex listening environments (Jaramillo and Zador 2011; Moore et al. 2013; Winkler et al. 2009).

Single-unit recordings from cat primary auditory cortex, using pure tones in an oddball paradigm, showed adaptation of the evoked response to the frequent tone on multiple time scales, both rapid (milliseconds, seconds) and slow (minutes) (Ulanovsky et al. 2004). Multiple time scales of adaptation for tone-evoked responses have also been identified in human cortex, based on scalp recordings (Costa-Faidella et al. 2011b). The multiplicity of time scales is considered especially useful for processing complex sounds and auditory scenes, because their features are distributed over different time scales (Costa-Faidella et al. 2011a, b; Pérez-González and Malmierca 2014), although this has not been investigated directly. In the human brain, complex sound processing is associated with higher-level (i.e., nonprimary) auditory areas, including auditory association (BA 22) or parabelt cortex (Boatman and Miglioretti 2006; Ulanovsky et al. 2003). The stimulus-specific properties of adaptation have been used in functional MRI studies to investigate regional specialization (Chong et al. 2008; Dragoi et al. 2000; Grill-Spector et al. 2006; Krekelberg et al. 2006) and are demonstrated using oddball paradigms, in which one stimulus is presented infrequently among a frequently repeated second stimulus (Escera et al. 1998; Näätänen et al. 2007; Sams et al. 1985). Short-term adaptation is thought to contribute to neuronal population-coding accuracy (Ahissar et al. 2000; Carandini and Ferster 1997; Gutnisky and Dragoi 2008; Ulanovsky et al. 2004) and in turn, may improve auditory perception in complex listening environments (Jaramillo and Zador 2011; Moore et al. 2013; Winkler et al. 2009).

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Because scalp recordings have limited spatial and spectral resolution, it has been difficult to localize adaptation effects or investigate adaptation of HG activity (>60 Hz). Conversely,
intrapranal ECoG recordings combine high temporal and spatial resolution (Lachaux et al. 2012) with the capacity to record cortical high-frequency activity with millisecond precision, directly from electrodes implanted over lateral cortex, including auditory association (parabelt) areas (Edwards et al. 2005; Sinai et al. 2009). ECoG recordings from auditory association cortex yield robust and reliable HG responses (Brugg et al. 2009; Cervenka et al. 2013; Nourski et al. 2014; Sinai et al. 2009; Steinschneider et al. 2011) and are well suited, therefore, for investigating adaptation of auditory HG responses on multiple time scales.

In a prior ECoG study, Edwards and colleagues (2005) reported larger HG responses to infrequent (deviant) tones vs. frequent tones, using a passive oddball paradigm to record from left auditory association cortex. This finding has been replicated by other ECoG studies (Cervenka et al. 2013; Rosburg et al. 2005). Although the observed differences in HG responses could reflect repetition-related adaptation of the frequent response, they could also be due to enhancement of the infrequent response, reflecting novelty or deviance-detection effects (Escera et al. 1998; Näätänen et al. 2007; Sams et al. 1985) or simply stimulus-acoustic differences. Without single-trial response measurements and adequate experimental controls, it is difficult to tease apart these different accounts.

In this study, we hypothesized that HG responses, recorded from human auditory association cortex, show adaptation on multiple time scales for simple and complex sounds. ECoG recordings were acquired using tone and speech stimuli presented in a passive oddball paradigm with a series of experimental controls borrowed from the animal literature (Taaseh et al. 2011). To investigate adaptation on multiple time scales, we used single-trial measurements and quantitative modeling of trial-to-trial changes in event-related HG power.

MATERIALS AND METHODS

Participants

We tested eight epilepsy patients (four men), ages 18–36 yr, who had intracranial electrodes implanted to evaluate their candidacy for surgical treatment of medically intractable seizures (Table 1). Seven patients were right handed; all were left-hemisphere dominant for language by Wada test (Wada and Rasmussen 1960). Five patients had normal MRI scans; one had a left frontal-lobe heterotopia; two had prior resections with recurrent seizures. All patients had normal hearing bilaterally (∼25 dB; 500–4,000 Hz) and normal speech-perception abilities in quiet (W-22 word-recognition test) (Hirsch et al. 1952) and in noise (SCAN-A auditory figure-ground subtest) (Keith 1994), based on audiometric screening. Patients had no cognitive impairments (full-scale intelligence quotient < 80) and no history of speech, language, or motor disorders. Two patients participated in a separate study conducted over multiple days to assess reliability of cortical spectral responses (patients 2 and 4) (Cervenka et al. 2013). All patients had seizure foci outside of perisylvian cortex and in the anterior basal temporal lobe (three patients) or anterior and/or superior frontal lobe (five patients), as confirmed by clinical intracranial EEG recordings. All subjects provided informed, written consent before participation in all auditory studies, which were approved by the Johns Hopkins Institutional Review Board.

Subdural 6 × 8 or 8 × 8 electrode arrays were implanted by craniotomy, with placement determined for each patient individually, based on clinical considerations. Electrodes were 2.3 mm-diameter, platinum-iridium disks embedded in medical-grade plastic with 10 mm center-to-center spacing (Ad-Tech Medical Instrument, Racine, WI). Seven patients had arrays implanted over the left hemisphere. Electrode locations were verified by coregistration of postsurgical-computerized tomography scans with presurgical MRI and intraoperative photographs (Boatman-Reich et al. 2010; Ritzi et al. 2007). All patients had electrode coverage of the superior temporal gyrus, as well as inferior frontal and parietal cortex. Several patients had additional electrode strips implanted over frontal, parietal, and temporal cortex.

Stimuli

Two single-frequency tones (1,000 and 1,200 Hz) and two speech syllables (/ba/ and /da/) were used in the main experimental oddball paradigm (Fig. 1A). The tones were generated in MATLAB 2012b (MathWorks, Natick, MA); speech stimuli were recorded from a male, native speaker of English and digitized (44.1 kHz, 16-bit sampling). Stimulus durations were 250 ms (patients 1–4) or 270 ms (patients 5–8), with 5 ms onset-offset ramps, and were consistent within patients. The 1,000-Hz tone was selected, because it was well above the ECoG recording frequencies and has been used in prior auditory oddball studies (Cervenka et al. 2013; Todorovic et al. 2011). The 1,200-Hz tone matched the second formant frequency of the steady-state vowel in the speech stimuli, as determined from the spectrum. The 200-Hz (20%) difference in tone frequencies is well within the range of human auditory discriminability. The two consonant-vowel syllables shared the same vowel but differed in their initial consonants. The initial stop consonants were contrasted by place of articulation, which is cued perceptually by the brief (<50 ms), rapid formant transitions to the following vowel (Fig. 1A). The use of syllables with different initial consonants but the same vowel allowed us to investigate adaptation for spectrally dynamic acoustic cues, such as formant transitions. All stimuli were root-mean-square amplitude normalized and presented binaurally through insert earphones (ER-2; Etymotic Research, Elk Grove Village, IL) at comfortable suprathreshold levels determined for each patient (∼40 dB sensation level).

Experimental Tasks

The main experimental task was a 300-trial passive auditory oddball paradigm. Oddball paradigms are commonly used to investi-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age, yr</th>
<th>Handedness</th>
<th>Seizure Onset Age, yr</th>
<th>Hemisphere Implanted</th>
<th>MRI</th>
<th>Seizure Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>18</td>
<td>Right</td>
<td>17 mo</td>
<td>Left</td>
<td>Normal</td>
<td>Left MTL</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>18</td>
<td>Right</td>
<td>13</td>
<td>Right</td>
<td>Normal</td>
<td>Right TL</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>28</td>
<td>Right</td>
<td>7</td>
<td>Left</td>
<td>Heterotopia</td>
<td>Left FL</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>36</td>
<td>Right</td>
<td>20</td>
<td>Left</td>
<td>Normal</td>
<td>Left MTL</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>24</td>
<td>Right</td>
<td>9</td>
<td>Left</td>
<td>Prior SMA resection</td>
<td>Left FL</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>23</td>
<td>Right</td>
<td>12</td>
<td>Left</td>
<td>Normal</td>
<td>Left FL</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>36</td>
<td>Left</td>
<td>29</td>
<td>Left</td>
<td>Prior AVM resection</td>
<td>Left FL</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>25</td>
<td>Right</td>
<td>14</td>
<td>Left</td>
<td>Normal</td>
<td>Left FL</td>
</tr>
</tbody>
</table>

MTL, mesial temporal lobe; TL, temporal lobe; FL, frontal lobe; SMA, supplementary motor area; AVM, arteriovenous malformation.
gate stimulus-probability effects in human and animal electrophysiology studies (Escera et al. 1998; Näätänen et al. 1982; Ulanovsky et al. 2004). In an oddball paradigm, one stimulus is designated as the frequent, or standard, and repeated with high probability over a series of consecutive trials. A second infrequent stimulus, sometimes referred to as novel or deviant, is repeated with low probability and interspersed on nonconsecutive trials among the frequent stimuli (Fig. 1B). We used a passive oddball paradigm for consistency with previous animal studies and human-evoked potential studies (Costa-Faidella et al. 2011b; Ulanovsky et al. 2004).

For the main experimental oddball paradigm, we used two tones (1,000 and 1,200 Hz) and two syllables (/ba/and/da/) in separate blocks. The frequent stimulus (1,000 Hz,/ba/) was presented with a probability of 0.82 ($n = 246/300$ trials); the infrequent stimulus was presented with a probability of 0.18 ($n = 54/300$ trials). The interstimulus interval (ISI) was 1,400 ms (onset–onset), within the 1,000- to 1,800-ms interval needed to elicit both reliable cortical responses (Edwards et al. 2005) and measurable adaptation effects (Taaseh et al. 2011). The order of speech and tone runs was randomized across patients, who watched a silent, animated movie to remain alert and to discourage active attending to the auditory stimuli. All eight patients completed the tone and speech oddball paradigms (Table 2). One patient (patient 8) also completed an additional oddball paradigm with 500 Hz (frequent) and 4,000 Hz (infrequent) tones.
Control Tasks

Two control conditions were used: a reversed-probability oddball control and an equal-probability control (Fig. 1B). The reversed-probability oddball was used to control for stimulus-acoustic differences. Two reversed-probability oddballs were implemented, one for tones and one for speech, by reversing the numbers of frequent and infrequent stimuli in the experimental oddball paradigm (Costa-Faidella et al. 2011a; Ulanovsky et al. 2004). The order of the reversed-probability and experimental oddball tasks varied across patients.

The equal-probability control condition was adapted from traditional N100 (N1) or “deviant-alone” (e.g., nonadapting) paradigms (Grimm et al. 2011; Kropotov et al. 2000; Sams et al. 1983; Taaseh et al. 2011; Ulanovsky et al. 2004). Equal-probability controls are used to test for deviance-related enhancement effects by comparing infrequent oddball responses with those elicited by the same low-probability stimulus in the absence of a high-probability stimulus (Fishman and Steinschneider 2012; Grimm et al. 2011; Optiz et al. 2005; Taaseh et al. 2011). Tones were presented in two versions of an equal-probability control. One equal-probability control used two tones (1,000 and 1,200 Hz) presented infrequently (54 trials each) and with equal probability (0.5). This was accomplished by modifying the experimental oddball paradigm: 1) to reduce the number of frequent (1,000 Hz) tone trials to match the number of infrequent trials (n = 54) and 2) to vary the ISI (mean 3,250 ms; range: 1,400–5,600 ms) to reduce stimulus predictability further (Costa-Faidella et al. 2011a); this was accomplished by replacing 192 of the original, frequent trials with one to four consecutive, silent trials. Other task parameters remained the same, including total number of trials (n = 300), test duration (~7 min), and trial length (1,400 ms). The order of trial presentation was pseudorandomized to ensure a minimum ISI of 2,800 ms between tone trials and no more than one consecutive repetition of either tone. The second equal-probability control comprised five tones (500, 1,000, 1,200, 2,000, and 4,000 Hz), presented with equal probability (0.2). Two of the tones matched the experimental oddball stimuli (1,000 and 1,200 Hz), and three tones (500, 2,000, and 4,000 Hz) were novel, i.e., had not been presented previously, allowing us to investigate cross-stimulus and longer-term adaptation effects (Jacobsen and Schröger 2001; Nelken and Ulanovsky 2007; Taaseh et al. 2011). Each tone was presented 55 times at an ISI of 1,400 ms for a total of 275 trials. Trial-presentation order was pseudorandomized to ensure no consecutive repetitions of the same tone.

Control tasks were administered to five of the eight patients (Table 2). The three other patients could not complete the control tasks due to clinical time constraints. Individual differences in the time available for research testing are common in ECoG studies, reflecting the primary clinical function of ECoG (Lachaux et al. 2012). All five patients completed the reversed-probability tone condition and either a two- or five-tone, equal-probability control task. Two patients also completed the speech reversed-probability task (patients 1 and 2). For consistency with the experimental tasks, the same visual distractor (silent movie) was used for all control conditions. Intertask intervals of at least 1 min were used to ensure that neuronal-population activity returned fully to baseline (Herrmann et al. 2014; Sams et al. 1993). Experimental and control paradigms were implemented using a NeuroScan Stim2 system (Compumedic, El Paso, TX) for the first four patients. Subsequent studies were implemented using a RZ6 system (Tucker-Davis Technologies, Alachua, FL).

Data Acquisition

ECoG studies were initiated 3–4 days after electrode implantation while patients were awake and fully responsive. Patients were tested individually at bedside in one of two electrically shielded and identically configured single-occupant rooms (ambient noise < 42 dB sound-pressure level). All patients had been discontinued from antiepileptic medications for clinical-seizure localization before the recordings. No patient experienced a clinical seizure within 6 h or more before the ECoG studies. Before each recording session, an epileptologist (N. E. Crone) reviewed the clinical intracranial EEG record to rule out epileptiform activity or other sources of artifact (e.g., poor ground electrode contact) that might interfere with recordings. Otolaryngoscopic examination confirmed patent external auditory canals. Recordings were performed over one to two sessions in a single day.

The continuous ECoG signal was amplified (5 × 1,000) and recorded digitally from all electrode channels simultaneously, using a referential montage, 1,000-Hz analog-to-digital sampling, and a bandwidth of 0.03–250 Hz (6 dB/octave), as described previously (Cervernka et al. 2013; Crone et al. 2001; Sinai et al. 2009). The reference was placed at an upper corner of the electrode array, outside of the perisylvian cortex. For one patient (patient 8), recordings were not acquired from the top three rows of the 8 × 8 electrode array, due to hardware-sampling limitations imposed by inclusion of additional depth- and microelectrode-recording elements. Stimulus-onset markers were recorded simultaneously to EEG marker channels. Recordings with the first five patients were acquired using a 128-channel Stellate Systems EEG (Montreal, Canada); the last three patients were tested with a 256-channel Niko Kohden system (Tokyo, Japan).

Data Analysis

Signal preprocessing. We analyzed ECoG recordings from the main 8 × 8 or 8 × 6 electrode arrays; additional electrode strips or depths were not included in the analysis, with the exception of patient 8, who had an electrode strip placed directly over the superior temporal gyrus. The continuous ECoG time series was down sampled at 500 Hz, with a Nyquist frequency of 250 Hz for the spectral analysis, and remontaged to a common average reference after visual inspection and removal of channels with excessive artifact, noise, or epileptiform activity. We used average referencing to correct for spatial differences between recording and reference electrodes (Boatman-Reich et al. 2010; Crone et al. 2001; Sinai et al. 2005). For the remaining electrode channels, the continuous ECoG signal was segmented into individual trials using a peristimulus window of 1,400 ms. Trials with excessive artifact or spiking were excluded (<2% of trials).

Table 2. Experimental and control paradigms

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Pt 1</th>
<th>Pt 2</th>
<th>Pt 3</th>
<th>Pt 4</th>
<th>Pt 5</th>
<th>Pt 6</th>
<th>Pt 7</th>
<th>Pt 8</th>
<th>Total No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tone oddball</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>8</td>
</tr>
<tr>
<td>Speech oddball</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>8</td>
</tr>
<tr>
<td>Reversed tone oddball</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Reversed speech oddball</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
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<td>Equal probability, 2 tones</td>
<td></td>
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<td>3</td>
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<tr>
<td>Equal probability, 5 tones</td>
<td></td>
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<td></td>
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<td>2</td>
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</table>

Pt, patient.

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trials). For patient 8, the additional oddball run (500 and 4,000 Hz) could not be analyzed, due to excessive noise across channels.

Identification of auditory sites. For each patient and electrode channel, time-frequency analyses were performed to identify auditory-related changes in the ECoG power spectrum (0.03–250 Hz). Electrode sites were defined as auditory responsive if they showed statistically significant increases in poststimulus spectral power relative to baseline (prestimulus). We analyzed the entire frequency spectrum to capture event-related changes in both high-frequency (i.e., HG) and low-frequency (i.e., evoked) activity (Brugge et al. 2009). Time-frequency analyses were performed separately for the tone and speech oddball recordings using an iterative matching pursuit algorithm that decomposes the ECoG signal into a linear combination of Gabor functions, or atoms (Franaszczuk et al. 1998; Mallat and Zhang 1993). The Wigner-Ville transform of these atoms was then used to compute the energy spectrum. For each trial, baseline power was calculated for each frequency by averaging over all time points in a 400-ms portion (−900 to −500 ms) of the prestimulus period and then across trials by corresponding frequency. For the poststimulus power calculations, the mean power and variance of each time-frequency point in the 400-ms poststimulus period (0–400 ms) were derived by averaging across trials. Line noise at 60 Hz and the 120- and 180-Hz harmonics were excluded from power calculations. In computing time-frequency responses to the frequent oddball stimuli (tone: 1,000 Hz; speech: ba), we eliminated the first three trials of each 300-trial block, as well as the first frequent trial following an infrequent, as is standard practice in oddball studies (Edwards et al. 2005; Escera et al. 2002; Sams et al. 1985; Sinai et al. 2009). However, because this approach precludes analysis of the full range and time course of spectral power changes (Woods and Elmasian 1986), no trials were eliminated a priori from the single-trial adaptation analyses.

Statistically significant (P < 0.05) changes in poststimulus spectral power relative to baseline were determined by comparing each poststimulus time-frequency point with the corresponding frequency-specific baseline value by paired t-test, using log transformation and assuming unequal variances (Zygierewicz et al. 2005). A false-discovery rate correction was applied to control for multiple within-subject comparisons that increase the likelihood of a type I error (Benjamini and Hochberg 1995; Boatman-Reich et al. 2010). Time-frequency points, representing statistically significant changes in spectral power from baseline, were plotted for each electrode channel. For visual clarity of the plots, time-frequency points that did not show significant changes from baseline were set to zero. Electrode sites that showed statistically significant power increases relative to baseline, for one or more stimulus conditions, were identified as auditory responsive (Fig. 2). Auditory responses were further characterized qualitatively as strong or weak, based on the percentage of poststimulus time-frequency points that showed significant power increases: stronger responses had >5%; weaker responses had 1–5% (note: responses were considered absent if <1%). All signal processing was performed using a distributed computing software system implemented on a multicore Linux workstation (Franaszczuk and Joupy 2004).

HG responses. HG responses were derived from the set of auditory responsive sites identified by time-frequency analysis and characterized by increases poststimulus spectral power at 70–150 Hz. We chose an upper limit of 150 Hz, based on prior studies showing stronger HG responses (<40 Hz) compared with HG responses (>40 Hz). For HG responses, the average time-domain (evoked) waveform was first subtracted from each trial. The evoked waveform was computed from the full spectrum of the preprocessed ECoG signal (0.03–250 Hz) using a 100-ms prestimulus and 400-ms poststimulus window (Sinai et al. 2009). Because HG responses are largely nonphase locked, phase-locked-evoked components are routinely subtracted before calculating power (Brugge et al. 2009; Edwards et al. 2005; Steinschneider et al. 2008; Towle et al. 2008). The resulting signal was then bandpass filtered using a 200-order finite impulse response filter with band limits of 70–150 Hz, followed by power calculations using the squared magnitude of a Hilbert transform. The mean baseline HG activity was subtracted from the poststimulus response to yield event-related changes in HG power (stimulus response). The presence of HG responses was verified by visual comparison with the original time-frequency plots that were bandpass filtered at 70–150 Hz. Single-trial HG responses were used in subsequent adaptation time-course calculations; trial-averaged HG responses were used for the mean HG response measurements, including latency, duration, and magnitude. The latency and duration of HG responses were measured from the onset of an oddball block (2–3 s); and consecutive, repeated (frequent) trials that depend on recent stimulus history, also referred to as local sequence effects (2–10 s); and history, also referred to as local sequence effects (2–10 s); and

Adaptation measurements. To quantify differences in HG responses as a function of stimulus probability, we used a normalized adaptation index (AI) defined as

\[ AI = \frac{(I(s_1) + I(s_2)) - (F(s_1) + F(s_2))}{(I(s_1) + I(s_2)) + (F(s_1) + F(s_2))} \]

where \( I(s_1) \) and \( I(s_2) \) are HG power responses to two stimuli, \( s_1 \) and \( s_2 \), each served as an infrequent \( [I(s_1) \) and \( I(s_2)] \) and a frequent \( [F(s_1) \) and \( F(s_2)] \). Adaptation to individual stimuli is calculated based on \( I(s_1) \) and \( F(s_2) \), where one stimulus \( (s_1) \) is presented infrequently \([I(s_1)] \) in one oddball block and frequently \([F(s_1)] \) in the reversed-probability oddball block. A positive AI value (0–1.0) indicates adaptation (infrequent > frequent), whereas a negative AI value indicates stronger responses to the frequent stimulus. This adaptation metric is common in animal studies (Ulanovsky et al. 2003), where it is used to correct for differences in overall firing rates between individual neurons; we used it to normalize differences between electrodes. For the three patients who did not complete the reverse-probability condition, the AI was calculated based on the single oddball run \([I(s_1)] \) and \( F(s_2) \). Equal-probability control responses were compared separately to frequent or infrequent responses using the same calculations. Statistical testing of the normalized AI values by stimulus type (tone, speech) and probability was performed using nonparametric Wilcoxon signed-rank testing or Friedman nonparametric ANOVA with Bonferroni correction. Correlation analyses were performed using Spearman rank correlations. Statistical tests were considered significant for \( P < 0.05 \).

Adaptation time-scale measurements. The time course (onset, rate, duration) and magnitude of trial-to-trial changes in HG power were measured on three time scales: 1) single-trial response adaptation at the onset of an oddball block (<2-3 s); 2) changes over a series of consecutive, repeated (frequent) trials that depend on recent stimulus history, also referred to as local sequence effects (2–10 s); and 3) longer-term changes over the course of an entire stimulus block (~7 min). The time course of onset adaptation was measured by fitting single-trial responses with a decaying exponential (e), according to

\[ R = Ae^{-\tau \cdot t} + B \]

where \( \tau \) represents the time constant of the decay, \( A \) is the initial response magnitude, and \( B \) the steady-state response. The time-series variable \( t \) represents the serial stimulus number, as in prior studies (Ulanovsky et al. 2004). Although our analysis focused on the time constant, all free parameters of the exponential were fit to the response adaptation. Population average responses that were pooled across electrodes, as well as individual electrode responses, were fit separately for frequent, infrequent, and equal-probability stimuli for comparison. Population averages of these single-trial measurements were also calculated across electrode channels using exponential fits based on trial number (position) within each block to derive time constants of adaptation. The magnitude of the initial-onset adaptation was measured separately by a power-adaptation fraction comparing
Fig. 2. Electrode sites responsive to auditory stimuli. Electrode locations are coregistered with each patient’s 3-dimensional MRI brain reconstruction; dashed gray outline denotes all electrodes recorded. Inset boxes show largest time-frequency responses for corresponding sites. Solid black circles represent sites with strong responses to tones and speech; time-frequency plots show stronger of the 2 (e.g., speech); open black circles denote weak responses to tone and speech. Sites only responsive to speech are shown by solid (strong) or open (weak) red circles. Sites only responsive to tones are shown by solid/open blue circles. Circles with red fill/blue outline denote strong speech, weak tone; blue fill/red outline denote strong tone, weak speech. Brown circles represent sites with no auditory response; white circles are sites excluded from analysis. Color bar indicates common scaling (decibel/hertz) for all time-frequency plots.
CORTICAL AUDITORY RESPONSE ADAPTATION

the response of the first stimulus ($X_1$) with the steady-state response ($X_{ss}$): $(X_1 - X_{ss})/X_{ss}$.

HG power adaptation was also measured across sequences of one to nine consecutively repeated trials (2–10 s) within a stimulus block to determine local sequence effects (i.e., local history effects). The magnitude of HG adaptation was computed based on the position of each frequent trial relative to the preceding infrequent trial. Due to sample-size limitations, a maximum of five consecutively repeated, frequent trials was analyzed. HG power was normalized by frequent trial position across all series of repeated frequent trials within a block. Linear regression across frequent trial positions was used to measure this local sequence adaptation further. Finally, we assessed the time course and magnitude of longer-term adaptation over the entire stimulus block by measuring the ratio of mean HG responses to the time course and magnitude of longer-term adaptation over the entire block. Linear regression across frequent trial positions was used to determine local sequence effects (i.e., local history effects). The magnitude of HG responses to frequently repeated tones ($n = 16$) and/or speech ($n = 24$; Fig. 2). For the main oddball paradigm, stronger HG responses were elicited for infrequent rather than for frequent tones across patients (mean difference ± SD: +3.02 ± 1.68 dB/Hz; $t = 6.95$, df = 21, $P < 0.001$) and speech (+5.60 ± 6.18 dB/Hz; $t = 4.88$, df = 28, $P < 0.001$), as measured by log-power density (Fig. 3). Across patients, the average duration of HG responses to infrequent tones (222 ± 93 ms) and speech (280 ± 92 ms) was longer than responses to frequent tones (175 ± 93 ms; $t = 3.60$, df = 21, $P = 0.001$) and speech (212 ± 98 ms; $t = 3.83$, df = 28, $P < 0.001$). Infrequent oddball stimuli elicited stronger responses regardless of which tone or speech syllable was designated as the infrequent stimulus (Fig. 3, A–C). The mean normalized population responses for tones and speech, across patients and electrode sites, showed the same pattern of larger responses to infrequent sounds than frequent sounds (Fig. 3D). These differences in HG responses emerged shortly after the response latency and were clearly evident by 100 ms for both tones and speech. When electrodes with strong HG responses to both tone and speech stimuli were compared, the AI values were similar (mean difference 0.02 ± 0.15) and did not correlate strongly ($r = 0.52$, $t = 1.81$, df = 8, $P > 0.05$), suggesting no systematic differences in response adaptation by stimulus type.

Adaptation Based on Stimulus Probability

At all electrode sites with strong auditory responses, the magnitude of HG responses to frequently repeated tones showed positive-adaptation values relative to infrequent tone responses (Fig. 4A). The across-patient population AI was distributed, with most values falling between 0 and 0.5 (0.23 ± 0.32; $z = 3.72$, df = 25, $P < 0.001$). For frequently repeated speech stimuli, HG responses showed a similar pattern of response adaptation (Fig. 4B), as reflected in the positive AI values (0.22 ± 0.25; $z = 4.88$, df = 31, $P < 0.001$). Weak HG responses showed similar adaptation effects but with greater variability (tones: 0.19 ± 0.46, $z = 3.51$, df = 54, $P < 0.001$; speech: 0.28 ± 0.43, $z = 5.14$, df = 53, $P < 0.001$). At a small number of sites that were weakly responsive to tones ($n = 11$) or speech ($n = 5$), HG responses to the frequent stimulus were comparable with or slightly larger than responses to the infrequent. AI values for each individual stimulus from the oddball, measured separately, were not correlated ($r = 0.07$, $t = 0.28$, df = 17, $P > 0.05$) but showed similar patterns of adaptation.

For the two-tone, equal-probability control paradigm (Fig. 4, C and D), HG responses were consistently larger than responses to frequent oddball tones (0.14 ± 0.45 dB/Hz; $z = 2.16$, df = 18, $P = 0.03$) but did not differ in magnitude from infrequent oddball tone responses ($-0.02 ± 0.40$ dB/Hz; $z = 0.63$, df = 18, $P > 0.05$). This pattern of similar control and infrequent tone responses was also evident in the mean population responses (Fig. 3D).

Results for the five-tone, equal-probability control were similar to the two-tone control results. HG responses to the five equal-probability tones were consistently larger than responses to frequent oddball stimuli (0.30 ± 0.36 dB/Hz; $z = 2.19$, df = 5, $P = 0.03$) but did not differ from infrequent tone responses ($-0.01 ± 0.44$ dB/Hz; $z = 0.76$, df = 5, $P > 0.05$). For one patient (patient 7), the largest responses were associated with the three “novel,” equal-probability tones (500, 2,000,
Reduced responses to the oddball-matched tones (1,000–1,200 Hz) compared with the novel tones suggest possible longer-term adaptation (i.e., across stimulus blocks). For the other patient (patient 8), all but one of the five equal-probability tones had been presented earlier (see MATERIALS AND METHODS). Interestingly, responses to all five equal-probability tones were similar in magnitude, although this could not be verified statistically, due to the small sample size.

**Time Scales of HG Adaptation**

The time course (onset, rate, duration) of trial-to-trial changes in HG power for tones and speech was examined on three time scales: 1) rapid single-trial adaptation during initial stimulus presentation (onset adaptation); 2) changes over consecutive, repeated trials (local sequence adaptation); and 3) changes that extended over the course of the entire stimulus block (longer-term adaptation). As expected, individual trial responses were noisy compared with averaged responses (Fig. 5A). For the majority of electrodes, the first trial in each block, which was always a frequent stimulus, showed increased HG power (onset response) that then decreased rapidly to a steady-state level after one to two repeated trials. The increased response to the first frequent trial often exceeded the response to infrequent stimuli and was observed across stimuli (tones, speech) and stimulus blocks (Fig. 5, A and B).

To quantify the large, rapid onset changes in HG power, observed over the first few trials in a stimulus block, we calculated population averages of single-trial responses to tones and speech, according to trial number (Fig. 5C). Rapid onset adaptation over the first several trials was observed for both frequent and equal-probability control stimuli and, surprisingly, for infrequent stimuli as well. Rapid onset adaptation was followed by slower, more gradual adaptation. Exponential fits of the population responses revealed an adaptation time constant for frequent tones of $\tau = 0.77$ stimuli [95% confidence interval (CI): 0.51 to 1.04], or $\sim 1.1$ s. Adaptation was somewhat slower for infrequent tones [$\tau = 1.30 (0.62$ to 2.00), or $\sim 9.2$ s] and equal-probability control tones [$\tau = 1.47 (0.97$ to 3.06), or $\sim 5.7$ s], possibly due to the irregular presentation or longer intervals. HG responses to speech also showed relatively fast adaptation rates [$\tau = 1.46 (1.05$ to 1.88), or $\sim 2.0$ s] for frequent and [$\tau = 0.63 (0.14$ to 1.11), or $\sim 4.4$ s] for infrequent. Although adaptation rates tended to be faster for frequent
speech stimuli, the differences were smaller than those observed for tones.

Although frequent and infrequent stimuli were fit separately by exponential functions to facilitate comparisons with prior animal and human oddball studies, it may be argued that the two types of stimuli were not truly independent, as they were embedded in the same stimulus sequence. To address this potential concern, we also analyzed the oddball response onset adaptation by fitting the exponential function for the entire stimulus sequence (including both frequent and infrequent stimulus responses, taken together). Results were comparable, with the adaptation for the frequent stimuli analyzed independently. Specifically, the time constants for tone and speech sequences were $0.69 \text{ s (95\% CI: 0.27–1.10, or 1.0 s)}$ for tones and $2.06 \text{ s (1.32–2.80, or 2.9 s)}$ for speech. The somewhat longer adaptation times for speech may be consistent with reduced cross-stimulus adaptation for these stimuli.

We also measured changes in single-trial HG power for individual electrodes (Fig. 6). We compared the magnitude of the onset HG power (first trial, always a frequent stimulus) with the mean steady-state power (Fig. 6A). Although a small number of sites showed decreased HG power for the first trial (25% tones, 8% speech), the majority of sites (≥74%) showed increased first-trial HG power for tones and speech. This was not surprising, since the first frequent trial in a block was preceded by silence. The magnitude of the onset power adaptation relative to the first trial was a median fractional decrease of 0.93 for tones [interquartile range (IQR) 0.70–0.98], 0.94 for speech (IQR 0.77–0.98), and 0.78 for the equal-probability tones (IQR 0.32–0.91). The adaptation time constants, measured individually for each electrode, were somewhat variable but were generally similar to those of the population average (Fig. 6B). The medians of these exponential time constants were $0.91 \text{ s (IQR 0.17–2.25)}$ for tones, $1.32 \text{ s (IQR 0.73–4.35)}$ for speech, and $5.80 \text{ s (IQR 2.81–13.24)}$ for control tones.

To determine whether additional, longer-term changes occurred over the course of the entire stimulus block after the initial adaptation, we compared mean HG responses with frequent stimuli during the first and last half of each stimulus block, excluding the first trial response (Fig. 6C). We found a median response ratio of 0.77 (IQR 0.17–1.19) for tones, 0.76 (IQR 0.46–0.98) for speech, and 0.80 (IQR 0.61–0.96) for controls, indicating further ongoing, slow adaptation throughout each stimulus block.

We next analyzed local sequencing effects on HG response adaptation. Such sequencing effects would reflect an updating of adaptation based on recent stimulus history. We measured changes in HG response magnitude as a function of trial position in a series of repeated frequent stimuli within a block. For HG responses to tones and speech, the first frequent trial following an infrequent generally showed a slight increase relative to the overall average frequent stimulus response (Fig. 7, A and B). Subsequent responses gradually decreased with increasing distance from the infrequent, although with some variability. These results suggest a slight release from adaptation following an infrequent, resulting in a transiently increased frequent stimulus response, followed by a
gradual buildup of adaptation with further repetitions of the frequent stimulus.

Local sequence effects were analyzed further by calculating median population HG responses across patients and electrodes for both tones and speech (Fig. 8A). The response to the first frequent trial, following an infrequent trial, showed only a small increase relative to the following frequent, and subsequent decreases in response power were associated with large and increasing variability. We quantified sequence effects by measuring the slope of the decrease in HG power with increasing stimulus position for each electrode (Fig. 8B). Linear fits of the population responses for consecutive frequent stimulus trials (P1–P5), following an infrequent stimulus, revealed broad distribution trends that were skewed toward negative slopes (decreasing power) for both tones (−0.30 ± 2.13; z = 2.43, df = 105, P = 0.015) and speech (−0.32 ± 1.38; z = 1.91, df = 101, P = 0.056).

Whereas local sequence effects do occur, they appear to be relatively weak, accounting for, at most, a 4–5% change in HG power. To compare better the relative contributions of local sequence effects and global stimulus probability with the overall HG response adaptation, we constructed a linear model of stimulus history, based on previous studies (Squires et al. 1976; Ulanovsky et al. 2004). The model assumes that responses are dependent on the “expectedness” of a stimulus, a combination of recent and global stimulus probability, and assumes a decaying memory function

\[ M_k(A) = \frac{1}{Z} \sum_{i=k-N}^{k-1} \alpha^{k-i} S_i \]

where \( S = 1 \) if stimulus \( i \) is \( A \), or \( S = 0 \) if \( B \); \( k \) is the current trial; \( N \) is the length of the memory sequence (\( N = 5 \) was used); and \( Z \) is the normalization constant to constrain \( 0 \leq M \leq 1 \) \( (Z = \sum \alpha^i) \). We computed the parameter \( \alpha \) by finding the largest negative correlation \( (r = -0.55) \) between memory \( M \) and the normalized HG response for tones. The derived \( \alpha \) was 0.57, similar to that of Squires et al. (1976) (0.6) and Ulanovsky et al. (2004) (0.51), and corresponds to a memory time constant \( [\tau = 2.32 \text{ stimuli (~3.3 s)}] \). A linear least-squares regression to the unexpectedness model \( U = a + bP + cM \), with \( P \) representing the global probability, yielded a reasonable fit \( (R^2 = 0.55, F = 12.0, P < 0.001) \). The coefficient for recent memory was −0.18 (95% CI: −0.49:0.13) and for probability was −0.72 (−1.20:−0.24). The ratio of these coefficients \( M/P \) was 0.25, indicating stronger response dependence on global probability than local memory. In comparison, both Squires et al. (1976) and Ulanovsky et al. (2004) reported larger local memory coefficients: \( M/P = 0.47 \) and 0.67, respectively. Our results suggest that whereas local sequence effects do contribute to adaptation, they are weaker than global-probability effects.

To summarize thus far, there appear to be multiple concurrent time scales of auditory HG response adaptation, including rapid (less than two stimuli) and strong (>80%) early-onset adaptation, followed by slower, longer-term adaptation over the course of a stimulus block. Additionally, there was a weaker local sequence effect, with adaptations dependent on the most recent stimulus history. The presence of strong onset adaptation could explain why only modest
local sequence effects were observed, as most of the adaptation had already occurred during the first few stimulus presentations.

Auditory-Evoked Potentials

AEPs, including the early N1 and P2, were identified at a total of 93 electrode sites across the eight patients tested. The strongest AEPs colocalized with HG responses to posterior perisylvian cortex; however, weak AEPs also occurred at sites that showed no HG responses. Tone-elicited AEPs were identified at 75 sites, 19 of which were also associated with HG responses. Speech AEPs were identified at 62 sites, 25 of which also showed HG responses. Visual inspection of the across-patient population average AEP waveforms showed larger responses to infrequent tone oddball stimuli than to frequent tone stimuli (Fig. 9A).

The population mean AI for the N1 peak amplitude was 0.13 ± 0.31 (z = 3.63, df = 74, P < 0.001) for tones and 0.09 ± 0.31 (z = 3.24, df = 61, P = 0.001) for speech. These positive-trending AI values suggest adaptation of the frequent N1 response. However, the noisy quality of individual-evoked responses precluded reliable, single-trial amplitude measurements or analyses. The average over all electrodes and subjects revealed a broad distribution of AI values (Fig. 9, B and C), qualitatively similar to that of HG power. For comparison, limiting this analysis to only those electrodes that also showed strong HG responses (n = 44) reveals even stronger adaptation for tones (0.21 ± 0.43; z = 2.74, df = 18, P = 0.006) but not for speech (0.11 ± 0.47; z = 1.10, df = 24, P > 0.05). There was no correlation between N1 and HG adaptation values for tone responses (r = 0.11, t = 0.44, df = 17, P > 0.05), whereas speech responses were correlated (r = 0.47, t = 2.55, df = 23, P = 0.02).

N1 responses to equal-probability (control) tones and infrequent tones (Fig. 9D) did not differ (AI = 0.05 ± 0.45; z = 1.50, df = 74, P > 0.05). However, sites with HG responses also had slightly larger N1 control responses (AI = 0.14 ± 0.34; z = 1.92, df = 18, P = 0.055) that were not correlated with the HG responses (r = −0.45, P > 0.05). The increased amplitude of N1 responses to control tones, but not infrequent tones, at sites where strong HG responses were also observed underscores the potential contribution of this cortical region to repetition-induced adaptation of auditory-evoked responses to frequently or infrequently repeated oddball stimuli.

Evoked P2 responses showed no clear adaptation or enhancement effects when peak amplitude measurements were quantified using the normalized AI, and AI values did not differ from zero for either tone (0 ± 0.29; z = 0.02, df = 74, P > 0.05) or speech (0 ± 0.33; z = 0.39, df = 61, P > 0.05) oddball stimuli, suggesting no strong or consistent changes in P2 peak amplitudes.

DISCUSSION

The main finding of this study is that HG responses recorded from human auditory association cortex show adaptation (attenuation) with stimulus repetition. Adaptation of HG power was evident for tones and speech on multiple concurrent time scales, from milliseconds to minutes. Single-trial analyses and quantitative modeling revealed rapid, strong onset adaptation, as well as slower, weaker adaptation within and across stimulus blocks. These results provide the first direct evidence for HG response adaptation in humans and suggest that adaptation in auditory association cortex unfolds on multiple time scales, thereby extending previous findings from single-unit recordings in primary auditory cortex (Ulanovsky et al. 2004) and scalp-recorded evoked potentials (Costa-Faidella et al. 2011b).

Results from the oddball paradigm revealed larger trial-averaged HG responses for infrequently presented tone and speech stimuli than for frequently repeated stimuli, consistent with prior ECoG auditory oddball studies (Cervenka et al. 2013; Edwards et al. 2005; Rosburg et al. 2005). With the use of single-trial analyses, in combination with a series of control conditions, we showed that adaptation (attenuation) of the fre-
quent response accounted for the differential HG responses observed.

HG Responses to Tones

Single-trial analyses showed exponential decreases in HG power across repeated trials of the same tone, consistent with adaptation of the frequent stimulus response. 

Fig. 7. Local sequence effects for individual patients and electrode sites. A: time-frequency plots of HG responses for an individual electrode; frequent stimulus positions are relative to the previous infrequent trial. B: HG power for frequent and infrequent tones and speech based on position relative to the infrequent stimulus. P1–P5, frequent stimulus trials following an infrequent, labeled as Post 1–Post 5 in A; Pre, the frequent (Frq) trial immediately preceding an infrequent. Gray bars, oddball responses; black and light-gray bars, reversed-probability and repeated tone oddball trials, respectively. Infrequent (Inf) trials (red) and equiprobable (blue) control (Ctrl) responses are outlined.

Single-trial analyses have been used previously to study adaptation of tone-evoked responses recorded from cat primary auditory cortex (Ulanovsky et al. 2004) and from scalp in humans (Costa-Faidella et al. 2011b). Our results extend previous evoked potential studies by showing that adaptation also modulates HG activity, which is predominantly nonphase locked and localized to human auditory association cortex. Our

Fig. 8. Local sequence effects in population median responses. A: population median HG power for tone (left) and speech (right) by trial position. The Pre label on the x-axis designates the frequent trial immediately preceding an infrequent; P1–P5 represent consecutive frequent trials following (post) an infrequent trial. B: slope of HG power adaptation for postinfrequent stimuli (all frequents) calculated using linear fits based on trial position (P1–P5). Note: equiprobable control condition was for tones only. *P < 0.05.
findings also extend prior ECoG oddball studies by establishing that differential HG responses to frequent and infrequent tones reflect trial-to-trial adaptation (attenuation) of HG power with tone repetition (Cervenka et al. 2013; Edwards et al. 2005).

Results from the reversed stimulus oddball control confirmed that repetition-related decreases in HG power occurred regardless of which tone (1,000 or 1,200 Hz) served as the frequent stimulus. This finding suggests that acoustic differences cannot account for larger HG responses to infrequent tones. Similarly, the magnitude of HG responses to infrequent and equal-probability tones did not differ, as reported in previous animal studies (Farley et al. 2010; Fishman and Steinschneider 2012; Ulanovsky et al. 2003, 2004). This finding does not support the view that larger infrequent responses reflect deviance-detection enhancement effects. Indeed, even HG responses to infrequent tones showed some weak adaptation over the stimulus block. Although three patients did not complete the control tasks, results from the five patients who did were strikingly similar and suggest that neither stimulus-acoustic differences nor deviance-detection-related enhancements of the infrequent response can account for differential HG responses to frequent and infrequent tones. Previous studies have reported that deviance detection does not occur in primary auditory cortex (Fishman and Steinschneider 2012; Taaseh et al. 2011). Our results extend the scope of this prior work to include higher-level auditory association areas as well. Our findings do not imply, however, that deviance detection does not occur elsewhere in the cortex (May and Tiitinen 2010); our results suggest only that HG responses recorded from auditory association cortex do not show deviance-related enhancement effects. Adaptation of the frequent response may serve to increase the salience of responses to novel or infrequent stimuli that, in turn, could trigger deviance detection elsewhere in the cortex, including frontal lobe and prefrontal areas directly connected with auditory association cortex (Fishman and Steinschneider 2012; Romanski et al. 1999).

Because our study was designed to investigate HG responses, which are nonphase locked and thought to have different neural generators than evoked responses (Edwards et al. 2005; Sinai et al. 2009), we cannot address directly current debate about the role of adaptation or earlier middle-latency, auditory-evoked responses in deviance detection, as measured by the oddball-evoked, mismatch-negativity (MMN) difference waveform (Alho et al. 2012; Costa-Faidella et al. 2011a; Escura and Malmierca 2014). We note, however, that the rapid onset of HG response adaptation (≤100 ms) is somewhat earlier than might be expected for the MMN, which typically occurs ≥150 ms poststimulus (Näätänen et al. 2007). Visual examination of the original time-frequency plots used to identify auditory-responsive sites in our study, including both evoked and nonevoked spectral-power changes, showed increased spectral power, −50 ms at 30–50 Hz, for five of the eight patients (Fig. 2), consistent with the timing and frequency range of the auditory-evoked, middle-latency activity. Additional studies are needed to investigate whether different types of adaptation affect HG and evoked responses and their potential contributions to deviance detection along the auditory-processing pathway (Grimm et al. 2011; Pérez-González and Malmierca 2014).

**HG Responses to Speech**

Single-trial analyses also revealed trial-to-trial decreases in HG power for repeated speech stimuli, consistent with response adaptation. The reversed-probability speech control condition confirmed adaptation of HG power regardless of
which syllable was selected as the frequent stimulus. These findings extend prior studies of single-frequency, steady-state tones and suggest that adaptation also occurs for complex sounds, such as speech. Although the reversed tone condition confirmed adaptation for the 1,200-Hz single-frequency component of the vowel in the frequently presented syllable (/ba/), single-frequency adaptation cannot account for the smaller response compared with that of the infrequent syllable (/da/), since both syllables share the same vowel. The larger response elicited by the infrequent syllable suggests that there was adaptation for the entire frequent syllable, including the brief, rapidly changing consonant formant transition that was the main perceptual cue differentiating the two syllables. This finding should be interpreted with caution, however, as only one speech contrast was examined.

Although HG responses to repeated (frequent) speech and tone stimuli showed similar reductions in magnitude, infrequent speech responses appeared to adapt less than tone responses in single-trial analyses. However, this difference was not reflected in the normalized index-based (AI) measurements. Comparisons by individual electrode showed no clear patterns of adaptation similarity. Whether these stimulus-related differences in adaptation reflect the special nature of speech processing or simply differences in the size and number of acoustic contrasts distinguishing frequent vs. infrequent speech and tone stimuli is not known.

The general trend of repetition-related decreases in HG responses observed in our study is not consistent with the view that stimulus repetition leads to increased synchronization of local neuronal-population activity, leading to increased, rather than decreased, HG power (Grill-Spector et al. 2006; Li et al. 1993). However, it may be argued that increased synchronization is accompanied by optimization (reduction) of the local neuronal circuitry, resulting in an overall decrease in HG responses. Alternatively, stimulus repetition may induce both response adaptation and enhancement, depending on the site (Gruber and Müller 2005; Henson et al. 2000). Potential candidate sites for repetition enhancement might include a small number of electrodes in our patients, where HG responses increased for frequent stimuli, although these were uncommon. Such sites were located throughout perisylvian cortex but outside of the main auditory response areas.

**Time Scales of HG Adaptation**

Adaptation of HG responses to tones and speech occurred on several time scales, including rapid onset and slower local sequence and longer-term adaptation. We observed rapid onset adaptation within both tone and speech stimulus blocks. Adaptation was also evident within individual stimulus trials by ~100 ms poststimulus and lasted for the duration of the 400-ms response period. Adaptation was strongest at the beginning of a stimulus block, over the first two to three stimulus repetitions. This followed an initial increase in HG power for the first trial of a stimulus block. This onset adaptation for frequent tones was both large (~90%) and rapid (time constants < one stimulus). A similar pattern of onset adaptation was observed for speech. Most oddball studies exclude the first several trials from analysis, which may explain why this rapid onset of adaptation has gone largely undetected in previous studies. Interestingly, rapid onset adaptation was also observed for infrequent tones and equal-probability tones, albeit at somewhat slower time constants, possibly due to the irregular presentation or longer intervals. Rapid onset adaptation is important in the auditory system, which relies on millisecond precision encoding of auditory information (Kayser et al. 2010).

The strong responses observed for the first frequent trial of each block were not surprising, given that they followed a period of silence, during which, there was no adapting stimulus and therefore, were effectively a novel (infrequent) stimulus (Costa-Faidella et al. 2011a, b). Rapid onset adaptation to tones has been documented in animal single-unit and human scalp recording-evoked potential studies (Costa-Faidella et al. 2011b; Ulanovsky et al. 2004; Woods and Elmasian 1986), although somewhat slower and weaker than that observed for HG responses. In cat primary auditory cortex, adaptation time constants of 18.7 s have been reported for frequent tones and 48.4 s for equal-probability tones (Ulanovsky et al. 2004), compared with our HG adaptation time constants of 0.77 s and 1.47 s, respectively. However, faster onset effects (τ ~3.2 s) were reported when stimulus probabilities were reversed in a rapidly switching oddball paradigm (control), suggesting longer-term stimulus statistics effects. Weaker onset adaptation was noted for equal-probability control stimuli (τ ~48.4 s), as in our study, but not for infrequent-evoked responses. HG adaptation to tones was generally faster than the adaptation time constants reported in human scalp-recording studies (Costa-Faidella et al. 2011b), although one study (Woods and Elmasian 1986) reported adaptation of the evoked N1 response that reached steady state within three stimulus repetitions, with adaptation magnitudes between 40% and 65%.

Overall, our onset adaptation results are consistent with animal and other human studies but with somewhat faster and stronger effects. The precise origin of these differences is unclear, although methodological differences in species, recording sites (primary vs. nonprimary auditory cortex), preparations (e.g., ±anesthesia), and experimental paradigm and recording methods (scalp vs. intracranial) likely account for some of the discrepant findings. Stimulus differences may also be a contributing factor. For the oddball paradigm, we used tones of 1,000 Hz and 1,200 Hz, a normalized frequency difference of 0.18. In contrast, animal studies have used a variety of frequency differences from 0.10 to 0.37 (Ulanovsky et al. 2003, 2004), with increased adaptation reported for larger frequency differences. Similar results have been found for human-evoked potentials (Näätänen et al. 2007). The relatively small tone-frequency differences in the present study might explain weaker responses to low-probability (infrequent) tones in oddball tasks.

Responses to infrequent stimuli also showed weak adaptation over a stimulus block. Previous work has shown weak effects for small (0.10) but not large (0.37) stimulus-frequency differences (Ulanovsky et al. 2004), suggesting that cross-frequency adaptation may affect infrequent responses. Likewise, the use of a sparse tone or deviant-alone control paradigm may be overly stringent, due to overall low-stimulus presentation rates (Nelken and Ulanovsky 2007). Conversely, “many-tone” controls, with multiple tone frequencies, maintain overall stimulus presentation rates, potentially allowing for greater cross-frequency adaptation. Results from our equal-probability controls suggest that cross-frequency adaptation
did not bias the results. However, the extent to which stimulus selection affects comparisons of ECoG results with animal single-unit and human scalp-recording studies requires further investigation.

The rapid onset of HG adaptation was followed by slower (~7 min) and weaker (20–40%) ongoing adaptation that evolved over the course of the stimulus block. Such longer-term, or global, adaptation has been noted previously over long stimulus blocks in cats (Ulanovsky et al. 2004), where a double exponential fit revealed a slow phase of adaptation (~630 s). The slow-scale adaptation was weaker than the effects of onset adaptation, as we also observed. Similar slow-scale adaptation has been documented in rodent inferior colliculus but with time constants of 30–60 trials (Pérez-González et al. 2012). Human AEP studies have also noted longer-term adaptation over repeated stimulus blocks (Woods and Elmasian 1986).

We also found weak (<10%) adaptation across short sequences of one to five repeated stimulus trials (~2–10 s) suggesting modest local sequence or stimulus history (context) effects. This local adaptation followed a weak increase in HG power for the first frequent stimulus following an infrequent stimulus. Such increases are termed one-trial effects and are thought to represent resetting of the sensory “memory” trace (Sams et al. 1985, 1993). Similar sequence position effects have been noted for rodent local field potentials and multiunit responses (Yaron et al. 2012). Strong HG onset adaptation could account, in part, for weaker within-sequence adaptation. A system that is largely adapted after a few trials may have less dynamic range for additional adaptation.

We examined further the dependence of adaptation on local stimulus history using a linear model of expectancy that integrates local memory and global probability. We found a memory constant of α = 0.57 (τ = 2.32 stimuli, ~3.25 s), similar to the 0.51 noted for cat single-unit recordings (Ulanovsky et al. 2004) and 0.60 for human P300-evoked potentials (Squires et al. 1976). A human-evoked potential study (Costa-Faidella et al. 2011b) noted a longer memory constant of 0.79 for the evoked P2 response, although the shorter ISI yielded a similar time dependence (τ = 4.67 stimuli, ~1.46 s). A notable difference between HG power adaptation and these studies is the relative contribution of local memory and global probability to adaptation, as measured using a linear-response model. We found a ratio of memory-to-probability weighting of 0.25, suggesting a larger contribution of global probability. In contrast, the same ratio calculation for cats was 0.67 (Ulanovsky et al. 2004) and 0.47–1.59 for human AEPs (Costa-Faidella et al. 2011b; Squires et al. 1976). These suggest a larger contribution of local memory adaptation than we observed, possibly related to weaker onset adaptation.

### Regional vs. Inherited HG Adaptation

Because we recorded only from nonprimary auditory cortex, we do not know whether HG adaptation may have been inherited from primary auditory cortex or from subcortical structures, including the inferior colliculus (Ayala and Malmierca 2012; Pérez-González et al. 2005) and thalamus (Ulanovsky et al. 2003). Adaptation clearly occurs in primary auditory cortex; however, nonprimary areas also receive inputs from the nonlemniscal auditory pathway whose adaptation properties have not been systematically examined. Because of these limitations, we cannot differentiate inherited vs. novel HG adaptation. However, two previous ECoG studies recorded from both primary and nonprimary auditory cortex, using depth and subdural electrodes, found differences in the timing and morphology of the AEP, with later, smaller responses recorded from nonprimary areas (Brugge et al. 2009; Nourski et al. 2013). The observed differences in the temporal dynamics of adaptation for tone and speech stimuli observed in our recordings from nonprimary auditory areas raise the possibility of additional de novo adaptation. This would be consistent with the claim that adaptation is a cascading phenomenon in human cortex, as demonstrated recently in visual cortex (Dhruv and Carandini 2014).

### Auditory-Evoked Potentials

AEPs and, in particular, the N1 response were larger for infrequent vs. frequent stimuli, consistent with previous scalp-recording studies (Alho et al. 2012; Lanting et al. 2013; Todorovic et al. 2011). The evoked N1 response showed adaptation for both tones and speech, beginning ~100 ms poststimulus, as reported previously (Herrmann et al. 2013, 2014; McEvoy et al. 1997; Näätänen et al. 1988; Sams et al. 1993). Comparisons of N1 amplitude for infrequent and equal-probability tones showed no differences, suggesting that the larger N1 infrequent response does not reflect deviance-detection-related enhancements (Fishman and Steinschneider 2012). Analysis of the P2 showed no clear adaptation or enhancement effects, in contrast to prior reports (Costa-Faidella et al. 2011a, b; Lanting et al. 2013). Failure to replicate previously reported P2 changes could reflect methodological differences (scalp vs. intracranial recordings) or the smaller number of stimulus trials recorded in our study.

### Limitations

ECoG is performed with individuals who have longstanding neurological disorders, potentially limiting the generalizability of our findings. ECoG also has limited spatial sampling. Although we focused on auditory cortex, and all patients had electrode coverage of this region, it has been shown recently that adaptation may have a large, distributed network effect that we were not able to capture (Patterson et al. 2014). Another issue is that intracranial electrodes are implanted over only one hemisphere. Because adaptation occurs bilaterally (Altmann et al. 2008), the lack of whole-brain coverage could constrain interpretation of our results.

In summary, our results demonstrate that human auditory HG responses are exquisitely sensitive to the probabilities of simple and complex sounds. HG response adaptation occurs on multiple concurrent time scales in auditory association cortex, including both rapid, strong onset adaptation and slower, weaker, longer-term adaptation. We find that HG responses show adaptation for high-probability tones and speech, underscoring their potential role in auditory perception and improved speech recognition in complex listening environments.

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