The specificity of stimulus-specific adaptation in human auditory cortex increases with repeated exposure to the adapting stimulus

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Briley PM, Krumbholz K. The specificity of stimulus-specific adaptation in human auditory cortex increases with repeated exposure to the adapting stimulus. J Neurophysiol 110: 2679–2688, 2013. First published September 18, 2013; doi:10.1152/jn.01015.2012.—The neural response to a sensory stimulus tends to be more strongly reduced when the stimulus is preceded by the same, rather than a different, stimulus. This stimulus-specific adaptation (SSA) is ubiquitous across the senses. In hearing, SSA has been suggested to play a role in change detection as indexed by the mismatch negativity. This study sought to test whether SSA, measured in human auditory cortex, is caused by neural fatigue (reduction in neural responsiveness) or by sharpening of neural tuning to the adapting stimulus. For that, we measured event-related cortical potentials to pairs of pure tones with varying frequency separation and stimulus onset asynchrony (SOA). This enabled us to examine the relationship between the degree of specificity of adaptation as a function of frequency separation and the rate of decay of adaptation with increasing SOA. Using simulations of tonotopic neuron populations, we demonstrate that the fatigue model predicts independence of adaptation specificity and decay rate, whereas the sharpening model predicts interdependence. The data showed independence and thus supported the fatigue model. In a second experiment, we measured adaptation specificity after multiple presentations of the adapting stimulus. The multiple adapters produced more adaptation overall, but the effect was more specific to the adapting frequency. Within the context of the fatigue model, the observed increase in adaptation specificity could be explained by assuming a 2.5-fold increase in neural frequency selectivity.

Sensory neural responses are known to depend on past stimulus experience. Perceptual learning through intensive training, for instance, has been shown to increase the representation of, and sharpen neural selectivity for, the trained stimuli (Yang and Maunsell 2004). Sensory responses also depend on the short-term stimulus history. The neural response to a probe stimulus tends to be suppressed, or adapted, when the probe is preceded by another stimulus, referred to as the adapter. Adaptation tends to be specific to the adapting stimulus, i.e., stronger when the adapter and probe are the same than when they are different. Stimulus-specific adaptation (SSA) is ubiquitous across the senses and can be observed at all levels, from single neurons to perception (e.g., Kadohisa and Wilson 2006; Kohn 2007; McLaughlin and Kelly 1993; Meiselman 1968; Ulanovsky et al. 2003). SSA has been used extensively to probe sensory representations (e.g., Blakemore and Campbell 1969; Grill-Spector et al. 2006; Kay and Matthews 1972; Näätänen and Picton 1987; Peirce and Taylor 2006). Its functional role, however, remains unclear. In the auditory system, SSA has been studied mainly at the single-neuron level and is hypothesized to play a role in change detection as indexed by the mismatch negativity (MMN) (Anderson et al., 2009; Jääskeläinen et al. 2004; Malmierca et al. 2009; May and Tiitinen 2007, 2010; Ulanovsky et al. 2003, 2004; Yu et al. 2009). In the visual system, on the other hand, SSA has been related to implicit memory, or priming (Desimone 1996; Schacter and Buckner 1998; Ungerleider 1995). The question of the functional role of SSA is intimately related with the question of the mechanism by which SSA arises. Three prominent models have been proposed (reviewed in Grill-Spector et al. 2006): according to the fatigue model, adaptation reflects a reduction in the sensitivity of neurons responsive to the adapting stimulus; according to the sharpening model, neurons responsive to the adapter become more sharply tuned, resulting in fewer responsive neurons and thus a reduction in the overall response to the probe; finally, the facilitation model assumes that the adapter causes faster processing, that is, a shorter latency and duration of the probe response.

The current study sought to investigate which of these adaptation models applies in human auditory cortex. For that, we measured event-related cortical potentials to pairs of adapter and probe stimuli (Fig. 1A). The adapter and probe were both pure tones, and the frequency separation and stimulus onset asynchrony (SOA) between them varied orthogonally. This enabled us to investigate the relationship between the degree of specificity of adaptation as a function of frequency separation and the rate of decay of adaptation as a function of SOA. Using simulations of tonotopic neuron populations, we demonstrate that the different adaptation models make distinct predictions of the form of this relationship. We found that the data were best matched by the predictions of the fatigue model.

In a second experiment, we measured adaptation specificity after multiple presentations of the adapter (see Fig. 3, A and B). This mimics the situation in the oddball paradigm, used to measure the MMN, where the infrequent “deviant” stimulus is typically preceded by multiple instances of the frequent “standard” stimulus. We found that the degree of specificity of adaptation increases for multiple adapters. Within the context of the fatigue model, this increase in adaptation specificity could be explained by increasing the single-neuron frequency selectivity in the simulated population.
MATERIALS AND METHODS

Stimuli

The probe and adapter stimuli were 110-ms tone pips, gated on and off with 10-ms cosine-squared ramps to avoid audible on- and offset clicks. They were presented in trials of 5-s duration. Each trial started with either a single (Experiment 1) or two or three adapters (Experiment 2), followed by the probe (see Fig. 1A and Fig. 3, A and B). In Experiment 1, the SOA between the adapter and probe was varied parametrically from 125 to 1,000 ms in doublings (125, 250, 500, and 1,000 ms). In Experiment 2, the SOA between consecutive adapters, and between the last adapter and the probe, was fixed at 500 ms (see Fig. 3, A and B). In both experiments, the probe frequency was fixed and the adapter frequency was varied in relation to it. The reason for fixing the probe frequency was to avoid confounding any changes in the probe response due to adaptation with changes due to changes in the probe frequency. The adapter frequency was either the same as, or 1/6, 1/2, or 1.5 octaves above, the probe frequency. In Experiment 2, all adapters within each trial had the same frequency. The probe frequency was nominally 1,000 Hz but was randomized from trial to trial within a 1/3-octave range around that frequency to avoid across-trial adaptation.

All stimuli were generated digitally at a sampling rate of 25 kHz followed by digital-to-analog conversion with 24-bit amplitude resolution using TDT System 3 (Tucker Davis Technologies, Alachua, FL) and Matlab (The MathWorks, Natick, MA). They were presented identically to both ears at a level of 60 dB SPL using AKG K240 DF headphones (AKG, Vienna, Austria). To equalize hearing thresholds across frequencies and participants, the stimuli were presented in a continuous noise background, filtered to contain equal energy within all cochlear filters and presented at a level of 20 dB per equivalent rectangular filter bandwidth (ERB) (Glasberg and Moore 1990).

Procedure

Experiment 1 consisted of three sessions. The two longer SOAs (500 and 1,000 ms) were presented within the same session. For the two shorter SOAs (125 and 250 ms), the responses to the adapters partially overlapped the probe response (Fig. 1B). Therefore, these SOAs were presented in a separate session each, and the probe was omitted on half of the trials to measure the adapter responses in isolation. The adapter-only responses ([A]) were subsequently subtracted from the overlapping responses to the adapter and probe pairs ([A + P]) to isolate the probe response ([P] = [A + P] − [A]; Fig. 1B). Subtraction of the adapter-only response is also commonly applied in adaptation experiments using functional magnetic resonance imaging (e.g., Boynton and Finney 2003). The two- and three-adapter conditions of Experiment 2 were presented within a single session. In both experiments, each session comprised eight conditions (4 adapter-probe frequency separations × 2 SOAs or numbers of adapters) and was split into four 20-min runs. Each condition was presented 30 times per run in a random order, yielding a total of 120 trials per condition. Throughout the recordings, participants watched a silent, subtitled movie of their own choice to remain alert.

Data Acquisition

Late auditory-evoked cortical potentials were recorded with 33 Ag-AgCl ring electrodes (EasyCap, Herrsching, Germany) and an electroencephalography (EEG) amplifier (BrainAmp DC, Brain Products, Gilching, Germany). The electrodes were placed according to the standard 10–20 arrangement (Jasper 1958). Skin-to-electrode impedances were kept below 5 kΩ throughout the recordings. The recording reference was the vertex (Cz) channel, and the ground was placed on the central forehead (AFz). The electrode signals were bandpass filtered online between 0.1 and 250 Hz, sampled at 500 Hz, and stored for off-line analysis using BrainVision Recorder (Brain Products).

Data Analysis

Preprocessing. The raw data were preprocessed with the EEGLAB toolbox (Delorme and Makeig 2004), which runs under Matlab. They were 1) low-pass filtered at 35 Hz using a –48 dB/oct zero-phase infinite impulse response filter, 2) downsampled to 250 Hz, 3) re-referenced to average reference, 4) segmented into 600-ms epochs ranging from 100 ms before to 500 ms after the probe onset, and 5) baseline-corrected to the 100-ms prestimulus period. Epochs containing unusually large potentials across many electrodes (joint probability ≤ 3 SD) were rejected automatically. On average, 15% of trials were rejected in this way; for any given condition and participant, the minimum number of included trials was 91. The remaining epochs were submitted to an independent component analysis (ICA) based on the extended infomax algorithm. Components representing eye blinks, lateral eye movements, and electrocardiac activity were removed by manual inspection. Epochs were then averaged for each participant and condition.

To reduce the dimensionality and improve the signal-to-noise ratio of the data, the averaged responses were converted from sensor to
source space using the Brain Electrical Source Analysis software (BESA, Gräfelfing, Germany). The source model consisted of two equivalent current dipoles placed at the centroids of the primary area TE1.0 in the left and right hemispheres (Morosan et al. 2001), and the head model was a four-shell ellipsoidal volume conductor. The dipole orientations were fitted within a time window encompassing the P1, N1, and P2 deflections (0–250 ms) of the grand-average probe response across all conditions and participants to obtain a representative auditory cortex source. Source waveforms were averaged across hemispheres, because none of the statistical analyses applied yielded any interactions with hemisphere (all $p > 0.05$).

Further analyses. Adaptation was measured by expressing the size of the adapted probe response ($P$) as a fraction of the unadapted probe response size ($P_u$). The unadapted probe response size was taken as the size of the response to the first adapter (or, where available, the adapter in isolation), averaged over all conditions where the adapter frequency was the same as the probe frequency. The result was subtracted from unity and expressed as a percentage $\left(1 - P/P_u\right) \times 100$. The adapter and probe response sizes were measured as the peak-to-peak difference between their P2 and N1 deflections (Fig. 1B). The N1 and P2 deflections have opposite polarities and overlapping time courses and thus partially cancel each other (Makeig et al. 1997; Näätänen and Picton 1987). Thus a decrease in one deflection can cause the other deflection to appear increased, and vice versa. The enhancement of the N1 deflection at very short adapter-probe SOAs observed in previous studies is an example of this effect (Budd and Michie 1994; Wang et al. 2008). Use of the peak-to-peak difference to measure response size minimizes this problem.

The stimulus sequences elicited an unexpected sustained response (SR) with vertex-negative polarity. We compared the scalp topography of the SR with that of the vertex-negative N1 deflection in the grand-average onset response to the first adapter using a global dissimilarity (DISS) analysis as described by Lehmann and Skrandies (1980) and Murray et al. (2008). We also estimated the cortical source distributions of the SR and N1 using the iterative sLOFO algorithm (Liu et al. 2005) as implemented in BESA.

Participants

A total of 15 participants (5 men; mean age = 24.8 yr, SD = 6.5 yr) took part in this study after having given written informed consent. At least 11 participants took part in each session, and 6 participants took part in all sessions. All participants had hearing thresholds at or below 20 dB HL at all audiometric frequencies (250–8,000 Hz) and had no history of audiological or neurological disease. The procedures accorded with the Declaration of Helsinki and were approved by the Ethics Committee of the University of Nottingham School of Psychology.

RESULTS

Adaptation by Single Adapters

Experiment 1 measured adaptation by single adapters as a function of the frequency separation and SOA between the adapter and probe (Fig. 1A). Adaptation decreased with increasing frequency separation (Fig. 1C), indicating that adaptation was specific to the adapting frequency, and decreased with increasing SOA (Fig. 1D), indicating that adaptation decayed over time (tested with a linear mixed-model (LMM) analysis of the log-transformed adaptation, with frequency separation as fixed factor and SOA as covariate; here, and in all subsequent LMM analyses, participants were entered as random factor; main effect of frequency separation: $F(3,157.670) = 10.603, p < 0.001$; main effect of SOA: $F(1,169.495) = 112.111, p < 0.001$. This was expected on the basis of results from previous studies, which varied either frequency separation or SOA separately (e.g., Butler 1968; Nelson and Lassman 1968). Importantly, the functions relating adaptation to frequency separation (referred to as adaptation tuning curves) for different SOAs appear parallel, as do the functions relating adaptation to SOA (referred to as adaptation decay functions) for different frequency separations. This indicates that the degree of frequency specificity of adaptation was independent of SOA and that the rate of decay of adaptation with SOA was independent of frequency separation [confirmed by the nonsignificance of the interaction between frequency separation and SOA: $F(3,154.677) = 0.267, p = 0.849$].

The adaptation decay functions (Fig. 1D) appear linear when adaptation is plotted on a logarithmic scale. This indicates that adaptation decayed at a single-exponential rate.

Population Models of Neural Fatigue and Neural Sharpening

Experiment 1 showed that even single adapters can cause substantial reductions in the probe response size (adaptation) and that adaptation decreases with increasing frequency separation (adaptation specificity) and SOA (adaptation decay). Moreover, Experiment 1 showed that adaptation specificity and adaptation decay are independent processes. These findings might help to discriminate between the three suggested adaptation models (fatigue, sharpening, and facilitation). The facilitation model can be discarded straight away, because it predicts reductions in the probe response latency and duration but not in the probe response size, which is inconsistent with the current data. In contrast, both the fatigue and sharpening models predict reductions in the probe response size, as observed. To discriminate between these two models, we implemented them in a model population of tonotopic neurons.

The population consisted of 3,711 neurons, $n$, each with a limited frequency response function, $r(f)$ (Fig. 2A). Each response function was modeled as a sum of two rounded exponential (roex) functions to create a sharper tip and a broader tail:

$$r(f) = \left[\left(1 + p_{\text{tip}} \Delta f\right)e^{-r_{\text{tip}} \Delta f} + G(1 + p_{\text{tail}} \Delta f)e^{-r_{\text{tail}} \Delta f}\right]/(G + 1) \ .$$

where $\Delta f$ is the normalized absolute separation between the given frequency, $f$, and the neuron’s characteristic frequency, $f_c$; $G$ is the gain of the tail relative to the tip; and $p_{\text{tip}}$ and $p_{\text{tail}}$ determine the widths of the tip and tail, $W_{\text{tip}}$ and $W_{\text{tail}}$, respectively ($W_{\text{tip/tail}} = 4f_{\text{tip/tail}}^{-1}$; see Patterson et al. 1982). A roex model with a sharper tip and a broader tail is often used to characterize cochlear filters estimated behaviorally (e.g., Glasberg and Moore 2000). In the current study, the model enabled us to explain the relatively sharp tip and shallower tail of the adaptation tuning curves. The response functions’ best frequencies were spaced at 100 per ERB.

For the fatigue model, we assumed that the adapter suppresses each neuron’s response to the probe, $p$, by a factor of $s_1 = 1 - S(\text{SOA})g(a)$, where $S(\text{SOA})$, the adaptation strength, is the maximum adaptation across neurons, which was assumed to depend on SOA, and $g(a)$, the adaptation profile, is a monotonically increasing function of the adapter activation, $a$. $S(\text{SOA})$ models the decay of adaptation as a function of SOA, and $g(a)$ models the specificity of adaptation to the
adapter frequency. S(SOA) was assumed to be equal to 1 for zero SOA and decay exponentially with increasing SOA:

\[ S(SOA) = e^{-\mu SOA} \] (2)

The rate of adaptation decay, \( \mu \), was estimated by log-linear regression of the adaptation decay functions in Fig. 1D. It was found to be equal to 1.04/s, which corresponds to a time constant of 957.56 ms. \( g(a_i) \) was assumed to be a compressive function of the normalized adapter activation:

\[ g(a_i) = \frac{a_i}{\text{max}(a)} \] (3)

where \( \beta \) is the compression exponent and \( \text{max}(a) \) is the maximum adapter activation across the neuron population. \( \beta \) was allowed to vary between 0 and 1, where 0 means total compression and 1 means no compression. Compression increases suppression in neurons where the adapter activation is weak. Increasing the compression increases the predicted adaptation at all frequency separations and SOAs. The adapted population response to the probe, \( P \), was estimated by summing across all adapted single-neuron responses: \( P = \sum_i s_iP_i \).

As for the data, the adapted probe response was divided by the unadapted probe response, \( P_0 = \sum_i p_i \), and the result was subtracted from unity and multiplied by 100 to obtain the amount of adaptation as a percentage. The tip widths of the neural frequency response functions, \( W_{\text{tip}} \), were set equal to the tip widths of the cochlear filters as estimated behaviorally \( [W_{\text{tip}} = 24.67(4.37f + 1)(1,000 \text{ kHz}); \text{Glasberg and Moore 1990}] \), and the tail widths were assumed to be a constant multiple, \( C_{\text{tail}} \), of the tip widths. \( C_{\text{tail}} \) was a free parameter of the model, as were the relative tail gain, \( G \) (see Eq. 1), and the compression exponent, \( \beta \). These parameters were least-squares fitted to the extrapolated adaptation tuning curve for zero SOA (shown in Fig. 1C). This curve was derived from the log-linear regression fits to the adaptation decay functions mentioned earlier.

For the sharpening model, we assumed that the adapter reduces the width of each neuron’s frequency response function, \( r_j \), by a factor \( c_j = [S(SOA) - 1]g(a_i) + 1 \). In this case, the adaptation strength, \( S(SOA) \), determines the maximum amount of sharpening across neurons. As before, \( S(SOA) \) was allowed to vary with SOA. The adaptation profile, \( g(a_i) \), which models adaptation specificity as a function of frequency separation, was defined in the same way as in the fatigue model (see Eq. 3). For parsimony, the sharpening was applied equally to both the tips and tails of the frequency response functions. The sharpening model was fitted in two stages. In the first stage, the model was fitted to the extrapolated adaptation tuning curve for zero SOA (like the fatigue model). The free parameters in this fit were the tip width multiple, \( C_{\text{tip}} \), the tail gain, \( G \), and the compression exponent, \( \beta \), as for the fatigue model, and, in addition, the adaptation strength at zero SOA, \( S(SOA) = 0 \). The tip widths of the neural frequency response functions, \( W_{\text{tip}} \),
were set equal to the tip widths of the cochlear filters estimated behaviorally (Glasberg and Moore 1990) as before. In the second stage, the model was fitted to the data for each SOA. The only free parameter in this case was \( S(\text{SOA}) \); all other parameters (\( C_{\text{tail}}, G, \beta \)) were carried over from the first stage.

The goodness of the fatigue and sharpening model fits was compared by calculating bootstrap distributions of the root-mean-square deviation (RMSD) between the modeled and observed adaptation (based on 1,000 bootstrap resamples; Efron and Tibshirani 1993) and comparing the distributions with a two-sample Kolmogorov-Smirnov (KS) test.

The fatigue and sharpening models yielded similarly sharp single-neuron frequency response functions (Fig. 2A). The tip widths of the response functions were fixed to the same values in both cases. The response function tails were wider than the widths of the response functions were fixed to the same values in the fatigue model, the adaptation strength, \( S(\text{SOA}) \), was derived from the log-linear regression of the adaptation decay functions. In the sharpening model, the adaptation decay rate, \( \mu \), and the compression exponent of the adaptation profiles, \( \beta \), were carried over from the single-adapter fit. \( G \), gain of the tail relative to the tip; RMSD, root-mean-squared difference.

Despite having fewer free parameters (4 vs. 8), the fatigue model fitted the data significantly better (RMSD = 2.3% ) than the sharpening model (RMSD = 4.3%; KS = 0.488, \( p < 0.001 \)). The better fit was because, in the fatigue model, the shape of the adaptation tuning curves as a function of frequency separation was independent of SOA (Fig. 2C) and the rate of decay of adaptation with SOA was independent of frequency separation (Fig. 2D). In contrast, in the sharpening model, the shape of the adaptation tuning curves varied with SOA (Fig. 2E) and the rate of adaptation decay varied with frequency separation (Fig. 2F).

### Adaptation by Multiple Adapters

In Experiment 1, the probe was preceded by a single adapter. To mimic the situation in the oddball paradigm, where the deviants are typically preceded by multiple standards, we conducted a second experiment in which each probe was preceded by either two or three adapters (Fig. 3, A and B). As in Experiment 1, the frequency separation between the adapter and probe was varied to measure the degree of frequency specificity of adaptation, but the SOA was fixed at 500 ms in this case. As would be expected, the multiple adapters produced more adaptation overall than the single adapters with the same SOA [Fig. 3C; tested with an LMM analysis of the single-adapter data for SOA = 500 ms and the geometrically averaged data for the 2 and 3 adapters, with frequency separation and number of adapters as fixed factors; main effect of number of adapters: \( F(1,74.813) = 12.527, p = 0.001 \). As for the single adapters, adaptation for the multiple adapters decreased with increasing frequency separation between the adapters.
adapter and probe [marginal effect of frequency separation for the multiple adapters: $F(3,67.104) = 30.100, p < 0.001$]. However, the decrease was considerably steeper for the multiple than for the single adapters [interaction between frequency separation and number of adapters: $F(3,67.104) = 3.478, p = 0.021$], indicating greater adaptation specificity for the multiple adapters. The increase in adaptation specificity was similar between the two- and three-adapter conditions [LMM analysis of 2- and 3-adapter conditions with fixed factors frequency separation and number of adapters; interaction between frequency separation and number of adapters: $F(3,70) = 0.215, p = 0.886$].

**Fatigue Model of Increased Adaptation Specificity for Multiple Adapters**

In the fatigue model, the specificity of adaptation is determined by the widths of the single-neuron frequency response functions; the sharper the response functions, the greater the adaptation specificity (the sharper the adaptation tuning curve). According to the fatigue model, the increased adaptation specificity for the multiple adapters would thus suggest that adaptation was caused by a neuron population with sharper frequency response functions. Here, we used the same fatigue model as before to examine how much sharper the response functions would have to become to explain the observed increase in adaptation specificity. In the fatigue model, the adaptational effects of multiple adapters aggregate multiplicatively (Eggermont 1985). The adapted probe response of each neuron, $n_i$, was thus modeled as $\prod s_j p_i$, where $p_i$ is the neuron’s unadapted probe response, as before, and $s_j$ is the adaptational effect of the $j$th adapter ($j \in \{1,2\}$ or $\{1,2,3\}$ for the 2 or 3 adapters, respectively). As before, $s_j$ was assumed to depend on both SOA and frequency separation: $s_j = 1 - S(SOA_j) g(a_j)$, where $S(SOA_j)$ is the adaptation strength at the SOA of the $j$th adapter and $g(a_j)$ is the adaptation profile for the given adapter frequency. $S$ and $g$ were defined in the same way as before (Eqs. 2 and 3), with the relevant parameters, $\mu$ and $\beta$, carried over (see Table 1). In the current fit, the widths of both the tips and tails of the neural frequency response functions, $W_{tip}$ and $W_{tail}$, were free parameters, as was the relative gain of the tails, $G$ (Eq. 1). Both the tip and tail widths were assumed to be constant multiples of the tip widths of the cochlear filters estimated behaviorally (see above). The model was fitted to the geometric average of the two- and three-adapter data.

The fatigue model fitted the multiple-adapter data similarly well as the single-adapter data (Fig. 3C; RMSD = 2%). The tips of the frequency response functions yielded by the fit to the multiple-adapter data were narrower by a factor of 1.86 than those yielded by the fit to the single-adapter data (Fig. 3D). The tails were narrower by a factor of 1.47 and also had a lesser relative gain of $-23.4$ dB (compared with $-14.3$ dB for the single adapters). This meant that the overall widths of the frequency response functions (measured as equivalent rectangular widths) were narrower by a factor of 2.5. The significance of this difference was confirmed by calculating bootstrap distributions of the width of the frequency response function at 1 kHz (using 1,000 bootstrap resamples, as before) and submitting the distributions to a two-sample KS test ($KS = 0.994, p < 0.001$).

**Increased Adaptation Specificity for Multiple Adapters Was Not Caused by a Superposed MMN**

In the previous section, we assumed that the observed increase in adaptation specificity for the multiple adapters was due to adaptation being caused by a neuron population with sharper frequency response functions. Alternatively, however, the increase might also have been caused by the superposition of an MMN response. The MMN is elicited by deviations in otherwise regular stimulus patterns (Näätänen et al. 2011). An MMN may thus have been elicited in the multiple-adapter conditions where the probe and adapter frequencies were different. In contrast, the single-adapter conditions would not have been expected to elicit an MMN. The MMN is thought to be an endogenous response. Unlike the stimulus-driven response, it is monophasic with negative polarity at the vertex. Any MMN response should be reflected in the difference responses between the non-zero and zero frequency separations. Figure 4 shows the average difference responses across all non-zero frequency separations for the single-adapter condition with the 500-ms SOA and for the two- and three-adapter conditions. The difference response for the single adapters would be assumed to solely reflect the larger stimulus-driven responses for the non-zero than for the zero frequency separations. The fact that this response was biphasic, with an initial negative and subsequent positive deflection, indicates that both the N1 and P2 deflections were enlarged. If the increased adaptation specificity for the multiple adapters was due to superposition of an MMN, the negative deflection in the difference responses for the multiple adapters should be enlarged, but the positive deflection should be reduced. This, however, was not the case; rather than being reduced, the positive deflection became progressively larger with increasing number of adapters [LMM analysis with frequency separation and number of adapters as fixed factors; main effect of number of adapters: $F(2,90.546) = 5.112, p = 0.008$]. This indicates that the sharpening effect for the multiple adapters was due to an increase in the size of the stimulus-driven response to the

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*Fig. 4.* Bold lines show the difference responses between the non-zero and zero frequency separations for the single-adapter condition with the 500-ms SOA from Experiment 1 (solid black line) and the 2- and 3-adapter conditions from Experiment 2 (solid blue and magenta lines). The difference responses were averaged across all non-zero frequency separations. The thin dashed lines show the SE of the responses.
probe, rather than the superposition of an endogenous MMN response.

Sustained Activity Across the Silent Gaps Between the Stimuli

In the oddball paradigm, the stimuli are presented in a continuous sequence, so the responses have to be baseline-corrected to the silent period before each stimulus. In the current study, the stimuli were presented in discrete trials. This allowed us to baseline correct to the silent period before each trial and thus examine the response to the trial as a whole. This revealed a surprising SR, which persisted from just after the onset response to the first adapter (OnR) to several hundred milliseconds after the probe (Fig. 5, A–D). As is the case for sustained responses elicited by ongoing sounds (e.g., Picton et al. 1978), the SR had vertex-negative polarity. Irrespective of the SOA or the number of adapters preceding the probe, the SR seemed to continue at a fairly constant level through the silent gaps between the stimuli. A DISS analysis (Lehmann and Skrandies 1980; Murray et al. 2008) showed that the scalp topography of the SR differed significantly from that of the stimulus-driven N1 response, indicating differences in the underlying generator configurations. Comparison of the current source density (CSD) maps (Fig. 5, E and F) and distributed source images (Fig. 5G; see MATERIALS AND METHODS) of the SR and N1 suggests that the SR received contributions from a bilateral supratemporal source, located anterior to the source of the N1, and possibly also from a source in the inferior frontal gyrus.

DISCUSSION

This study was aimed at investigating whether stimulus-specific adaptation (SSA), measured in human auditory cortex, is mediated by neural fatigue or neural sharpening. For that, we examined the relationship between the degree of specificity of adaptation as a function of the frequency separation between the adapter and probe and the rate of decay of adaptation as a function of the frequency separation between the adapter and probe and the rate of decay of adaptation as a function of the frequency separation between the adapter and probe and the rate of decay of adaptation as a
function of their SOA. We found that the degree of adaptation specificity was independent of SOA, and the rate of decay of adaptation was independent of frequency separation. We fitted the data with population models of neural fatigue and neural sharpening and found that the fatigue model fitted the data significantly better, because only this model predicted independence of the effects of frequency separation and SOA, as observed. This suggests that SSA in human auditory cortex is caused by neural fatigue. In the fatigue model, the rate of decay of adaptation with SOA is determined by the decay rate of the processes causing fatigue. In the current study, adaptation decayed at a single-exponential rate of 1.04/s (corresponding to a time constant of 957.56 ms), suggesting that it was caused by synaptic depression (Asari and Zador 2009; Wehr and Zador 2005; Zucker and Regehr 2002), and possibly also slow afterhyperpolarization (Faber and Sah 2003; Schwindt et al. 1988a, 1988b).

In a second experiment, the adapter was presented multiple times to mimic the situation in the oddball paradigm, where the deviants are typically preceded by multiple standards. The adaptation tuning curves for the multiple adapters were considerably sharper than those for the single adapters. Figure 6 shows that the adaptation tuning curve for the three adapters was similar to the adaptation tuning curve obtained by Butler (1968). Similar to the current experiment, Butler measured the N1–P2 response to a 1-kHz probe preceded by three identical adapters while varying the frequency separation between the adapters and the probe. Butler observed less adaptation overall, but that is probably because he used a longer SOA (1,250 ms compared with 500 ms used in the current study). He also presented the stimuli in a continuous sequence, rather than in discrete trials.

In the fatigue model, the degree of frequency specificity of adaptation is determined by the overlap between the neuron groups responding to the adapter and probe, respectively, which is, in turn, determined by the widths of the neurons' frequency response functions. To explain the observed sharpening of the adaptation tuning curves for the multiple adapters, the widths of the frequency response functions had to be decreased by a factor of 2.5. In the simulation of the single-adapter data, we assumed the tip widths of the frequency response functions to be the same as the tip widths of the cochlear filters as measured behaviorally. The simulation results for the multiple-adapter data thus suggest that adaptation by multiple adapters is underpinned by neurons with considerably sharper frequency response functions than the cochlear filters. However, it has been suggested that the original behavioral measurements of the cochlear filter widths overestimate the true filter widths by a factor of two or more (Joris et al. 2011; Shera et al. 2002; see, however, Eustaquio-Martin and Lopez-Poveda 2011; Ruggero and Temchin 2005). Under this assumption, the single-adaptor data might reflect the frequency tuning of the cortical neurons that generated the probe response (compare Scholes et al. 2011). In contrast, the multiple-adaptor data might reflect frequency tuning at a more peripheral level with sharper frequency tuning. Mill et al. (2011) showed that, in a system where neural selectivity decreases toward central processing levels due to convergence, repeated or prolonged presentation of the adapter will give the more broadly tuned central neurons time to recover from initial adaptation. As a result, the specificity of adaptation measured at any level will reflect the selectivity of the more sharply tuned peripheral neurons. This model would also explain previous findings of sharper adaptation than response tuning in the auditory oddball and classical visual adaptation paradigms (Sawamura et al. 2006; Ulanovsky et al. 2003). The model would also explain the finding by Taaseh et al. (2011) that the standards in the oddball paradigm are less effective at adapting the deviants than would be expected on the basis of the adaptational effect of each standard separately.

Alternatively, the sharper adaptation tuning for the multiple adapters might reflect a sharpening of the response tuning of the cortical neurons that generated the probe response beyond the tuning of their peripheral inputs. As suggested in hierarchical predictive coding models, such receptive field sharpening might be mediated by top-down processes, invoked as a result of the repeated adapter presentation (e.g., Friston 2005). The SR that persisted through the stimulus sequences may represent a correlate of such top-down processes. Distributed source analysis indicated that, like the MMN (Alho 1995; Doeller et al. 2003; Opitz et al. 2002; Rinne et al. 2000; Schönwiesner et al. 2007), which has also been suggested to be involved in predictive top-down processing (Garrido et al. 2008, 2009), the SR receives contributions from anterior superior temporal, and possibly also inferior frontal cortex. Given that the adapter frequency varied from trial to trial, any receptive field sharpening would have had to occur over a timescale of only a few hundred milliseconds. Similarly, rapid receptive field plasticity has previously been suggested to play a role in mediating selective attention and task-related learning (Ahveninen et al. 2011; Fritz et al. 2003, 2007; Murray and Wojciulik 2004).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

P.M.B. and K.K. conception and design of research; P.M.B. and K.K. performed experiments; P.M.B. and K.K. analyzed data; P.M.B. and K.K. interpreted results of experiments; P.M.B. and K.K. prepared figures; P.M.B. and K.K. drafted manuscript; P.M.B. and K.K. edited and revised manuscript; P.M.B. and K.K. approved final version of manuscript.

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