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Research paper

Acoustic experience but not attention modifies neural population phase expressed in human primary auditory cortex

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ABSTRACT

We studied the effect of auditory training on the 40-Hz auditory steady-state response (ASSR) known to localize tonotopically to the region of primary auditory cortex (A1). The stimulus procedure was designed to minimize competitive interactions among frequency representations in A1 and delivered target events at random times in a training window, to increase the likelihood that neuroplastic changes could be detected. Experiment 1 found that repeated exposure to this stimulus advanced the phase of the ASSR (shortened the time delay between the 40-Hz response and stimulus waveforms). The phase advance appeared at the outset of the second of two sessions separated by 24–72 h, did not require active training, and was not accompanied by changes in ASSR amplitude over this time interval. Experiment 2 applied training for 10 sessions to reveal further advances in ASSR phase and also an increase in ASSR amplitude, but the amplitude effect lagged that on phase and did not correlate with perceptual performance while the phase advance did. A control group trained for a single session showed a phase advance but no amplitude enhancement when tested 6 weeks later (retention). In both experiments attention to auditory signals increased ASSR amplitude but had no effect on ASSR phase. Our results reveal a persistent form of neural plasticity expressed in the phase of ASSRs generated from the region of A1, which occurs either in A1 or in subcortical nuclei projecting to this region.

1. Introduction

Animal studies have established that the response properties of neurons in primary auditory cortex (A1) are remodeled by auditory training to detect behaviourally significant environmental sounds (Weinberger, 2004). Among the response properties affected are (i) shifts in the tuning preference of auditory neurons toward the trained stimuli (Fritz et al., 2005; Weinberger, 2007); (ii) spike rates induced by these stimuli (Blake et al., 2002); (iii) tuning bandwidth (Brown et al., 2004; Kilgard et al., 2001); (iv) response latency in post-stimulus time histograms (Brown et al., 2004; Kilgard and Merzenich, 2002); (v) tonotopic map expansions for the trained stimuli (Recanzone et al., 1993); and (vi) consolidation of learning effects over an interval of 24–72 h without intervening training experience (Galvan and Weinberger, 2002). Cholinergic projections to the neocortex from nuclei in the basal forebrain (BF) appear to modulate neural plasticity by making cortical neurons more sensitive to their afferent inputs (Metherate and Ashe, 1993; Weinberger, 2004). The role of the BF in enabling plasticity may arise because this system can itself be brought under task control (Rigdon and Pirch, 1986) and appears to perform some of the functions of attention (Sarter et al., 2005). Plastic changes can also be induced by pairing auditory stimuli with electrical stimulation of the BF (Kilgard and Merzenich, 2002). Tonotopic map expansions observed when single sound frequencies signal reward are reduced when multiple frequencies are used (Kilgard et al., 2001), suggesting that competitive interactions in A1 may normalize frequency representations when several sounds are present.

These principles based on animal studies identify a learning system that would be expected to be at work when neural population activity expressed in auditory evoked potentials (AEPs) is remodeled by acoustic experience in the human brain. Measurement of AEPs and their magnetic counterparts auditory evoked magnetic fields (AEFs) can reveal neural population activities that are involved in this system and provide information about the

Abbreviations: A1, primary auditory cortex; A2, secondary auditory cortex; 2IFC, two interval forced choice procedure; ABRs, auditory brain stem responses; AEF, auditory evoked field; AEP, auditory evoked potential; AM, amplitude modulated; ANOVA, analysis of variance; ASSR, auditory steady-state response; BESA, brain electrical source analysis; BF, basal forebrain; EEG, electroencephalogram; FFRs, frequency-following responses; FFT, fast Fourier transform; HG, Heschl's gyrus; ITI, intertrial interval; LFP, local field potential; LTP, long-term potentiation; MEG, magnetoencephalography; TH, threshold.

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mechanisms involved, even though events operating at the level of single or local networks of neurons cannot be specified. Consistent with this expectation, the amplitude of several long latency (>100 ms) AEPs or AEFs localizing to sources in secondary auditory cortex (A2) has been found to increase with acoustic training in the laboratory (in order of increasing latency, N1: van Wassenhove and Nagarajan, 2007; Ta: Alain et al., 2007; N1c: Bosnyak et al., 2004; P2: Tremblay et al., 2001; mismatch negativity: Menning et al., 2000) or to be enhanced for musical sounds in trained musicians (N1c: Shahin et al., 2003; P2: Kuriki et al., 2006; Shahin et al., 2003, 2004; N2: Fujioka et al., 2006) implying neuroplastic effects expressed in these regions. Evoked activity in frontotemporal cortex (Shahin et al., 2007) including late oscillatory brain activity for timbres of the instrument of practice (Shahin et al., 2008) is also enhanced by musical training, which may reflect multidimensional sensory integration and the formation of memory for complex auditory skills. The processing that results in these higher order changes begins in subcortical nuclei where auditory brain stem responses (ABRs) are modulated by musical training (Musacchia et al., 2008) and where frequency-following responses (FFRs) recorded putatively from the inferior colliculus reflect language-specific learning in adults (Krishnan et al., 2009) and show enhanced phase locking to the fundamental frequency when novel speech sounds are trained in the laboratory (Song et al., 2008). Conspicuously lacking from human studies, however, is evidence from laboratory training for plasticity expressed in A1, which is the auditory region investigated by most animal models and on which prevailing concepts are based.

A response of importance in this regard is the stimulus-driven *auditory steady-state response* (ASSR). This response reaches its amplitude maximum when sounds are amplitude modulated (AM) at rates near 40 Hz (Ross et al., 2000) and localize in intracerebral recordings to posterior-medial Heschl's gyrus (Bidet-Caulet et al., 2007; Brugge et al., 2009), which is believed to correspond to the region of A1 in the human brain. ASSR sources determined by inverse modeling from MEG (Pantev et al., 1996b; Wienbruch et al., 2006) and EEG (Gander et al., 2010) data show a high-frequency medial, low-frequency lateral tonotopic ordering in this region that is consistent with tonotopic organization described in human fMRI studies (Formisano et al., 2003; Petkov et al., 2004) and with reversing tonotopic maps in A1 of the macaque monkey, which share a low-frequency border situated laterally in the superior temporal gyrus (Kaas and Hackett, 2000). The ASSR waveform extracted by temporal deconvolution of ASSRs recorded at AM rates from 10 to 50 Hz approximates the Na/Pa/Nb/Pb waveform of auditory "middle latency" responses that are evoked in the interval ~19–55 ms post-stimulus and represent the earliest stages of sound processing in the auditory cortex (Gutschalk et al., 1999). Middle latency responses also localize in human intracortical measurements to Heschl's gyrus (Godey et al., 2001) and when modeled over the interval 30–45 ms show a tonotopic ordering similar to that of ASSR sources (Poghosyan and Ioannides, 2008) with which they may overlap. Linear summation of the deconvolved middle latency-like ASSR waveform (which has a wave period of ~25 ms) gives a reasonable approximation of ASSRs recorded at different AM rates including its amplitude maximum at ~40 Hz (Bosnyak and Roberts, 2001; Gutschalk et al., 1999), although the specific neurons contributing to ASSR generation likely differ as a function of AM rate (Lu et al., 2001). The 40-Hz ASSR is of interest for studies of auditory plasticity, because it can give a picture of neural dynamics expressed in the region of A1 during human auditory learning.

We report two experiments that assessed the effects of attention and plasticity on ASSR *amplitude* (reflecting the number of synapses depolarizing synchronously in A1) and ASSR *phase* (the time delay between the 40-Hz stimulus and response waveforms, reflecting temporal population activity in A1). We used a stimulus consisting of a single carrier frequency to minimize competitive interactions in A1 (Kilgard et al., 2001) and delivered acoustic targets randomly in an extended time window, in order to increase the likelihood that effects of attention and plasticity would be detected. Under these conditions we found that repeated exposure to auditory stimulation shortened the time delay between the 40-Hz stimulus and response waveforms, yielding an ASSR phase advance. In Experiment 1 the phase advance appeared at the outset of the second of two sessions separated by 24–72 h, was equally large in groups that were explicitly trained or given only passive exposure, and was not accompanied by changes in ASSR amplitude over this time interval. When in Experiment 2 training was extended to 10 sessions both response attributes were now modified by auditory experience, but the training effect on ASSR amplitude lagged that on phase and did not correlate with auditory perception while the phase advance did. In both experiments attention to the task increased ASSR amplitude but had no effect on ASSR phase. Our findings (1) dissociate the effects of task attention on ASSR amplitude and ASSR phase and (2) reveal a form of neural plasticity expressed in A1 that correlates with auditory perception and modifies ASSR phase.

2. Experiment 1

2.1. Materials and methods

2.1.1. Participants

Sixty-three students at McMaster University aged 17–44 years (mean 20.6 years, 6 left-handed, 18 male) received course credit for participating in a single session. Twenty-one participants (8 male) agreed to return for a second session within 3 days of the first session for a payment of $20. All participants signed a consent form approved by the Research Ethics Board of McMaster University. Participants sat in a chair placed 1.4 m in front of a computer monitor in a sound attenuated (ambient noise level 16 dBA SPL), electrically shielded booth. Normal hearing status at 2 kHz was confirmed by threshold measurements taken for each participant.

2.1.2. Design and procedure

The design of Experiment 1 is shown in Fig. 1a. Participants were assigned to one of three groups, a training group (Group E, $n = 31$) and two control groups (Group C1, $n = 17$ and Group C2, $n = 15$). Assignment was random with the restriction that Groups C1 and C2 combined should contain approximately as many participants as Group E. In each session participants received three stages of the experiment in the order Passive 1 (P^1), Task (T^R), and Passive 2 (P^2). Stages were 15–20 min in duration and separated by a brief pause. Ten participants in Group E and 11 participants in Group C1 returned for a second session.

The P^1 and P^2 stages were identical for all groups. During these stages participants viewed a subtitled movie (*The Matrix*) while auditory stimuli were presented in the background. The auditory stimuli (see later) were identical in all groups and stages of the experiment. The groups differed in the intervening T^R stage. For Group E the video was switched off during the T^R stage while participants were informed about and then performed the auditory task described below. Groups C1 and C2 had no knowledge of the auditory task. Group C1 continued to view the movie during the T^R stage with the auditory stimuli playing in the background (this procedure was identical to the passive stages). For Group C2 the video was switched off in T^R. Group C2 provided a check on whether AEP changes found during the T^R stage in Group E were a consequence of the auditory task they performed and not the

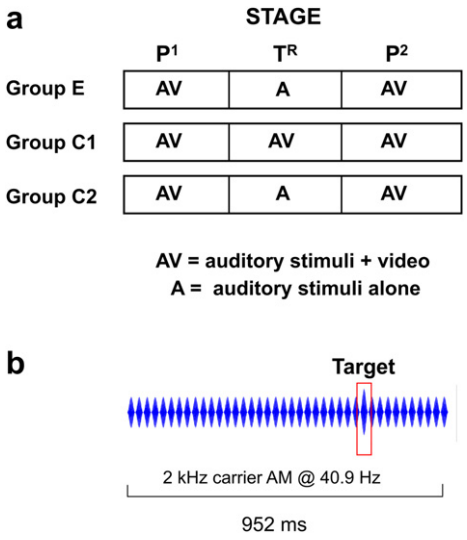

Fig. 1. (a) Design of Experiment 1 (see text for details). (b) Auditory stimulus for Experiments 1 and 2. A 2-kHz carrier frequency was amplitude modulated at 40.9 Hz (stimulus duration 952 ms). The participant's task was to detect a single AM pulse of enhanced amplitude (target) delivered at a random time point in the second half of the stimulus. Target probability was 0.5 in Experiment 1 and 0.67 in Experiment 2.

absence of the video. Because the task administered in the T^R stage was a training task, it necessarily required not only attention to the training stimuli, but also behavioural responses and the provision of knowledge of results. Companion experiments by Gander et al. (2010) discussed later confirmed that attention to the auditory signals is the element responsible for the effects of task on ASSR amplitude that were found in the T^R stage.

At the outset of the experiment all participants were told that their brain activity would be measured while they viewed a subtitled movie. Sounds would be presented in the background, but these were to be ignored in favor of watching the movie (the movie was chosen to be attention-consuming). These were the only instructions given to Group C1. Instructions for the auditory task were given to participants in Group E only after stage P^1. After P^1 participants in Group C2 were told that the film would be switched off and that the auditory stimuli should be ignored. The video resumed in P^2 for all participants.

2.1.3. Auditory stimuli and task

The auditory stimuli were 2-kHz pure tones (duration 952 ms) presented at 60 dB SPL, AM with a 40.96-Hz sinusoid (called 40 Hz herein, 100% modulation depth, onset and offset following the modulation wave). Stimuli were presented in S1/S2 pairs separated by 500 ms, S1 offset to S2 onset. Herein such pairs are called a "trial" for Experiment 1. There were 240 trials in each of stages P^1 and P^2 and 300 in stage T^R. The intertrial interval (ITI, offset of S2 to the onset of S1) was fixed at 1900 ms in the passive stages. In the T^R stage the ITI varied randomly between 1900 ms and 2500 ms in Groups C1 and C2, in order to achieve stimulus timing similar to Group E where the ITI depended on behavioural responses. Stimuli were generated by a digital signal processor (Tucker Davis RP2.1) and presented binaurally via ear inserts (Etymotic Research ER-2).

On each trial, one of the two stimuli (S1 or S2, $P = 0.5$) contained a single 40-Hz AM pulse of increased amplitude (designated a "target" pulse herein; see Fig. 1b). Target pulses occurred randomly within the interval 488–830 ms after stimulus onset (pulses 20–34). Pilot measurements taken on 10 additional participants indicated that an amplitude increase of 35% corresponded initially to the detection threshold (TH) for most cases. Targets of TH, TH ± 5%, TH ± 20%, and TH + 50% (six levels in all) were programmed to occur in equal numbers for all participants in each stage of the experiment. An exception to this procedure was adopted for Group E during the T^R stage only. Following auditory task instructions, a staircase procedure was used to measure the target detection threshold for each participant in Group E. The threshold determined by the staircase procedure (mean TH = 28.2%, slightly lower than TH = 35% in stages P^1 and P^2) was used to generate an individual stimulus set (again TH, TH ± 5%, TH ± 20%, and TH + 50%) suitable for learning in the T^R stage. Because only one of 78 AM pulses on each trial was a target, the impact of the threshold difference (a small reduction in target amplitude augmentation) on stimulus spectral power was negligible in the T^R stage.

During the T^R stage participants in Group E indicated by means of a button press after each trial which of the two stimuli (S1 or S2) contained the target (2IFC procedure). Five blocks of 60 trials each were administered with a brief pause between blocks. Coincident with the onset of S1, the word 'Listen' appeared in a text box on the computer monitor and continued until S2 offset when it was replaced by 'Respond'. Participants registered their response on a button box (left thumb press for S1, right thumb press for S2). If the response was correct, the text box turned green for 400 ms and the next trial commenced 1400 ms later giving an ITI of about 1900 ms depending on behavioural response latency. If the response was incorrect the box turned red for 1000 ms (the additional time delay of 600 ms was designed to punish incorrect responding).

2.1.4. Electrophysiological recording

The electroencephalogram (EEG) was sampled at 2048 Hz (DC to 417 Hz) using a 128-channel Biosemi ActiveTwo amplifier (Cortech Solutions, Wilmington, NC). The electrode array was digitized for each participant (Polhemus Fastrak) prior to recording. EEG data were stored as continuous data files referenced to the vertex electrode.

2.1.5. Signal processing of EEG data

Eye blink artifacts were removed from the raw continuous data files by the spatial filtering option of BESA (version 5.0, MEGIS Software GmbH, Gräfelfing, Germany). EEG responses to S1 stimuli (128 channels) were then epoched including 200 ms pre- and post-stimulus baselines. S1 stimuli were chosen for analysis because they were preceded by an ISI of at least 1900 ms which favored robust transient responses.

2.1.5.1. Transient responses. EEG responses for ~75% of trials (rejecting trials with surviving artifacts > 150 μV) were used for the analysis of transient responses. The data were averaged and interpolated to the 81-channel 'reference free' average reference montage of BESA using each participant's digitized electrode array. Subsequent filtering (0.2–20 Hz, zero phase) extracted P1, N1, P2, and N2 transient responses and the auditory sustained response (SR). Responses were measured at electrode Fz where they reached their amplitude maxima. Peak amplitude and the corresponding latency were recorded for the latency windows 30–85 ms (P1), 85–140 ms (N1), 140–230 ms (P2), and 250–350 ms (N2). The amplitude of the SR was measured as the mean over the interval 400–900 ms after S1 onset.

2.1.5.2. 40 Hz steady-state response. EEG responses for ~90% of trials (rejecting trials with amplitude changes > 100 μV) were averaged for analysis of the ASSR, and filtered 40–42 Hz (zero phase) after conversion to average reference. The scalp topography of the ASSR and a digitized electrode array are shown in Fig. 2a for a representative participant. The 128-channel data for each participant for the interval 244–952 ms were collapsed into a two-

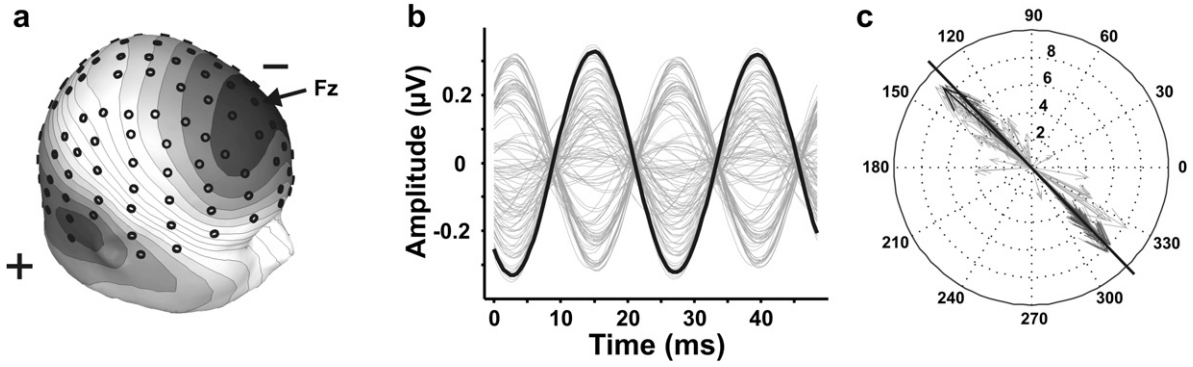

Fig. 2. Analysis of unmodeled ASSR data from a representative participant. (a) Digitized montage shows the location of 128 electrodes and the voltage map of the ASSR. The ASSR reached its amplitude maximum at electrodes near Fz. (b) The 128-channel data are collapsed showing two modulation cycles of the ASSR. The Fz electrode is highlighted in black. These data were used for source analysis. (c) Compass plot of the 40-Hz component of the FFT of the two-cycle waveform, showing all 128 electrodes. The length of each vector gives ASSR amplitude and the angle gives ASSR phase at 40 Hz. The arrows colored dark grey were those determined by an algorithm to contribute 50% of the 40 Hz total power with the smallest angle and were used to compute ASSR phase (see Section 2.1.5.2). The single black electrode is Fz.

pulse wide waveform (Fig. 2b), and the amplitude and phase at 40 Hz were determined for each electrode by FFT (Fig. 2c). ASSR amplitude was calculated as the total field power at 40 Hz summed over 128 electrodes. For calculation of ASSR phase a search algorithm, moving in steps of 0.5°, found the minimum angle width, encompassing electrodes on both sides of the dipolar field pattern, comprising 50% of the total 40-Hz power across the array. The value (in degrees) in the middle of that width was taken as the phase of the ASSR (Fig. 2c). Phase determined by this method was very close to lines determined by spatial principal component analysis but was not influenced by noisy electrodes and spurious data that do not represent the ASSR. This method of analysis had the advantage of using all of the unmodeled data available from each participant. It should be noted, however, that the results reported below were obtained as well when ASSR amplitude and phase were analyzed at electrode Fz where the response typically reached its amplitude maximum (Fig. 2a and b). The findings were also corroborated when the cortical sources of the ASSR were modeled by inverse methods, as described next.

2.1.5.3. Source analysis. Electrical fields generated by current sources in the left and right auditory cortices summate at the vertex in EEG recordings. It is therefore necessary to use inverse methods (source analysis) to localize and model current sources in each hemisphere, in order to evaluate hemisphere effects on AEPs. Our source analyses also assessed whether a putative weak second ASSR source in Heschl's gyrus described by Gutschalk et al. (1999) in ~50% of hemispheres may have contributed to the ASSR when task attention was required. Because the second weaker source localized ~10 mm lateral to and responded ~5 ms after a stronger primary ASSR source that was present in all hemispheres, it was expected to generate a lateral shift in 3D source location and a lag in ASSR phase between the P^1 and T^R stages if activated by attention.

Source analyses were performed by fitting two symmetrical regional sources (one for each hemisphere) to the ASSR, N1, and P2 field patterns using BESA. Source fits were determined using the 128-channel data and digitized electrode locations for each participant for the P^1 stage, and for stages T^R and P^2 on days 1 and 2 for participants in Group E who returned for two sessions. N1 and P2 regional sources were fit to the peak of their respective field patterns in the time windows stated above. Sources accounted for an average of 82% and 73% of the variance in the field patterns (goodness of fit) for N1 and P2, respectively. Regional sources were determined for the ASSR using the collapsed two-pulse wide waveform for each participant (Fig. 2b). Goodness of fit averaged 82% for the ASSR sources. The medial–lateral (x), anterior–posterior (y), and inferior–superior (z) coordinates of the sources were recorded for each participant and AEP for stage P^1 on day 1, and for participants in Group E for stages P^1 and T^R on both days.

The orientation of ASSR sources in both hemispheres in Group E was also assessed. Regional sources determined as described above for each participant (each regional source consisting of three orthogonal dipoles) were first re-oriented so that one dipole accounted for the maximum field variance. This dipole provided a common reference point for each participant (for 25/31 participants in stage P^1 for both hemispheres, this dipole was oriented frontocentrally). The Cartesian coordinates of this dipole were recorded in each hemisphere for the P^1 stage on day 1, and in Group E in stages P^1 and T^R and P^2 on both days. The source waveform for this dipole was also extracted for each participant, stage, and hemisphere on days 1 and 2, for the entire 1-s epoch of the S1 stimulus in stages P^1, T^R, and P^2. A Hilbert transform of the source waveform obtained the instantaneous ASSR amplitude (dipole moment) and phase over the 1-s interval, to depict changes occurring in ASSR amplitude and phase over the duration of the S1 stimulus in each hemisphere.

2.1.6. Statistical evaluation

Repeated measures ANOVAS were performed using the General Linear Model of Statistica (version 6.0). Repeated measures having more than two levels were Greenhouse–Geisser corrected. Unless stated otherwise, significance level was set at $\alpha = 0.05$ (two-tailed). Least Significant Difference (LSD) tests were used to describe significant main effects and interactions.

2.1.6.1. Behavioural data. Behavioural performance was evaluated during the T^R stage for each participant in Group E by calculating the mean probability of a hit [P(Hit)] across the seven target amplitudes and contrasting the group results against the null value of 0.5 by a sign test. A psychophysical function was also constructed for each participant by plotting P(Hit) as a function of target amplitude and fitting a logistic [$f(x) = 0.5/(1 + \exp(-\text{slope} \times (\text{amp increase} - \text{threshold}))) + 0.5$]. The thresholds (the amplitude increase corresponding to 75% correct) and slopes of the psychophysical functions were used to assess behavioural improvement over blocks in the T^R stage and (for returning participants) between sessions by ANOVA.

2.1.6.2. EEG data. ASSR amplitude (total 40 Hz power over the array of Fig. 2c) was normalized separately for each group by dividing each participant's mean power for each stage and day by their respective

group mean for P^1 on day 1. Performance on this initial passive stage (where all participants were treated identically) thus became the reference point for evaluating effects of the training task introduced in the T^R stage, and the effects of training between groups and days. (A preliminary report of the amplitude data is found in Gander et al. (2007).) The same procedure was applied to ASSR phase. In infrequent cases where the absolute phase change between conditions was greater than π, phases were unwrapped by adding or subtracting 2π to minimize the phase differences. After unwrapping, phases for all participants fell within an arc of 159° centered at 150°, and linear statistics were used to evaluate the significance of the phase changes. Effects attributable to introduction of the task in the T^R stage (called "task attention" herein) on day 1 were assessed by an ANOVA including the variables Group (E, C1, C2) and Stage (P^1, T^R, P^2). For returning participants the effect of days (called "training" herein) was evaluated in a separate ANOVA that employed the variables Group (E, C1), day (1, 2), and stage (P^1, T^R, P^2).

Transient responses (N1, P2, and N2 amplitude and the SR) were subjected to ANOVAs paralleling those of the ASSR. To simplify the statistical presentation of these data, we report the least significant *P*-value obtained for these responses taken from ANOVAs comparing the three stages on day 1. For returning participants N1 amplitude and P2 amplitude were also contrasted between days by an ANOVA employing the variables Group (E, C1), day (1, 2), and stage (P^1, T^R, P^2).

Differences in the 3D location of cortical sources determined for the ASSR, N1, and P2 responses were assessed in P^1 on day 1 where the sample size was large ($n = 31$ participants). ANOVAs were conducted separately for each coordinate employing AEP (N1, P2, and ASSR) as the variate. To reduce between-subject variability related to cortical anatomy, the 3D locations for P2 and ASSR sources were referenced to each participant's N1 location. Effects on 3D location attributable to task attention were evaluated in Group E by contrasting 3D locations between the P^1 and T^R blocks of day 1. Effects of training on 3D location and on ASSR amplitude measured as dipole moment were assessed by ANOVAs conducted for each coordinate and AEP including the variables day (1, 2) and Group (E and C1). The orientation of ASSR sources was similarly assessed.

T-tests were used to contrast ASSR source waveforms (amplitude and phase) between the T^R and P^1 stages at successive time points after stimulus onset on day 1, for each hemisphere separately (see Fig. 4b). The same procedure was applied contrasting ASSR amplitude and phase between days 1 and 2 (see Fig. 5b, electrode Fz). Significance level was lowered to $\alpha = 0.01$ for these analyses, but because the time points were not independent, correction for multiple tests was not applied.

2.2. Results

2.2.1. Psychophysical measures

Participants in Group E were informed about and performed the 2IFC task in the T^R stage. Logistic functions fit to the behavioural data of each participant are shown in Fig. 3a. Performance was well above the chance level of 50% (overall mean/SD 76.6 ± 0.047% trials correct; $P < 0.0001$, sign test), indicating that participants attended to and processed the 2-kHz sounds during the T^R stage. The performance of participants who completed two sessions is shown in the inset of Fig. 3a. The threshold of detection decreased from an intensity augmentation of 26.0% on day 1 to24.9% on day 2, while the mean slope of their psychophysical functions increased from 0.026 to 0.040 over days. These changes were in the direction of improvement but did not reach significance given the brief training that participants received.

2.2.2. Steady-state response

The ASSR recorded at the Fz electrode (S1 stimulus) developed over the first 250 ms of the stimulus and stabilized at higher levels during the T^R stage compared to the P^1 stage (Fig. 4a, left panel, top trace), with no effect of stage on ASSR phase (Fig. 4a, left panel, bottom trace). When analyzed as total 40-Hz power in all electrodes (Fig. 4a, right panel), ASSR amplitude increased by 43.7% from P^1 to T^R in Group E (26/31 participants, $P = 0.0008$, sign test) compared to all other conditions (group × stage interaction $P = 0.0031$). ASSR amplitude did not change across stages within Groups C1 and C2, which also did not differ from one another. The latter result indicated that augmentation of ASSR amplitude in the T^R stage in Group E was caused by introduction of the training task and not by the absence of the video. ASSR amplitude decreased to previous levels after the T^R stage in Group E, indicating that its enhancement in T^R was an effect of the task requirements of this stage and did not reflect a neuroplastic change.

Source waveforms depicting ASSR dipole moment and phase in each hemisphere on day 1 are shown for Group E in Fig. 4b (middle and right columns). ASSR amplitude increased during task attention (stages T^R versus P^1) in the right ($P < 0.0001$) and left ($P = 0.014$) hemispheres, but more so in the right hemisphere (group × hemisphere interaction $P = 0.028$). These increases were most prominent in the second half of the stimulus where behaviourally significant task events were delivered. ASSR phase was not affected by task attention (stage) in either hemisphere (main effect of stage $P = 0.697$; interaction with stage $P = 0.6646$). Nor were any effects of task attention found on the 3D location or orientation of ASSR sources determined separately for each participant. The location of ASSR sources and their

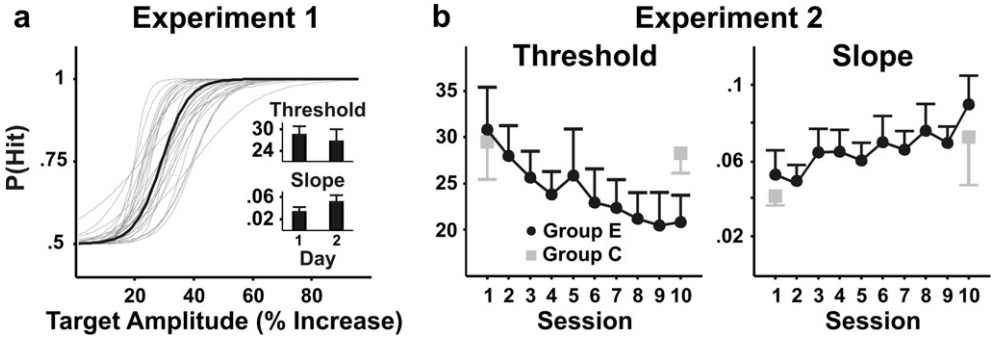

Fig. 3. Behavioural performance. (a) Experiment 1: Psychophysical functions are shown for each of 31 participants (light grey) in Group E on day 1. The mean function is in black. The inset shows the mean threshold (top) and slope (bottom) determined from these functions on days 1 and 2, for participants in Group E who participated in two sessions. (b) Experiment 2: Threshold (left) and slope (right) determined for Group E (dark circles) and Group C (light squares) for each of 10 training sessions. The bars are 1 standard error.

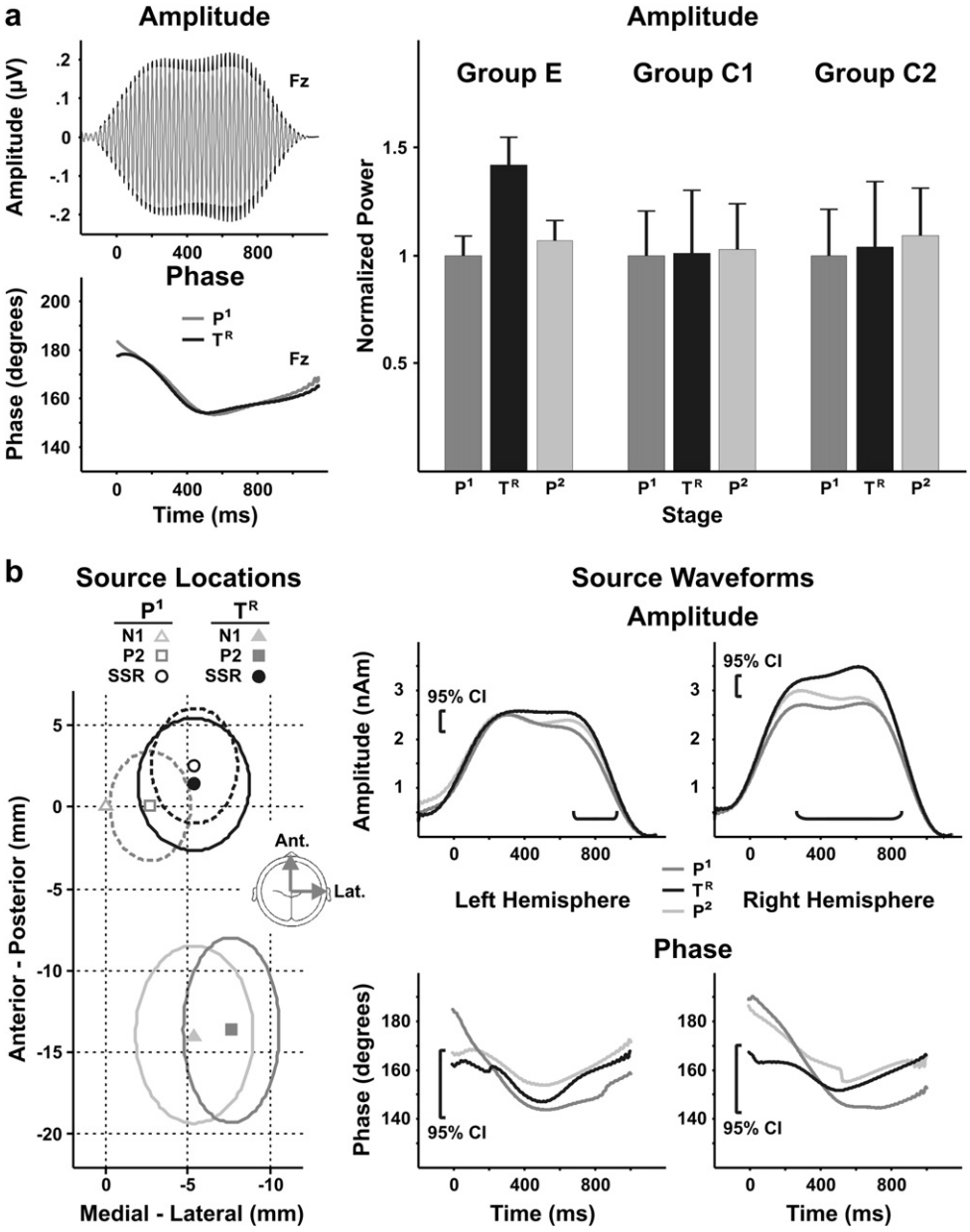

Fig. 4. ASSR amplitude increased during task attention with no effect on ASSR phase. (a) Unmodeled data, Fz electrode: Grand averaged ASSR amplitude is shown in the top left panel and the corresponding phase beneath. ASSR amplitude is larger in the T^R stage (black trace) compared to the P^1 stage (grey trace) with no effect on ASSR phase. The right panel shows total 40 Hz power calculated from 128 electrodes. ASSR amplitude is increased in stage T^R in Group E. The bars are 1 S.E. (b) Source analysis: *Left column*: Source locations determined for the P^1 and T^R stages on day 1 in Group E are shown in the axial plane for ASSR and P2 sources, referenced to each participant's N1 source determined for the P^1 stage (coordinates are averaged over 31 participants). Because N1 sources situate laterally in the superior temporal gyrus, negative values on the abscissa denote shifts in the medial direction. Negative values on the anterior–posterior axis denote posterior shifts. The circles show the 95% confidence limits. *Middle and right columns*: Source waveforms are shown for each hemisphere and stage (ASSR amplitude on top, ASSR phase on bottom). CI denotes 95% confidence limits determined for the T^R stage. The horizontal brackets show time points differing between the T^R and P^1 at $P < 0.01$.

confidence volumes in the axial plane are shown in Fig. 4b (left column) for the P^1 and T^R stages, referenced to N1 sources in P^1. The confidence volumes for the ASSR sources almost completely overlapped between stages P^1 and T^R.

A subset of participants from Groups E and C1 returned for a second session which was scheduled within 24–72 h of their first session. The ASSR results for this cohort are shown in Fig. 5a for days 1 and 2. On day 2 ASSR amplitude (Fig. 5a, upper row) increased in the T^R stage only in Group E (main effect of stage $P = 0.0009$; stage × group interaction $P = 0.0026$) and returned to baseline subsequently, replicating the effect of task attention on day 1 with no effect of days on ASSR amplitude. Attention to the task had no effect on ASSR phase on either day in Group E (Fig. 5a, lower row, main effect of stage $P = 0.513$). However, a shift in ASSR phase was detected on day 2 in all stages (P^1, T^R, P^2) in Group E and in Group C1 (16/21 participants overall, days main effect $P = 0.0030$), with no main effects or interactions involving stage or group. The phase shift averaged 6.6 ± 1.063° and reflected an advance of the ASSR waveform toward the stimulus waveform on day 2. The phase shift occurred at the outset of day 2 with no prior evidence of its appearance on day 1, suggesting that a consolidating process may have been at work between the two training sessions. The phase advance occurred regardless of whether the 2-kHz sounds were presented as background signals without task

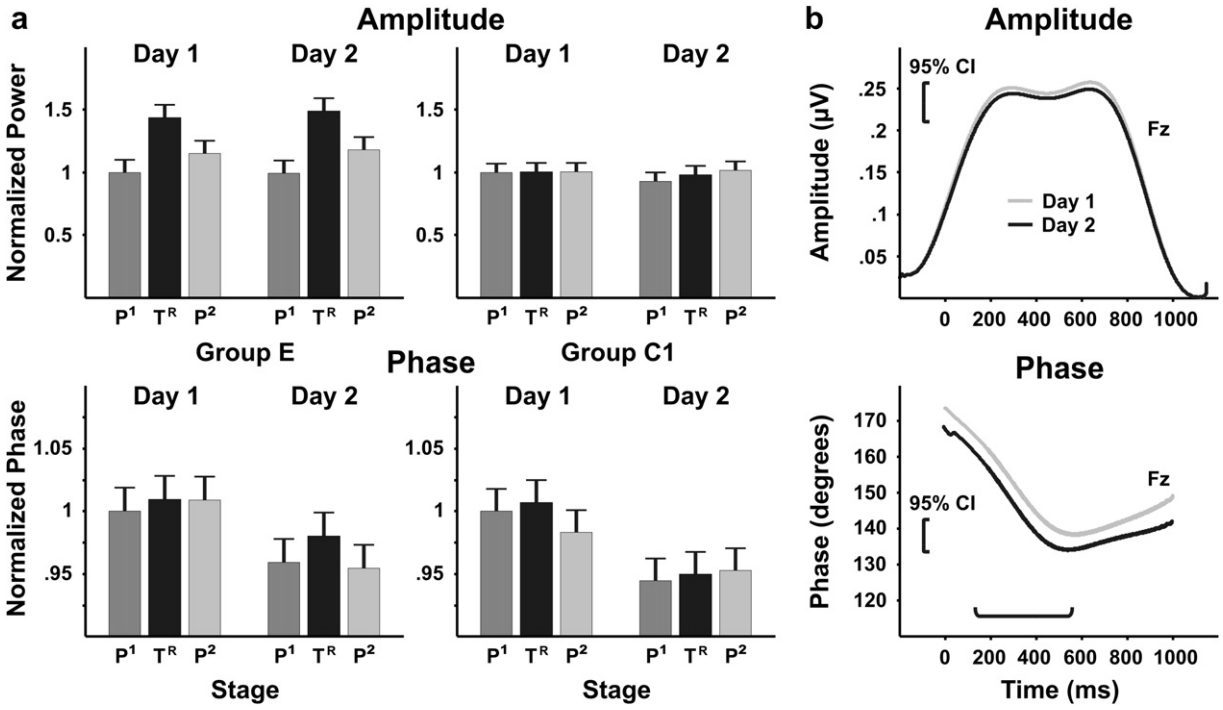

Fig. 5. Task attention modulates ASSR amplitude and auditory experience ASSR phase. (a) ASSR amplitude (top row, total 40 Hz power) increased in the T^R stage in Group E (left panel) on days 1 and 2, with no effect of days. ASSR amplitude did not change in Group C1 (right panels). ASSR phase (bottom row) advances between days 1 and 2 for both groups, with no effect of task attention. The bars are the mean standard error calculated within participants over stages and days, separately by group. (b) ASSR amplitude (top) and phase (bottom) during the stimulus are contrasted between days 1 and 2 collapsed over stages (Groups E and C combined, electrode Fz). CI denotes 95% confidence limits for day 1. The horizontal bracket shows time points differing between days at $P < 0.01$ (significant for phase only).

knowledge (Group C1, $P = 0.0165$) or with task knowledge and a performance requirement (Group E, $P = 0.0418$). Hilbert transform of the unmodeled data (Fz electrode) showed the phase advance to be expressed throughout the stimulus on day 2 (Fig. 5b, lower panel), with no effect of day on ASSR amplitude (Fig. 5b, upper panel).

2.2.3. Transient responses

Effects of attention on transient AEPs are shown in Fig. 6. On day 1 the amplitude of N1, P2, and N2 AEPs and the auditory sustained response (SR) increased from the P^1 stage to the T^R stage in Group E (all $Ps < 0.0023$) and returned to initial levels in the P^2 stage. In contrast, these responses tended to decrease over stages in the two control groups, this effect reaching significance for N1 ($P = 0.0001$) in agreement with previous findings in the literature for adaptation of the N1 (Näätänen and Picton, 1987). In addition, P2 amplitude (but no other response) increased between days 1 and 2 in Groups E and C1 (main effect of days $P = 0.0005$, data not shown) with no prior evidence for an increase within day 1 and no effect of stage or group. Hence effects of acoustic experience were detected in both A2 (P2 amplitude) and A1 (ASSR phase) at the outset of the second session following an interval of 24–72 h, regardless of the conditions of task attention. The expression of learning was different in the two regions, with P2 amplitude reflecting more neurons depolarizing synchronously in A2 and ASSR phase the temporal population response in A1.

Source localizations were determined for the transient responses, for comparison with the cortical sources of the ASSR. Localizations were performed for day 1 where the sample size was largest. Cortical sources for P2 localized medial to those of N1 and lateral to those for the ASSR (Fig. 4b, left column), in agreement with earlier findings (Bosnyak et al., 2004; Pantev et al., 1996a).

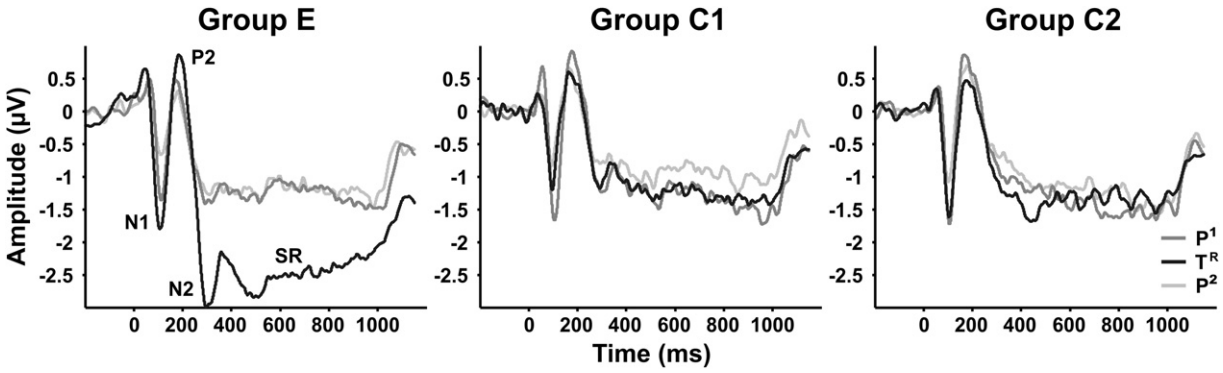

Fig. 6. Modulation of transient responses by attention on day 1. N1, P2, N2, and sustained responses (SRs) are identified in the left panel. Auditory attention was required in the T^R stage in Group E.

These localizations are consistent with generators in nonprimary cortex for N1 and P2 (Pantev et al., 1996a; Picton et al., 1999) and more medially in the region of A1 for the ASSR (Pantev et al., 1993), although previous reports of P2 sources anterior to N1 sources (EEG data: Bosnyak et al., 2004; MEG data: Ross and Tremblay, 2009) were not observed here. In addition, N1 and P2 sources shifted posteriorly during attention, with non-overlapping confidence volumes between the P^1 and T^R stages. As noted above, the 3D location of ASSR sources did not change with attention.

3. Experiment 2

The findings of Experiment 1 indicated that acoustic experience modified ASSR phase with no effect of task attention on this variable. The phase advance was statistically robust but small, equivalent to 0.44 ms or 1.8% of the modulation cycle. Experiment 2 examined changes in ASSR phase and amplitude when training was extended to 10 sessions. The questions were (1) whether ASSR phase would continue to advance with training and (2) whether more extensive training with a single carrier frequency would yield evidence suggesting a tonotopic map expansion for the trained frequency expressed in ASSR amplitude. Extended training also provided an opportunity to examine the within-subject relationship of changes in ASSR phase and amplitude to changes in behavioural performance induced by training over sessions.

3.1. Methods and materials

Only differences in procedure from Experiment 1 are described below. Other details were identical between the experiments.

3.1.1. Participants

Eighteen participants aged 18–28 years (mean 21.9 years, 8 male) were assigned randomly to a trained group (Group E, $n = 9$) or a control condition (Group C, $n = 9$). No participant had participated previously in Experiment 1.

3.1.2. Design and procedure

The 2IFC procedure of Experiment 1 was replaced by a continuous performance task in which the auditory stimuli were presented successively, separated by a variable ITI of approximately 1.9 s (offset to onset, including behavioural response latency). Approximately 2/3 of the stimuli (determined randomly) contained a single amplitude-enhanced 40-Hz pulse occurring within an interval 488–830 ms after stimulus onset (target, auditory stimuli identical to those of Experiment 1). On active blocks (see below) participants pressed one of two buttons after each stimulus, indicating whether a target was or was not detected. This was followed by feedback as in Experiment 1. Compared to the 2IFC procedure of Experiment 1, the continuous performance task required a behavioural response for every stimulus that was presented. It also increased the number of stimuli available for analysis of behavioural and EEG data.

Participants in Group E were trained for 10 sessions. The first five sessions were delivered at weekly intervals and the last five at intervals of approximately 2–3 days, which accommodated the academic schedule of the participants. EEG recordings took place on sessions 1, 2, 3, 4, and 10. Participants in Group C received two sessions (both EEG sessions) aligned in time to the first and last sessions of Group E. In each session all participants received 20 blocks, each about 2.5 min long and containing 54 stimuli. In EEG sessions, on alternate blocks participants were instructed by text on the computer monitor to perform the training task (active condition) or to ignore the sounds and wait until the next training block (passive condition). Each session began with an active block. Sessions without EEG contained the same total number of trials as sessions with EEG except that all blocks were now active blocks.

3.1.3. Statistical analyses

Training effects were evaluated in Group E by ANOVAs including the variables Session (1, 2, 3, 4, and 10) and Task Attention (active/passive). Training effects were also assessed by ANOVAs including the variables Group (E, C), Task Attention (active/passive), and Session (first, last). For the latter analyses ASSR phase, ASSR amplitude, and P2 amplitude were normalized by dividing each participant's data by the mean of the passive blocks for their respective group on day 1. This step (analogous to that performed for the ASSR in Experiment 1) referenced effects of training and task attention to the passive baseline in session 1, setting these effects into relief (Fig. 7b). A supplementary analysis described below contrasted within-session changes observed in ASSR phase, ASSR amplitude, and P2 amplitude with the corresponding changes observed between sessions. Unlike ASSR phase and amplitude which were positive integers, P2 amplitude could be and occasionally was negative for some participants in the passive blocks. P2 amplitude was therefore linearly transformed by adding the constant 2.8 to each participant's P2 amplitude prior to normalization, which removed negative numbers and eliminated division by zero. Source analyses were performed for the ASSR on sessions 1 and 10 using the same methods described for Experiment 1.

3.2. Results

3.2.1. Psychophysical measures

Participants in Group E ($n = 9$) were trained for 10 sessions with the same stimuli used in Experiment 1, but delivered now as a continuous performance task. Compared to Experiment 1 where training was brief, detection thresholds improved over the 10 training sessions, decreasing from a mean amplitude enhancement of 30.5% on day 1 to 20.5% on day 10 in Group E (Fig. 3b, left panel, sessions main effect $P < 0.0001$). The mean slope of psychophysical functions increased from 0.053 to 0.089 over the same days in this group (Fig. 3b, right panel, sessions main effect $P = 0.0002$). Participants in Group C ($n = 9$) were trained only for two sessions aligned in time to the first and last sessions of Group E. Changes in the direction of improvement were observed for both variables in Group C (Fig. 3b), but did not reach significance.

3.2.2. Steady-state response

Results for ASSR phase and amplitude in Group E are shown in Fig. 7a. As in Experiment 1, ASSR amplitude (Fig. 7a, *middle* row) was enhanced by task attention (active/passive main effect $P = 0.0001$). In addition, ASSR amplitude increased over the 10 training sessions (8/9 participants, main effect of days $P = 0.0218$), with almost all of the training effect coming after session 4 and appearing equally in the active and passive blocks. When the first and last sessions were compared between Groups E and C (Fig. 7b, middle row), an effect of session was found for Group E ($P = 0.028$) but not Group C ($P = 0.498$). Compared to the slowly moving change in ASSR amplitude, ASSR phase (Fig. 7a, *top* row) changed incrementally over sessions in Group E, advancing by 14.7° over the 10 sessions (9/9 participants, sessions main effect $P = 0.015$) compared to 6.6° in Experiment 1. The main effect of task attention (active/passive) and its interaction with session were not significant for ASSR phase, although the training effect was descriptively larger on active blocks. Surprisingly, Group C also showed a phase advance between their two sessions (8/9 participants) which were separated by about 6 weeks, revealing an effect of the first session. Contrast of the first and last sessions gave $P = 0.049$ in Group C compared to $P = 0.002$ for Group E (Fig. 7b, top row, averaged over attention). No differences

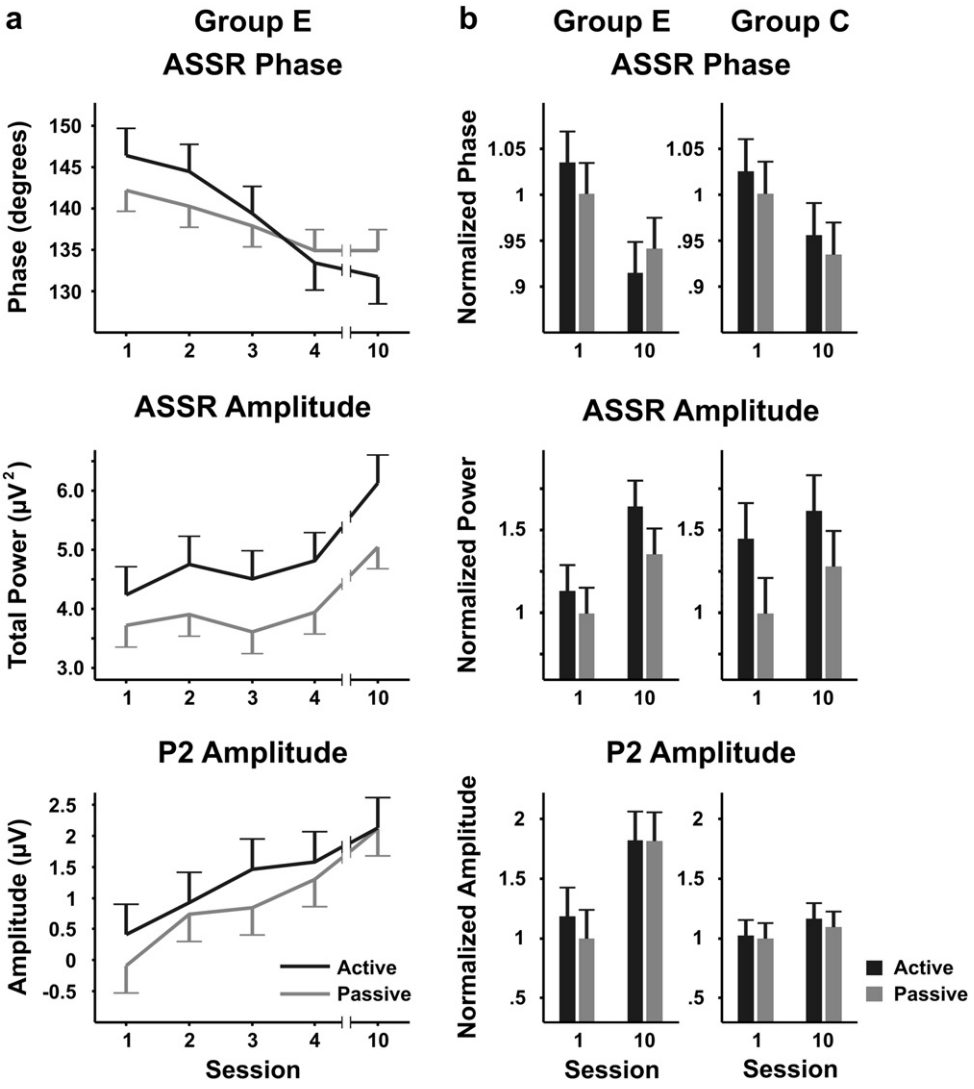

Fig. 7. Effects of extended training on ASSR phase and amplitude, and on the P2 transient response. (a) Response changes are shown over 10 sessions of training for ASSR phase (top), ASSR amplitude (middle), and the P2 transient response (bottom). In each panel, active and passive blocks are contrasted. Five training sessions without EEG intervened between sessions 4 and 10. The bars are the mean standard error calculated within participants over five sessions, separately for active/passive blocks and for Group. (b) Performance on the first and last sessions is contrasted between Groups E and C. The bars are the mean standard error calculated within participants over two sessions and active/passive blocks, separately for Group.

were found in the 3D coordinates of cortical sources determined for the ASSR between sessions 1 and 10 in Group E.

A subsequent analysis compared changes obtained within sessions to those obtained between sessions, in order to assess the possibility that a consolidating process may have contributed to the ASSR phase changes. For this purpose differences in ASSR phase observed between the first and last 216 trials of each session (within-session changes) were compared with those observed between the last 216 trials of one session and the first 216 trials of the next session (between-session changes), collapsing over active/passive to increase the number of trials available for study. ASSR phase advanced between the first/last 216 trials within sessions ($P < 0.019$), but the between-session contrast of the last/first 216 trials was not significant ($P = 0.506$). Thus, unlike Experiment 1 where almost all of the effect of auditory training on ASSR phase appeared between sessions (see Fig. 4 for ASSR phase), most of the training effect in Group E of Experiment 2 occurred within sessions, with the changes accumulating over subsequent sessions. Comparisons within and between sessions were not significant for ASSR amplitude in this analysis.

In order to assess whether training effects on the ASSR may have contributed to psychophysical performance in Group E, we calculated the within-subject correlation of ASSR phase and amplitude to threshold and slope over sessions and determined the mean correlation across participants. ASSR phase correlated positively with detection threshold for 9/9 participants (mean $r = 0.64$, $P = 0.0005$, shorter phase associated with lower threshold) and negatively with slope in 7/9 participants (mean $r = -0.56$, $P = 0.0029$, shorter phase associated with steeper slope), but correlations involving ASSR amplitude were not significant overall (mean $r = 0.22$ and -0.14 for slope and threshold, respectively, $P > 0.33$). The within-subject relationship of ASSR phase to threshold is shown in Fig. 8, where the results have been normalized between 0.0 and 1.0 for each participant to permit plotting all participants on the same graph (the correlation obtained for each participant is placed in parentheses next to their data for the last session of training). We also calculated between-subject correlations relating the magnitude of before/after changes in ASSR phase and amplitude with corresponding changes in the psychophysical measures. Participants showing the largest ASSR phase shifts after

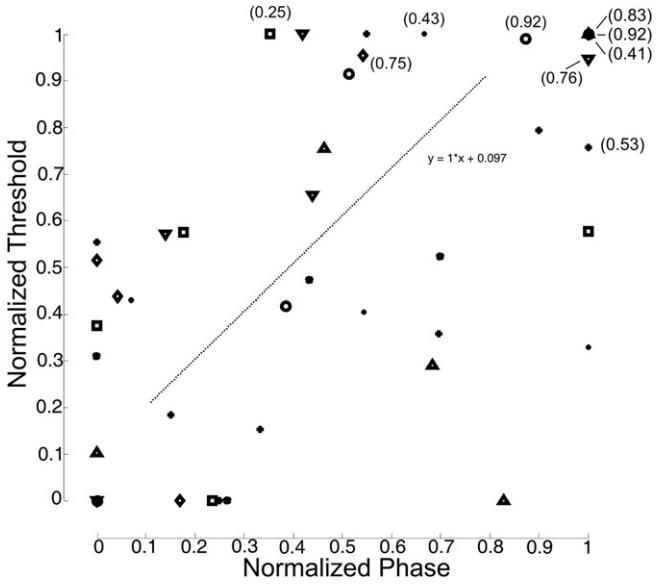

Fig. 8. Within-subject relation between ASSR phase and detection thresholds over the five training sessions in which the EEG was measured. Threshold and ASSR phase were normalized by assigning 1.0 to the shortest phase and lowest threshold and 0.0 to the longest phase and highest threshold, for each participant. All values therefore ranged between these limits. The numbers in parentheses are within-subject correlations calculated across sessions for each participant (the correlations are placed adjacent to the data for each participant's 10th training session). Each different symbol represents a different participant (five data points per participant). The correlation between ASSR phase and detection thresholds determined from this normalized data set was 0.62 ($P < 0.05$).

the 10 training sessions tended to show the largest threshold reductions ($r = 0.53$), but none of the between-subject correlations reached significance.

A final analysis of the ASSR collapsed the five sessions for each participant into one data set and then, for each participant, compared ASSR phase and amplitude between trials on which a target was present and detected (hits) with trials on which targets were present but missed (misses). This contrast was restricted to about 34% of the EEG data, because only active blocks could be included (50% of trials) and within these blocks only trials on which a target was present (67% of trials). A main effect of sessions was found for ASSR phase ($P = 0.012$) reflecting the training-induced ASSR phase advance over sessions, while the main effect of hit/miss approached significance ($P = 0.13$) reflecting shorter ASSR phase on trials where when targets were detected than on trials where they were missed. A main effect of sessions was also found when ASSR amplitude was analyzed ($P = 0.037$). ASSR amplitude tended to be larger when targets were detected, but only in the last two training sessions (interaction of sessions and trial type $P = 0.12$).

3.2.3. Transient responses

P1, N1, and P2 transient responses were analyzed for effects of training (sessions) and task attention (active/passive). No training effects were found for P1, although P1 amplitude increased ($P = 0.003$) and latency decreased ($P = 0.049$) with attention to the task. N1 latency decreased from 116.4 ms to 107.4 ms over training sessions ($P = 0.041$) but no other effects were found for N1. As expected, P2 amplitude increased over training in Group E (9/9 participants, shown in Fig. 7a, bottom row, $P = 0.0001$) with no change in Group C ($P = 0.256$, Fig. 7b). However, unlike the analysis of ASSR phase reported above, P2 amplitude increases in Group E occurred between the last and first 216 trials of successive sessions ($P = 0.0014$) and not within sessions where P2 amplitude did not change over trials ($P = 0.7$). P2 latency also decreased from 195.8 ms to 184.3 ms over sessions only in Group E (9/9 participants, $P = 0.008$, results not shown). No effect of task attention was found on P2.

Because P2 amplitude and latency were modified by training in Group E, and also N1 latency, we calculated the correlation of these responses to psychophysical performance over sessions for each participant, and then determined the group average, as was done for the ASSR. P2 amplitude correlated over sessions with threshold (mean $r = -0.52$, $P = 0.013$) and slope (mean $r = 0.45$, $P = 0.025$), as did P2 latency with each behavioural measure (mean $r = 0.42$ for threshold and -0.39 for slope, Ps < 0.024). These results confirm that, within subjects, larger P2 amplitude and shorter P2 latency were associated with improved behavioural performance. Changes in N1 latency correlated with changes in threshold (mean $r = 0.549$, $P = 0.005$) but no other correlations involving N1 were significant.

4. General discussion

We assessed the effects of auditory training on the 40-Hz ASSR that localizes tonotopically to cortical sources in the region of A1. In two experiments acoustic stimuli were presented either as background sounds (passive condition) or in the context of a task requiring discriminative responses (active condition). In both experiments ASSR amplitude (reflecting the number of neurons depolarizing synchronously) was larger in the active compared to the passive conditions, while ASSR phase (reflecting the timing of neural population activity in A1) was not affected by this manipulation. On the other hand, ASSR phase was modified by acoustic experience, advancing toward the stimulus waveform over sessions with little or no effect of active/passive presentation on the phase changes. In Experiment 1 the ASSR phase advance was observed at the outset of the second of two sessions separated by 24–72 h but was not accompanied by changes in ASSR amplitude over this time interval. When training was extended to 10 sessions in Experiment 2 using identical stimuli in a continuous performance task, both attributes of the ASSR now changed over sessions, with no significant effect of task attention (active/passive) on the magnitude of the changes induced by training. However, the effect of acoustic experience on ASSR amplitude lagged that on ASSR phase and did not correlate with auditory perception although the phase advance did.

In the following sections we discuss the effects of the active/passive task on ASSR amplitude first, and the effects of training on ASSR phase second.

4.1. Effects of active/passive task on ASSR amplitude

Because the task presented in the active blocks of both experiments was a training procedure, it required not only attention to the auditory stimuli, but also behavioural responses and feedback for the participant's discriminative choices (knowledge of results). Results reported by Gander et al. (2010) indicate that among these elements attention was the variable responsible for the increase in ASSR amplitude observed in active compared to passive conditions. Gander et al. (2010) presented participants with simultaneous 40-Hz auditory and 16-Hz AM visual stimuli of 1 s duration, two-thirds of which contained single AM pulses (auditory or visual, or both, determined randomly) of enhanced amplitude (targets). In alternating blocks participants attended to either the auditory or the visual stream and indicated with a button press after each trial whether the stimulus contained or did not contain a target. ASSR amplitude increased from a preceding bimodal passive baseline when auditory targets were attended ($P = 0.001$), and the amplitude of the 16-Hz visual steady-state response preferentially from this baseline when visual attention was required ($P = 0.017$), revealing modality-specific auditory and visual attention.

Importantly, ASSR amplitude did not change from baseline when participants attended to visual targets, indicating that a requirement for button pressing had no effect on ASSR amplitude unless the auditory signals were attended (the auditory stimuli were identical to those used in the present experiments). Knowledge of results also appears not to contribute to ASSR amplitude increases observed when participants respond behaviourally to auditory targets. Knowledge of results was provided in the present studies but omitted by Gander et al. (2010); however, the magnitude of ASSR amplitude increases observed during auditory attention in the two studies were similar and did not differ significantly. These results support the conclusion that the effect of active/passive presentation on ASSR amplitude seen in the present experiments was attributable to auditory attention and not to other features of the task presented during the active blocks.

ASSRs reflect changes in the polarization of extracellular spaces in the neocortical laminae that occur consequent on thalamic input to the auditory cortex. One mechanism known to modulate neural activity in A1 and A2 (and other sensory regions), and therefore a possible mechanism for ASSR amplitude increases induced by active tasks, is the BF attention system (Sarter et al., 2005). This system consists of a group of subcortical nuclei containing large cholinergic neurons that project to the sensory cortices in a broadly tuned corticotopic arrangement (Bigl et al., 1982) and make neocortical cells in these regions more sensitive to their afferent inputs (Metherate and Ashe, 1993). Paralleling these projections are GABAergic fibers that synapse on cortical inhibitory interneurons (Freund and Meskenaite, 1992) giving a synergistic effect. Activation of the BF system by a task requirement could increase cortical source activity underlying not only the ASSR but also cortical sources for transient AEPs that localize to the region of A2. In agreement with this hypothesis, the amplitude of N1, P2, N2, and SR responses, as well as ASSR amplitude, increased in the T^R stage of Experiment 1 (Fig. 5), and other research has shown that pharmacological blockade of muscarinic cholinergic receptors attenuates transient AEPs corresponding to the N1 in rats (Campbell et al., 1995) and cats (Dickerson and Buchwald, 1991). However, the site of action of cholinergic blockade is not known, and while the effects of anti-cholinergics on the ASSR have not been studied, auditory middle latency responses whose cortical sources overlap those of the ASSR are augmented by scopolamine (Jääskeläinen et al., 1999) which may alter the balance of excitation and inhibition in the neocortex (Ahveninen et al., 2002). It will require physiological and pharmacological studies in animal models to specify more clearly the mechanisms underlying effects of attention on ASSR amplitude.

Converging lines of evidence from intracerebral measurements (Bidet-Caulet et al., 2007; Brugge et al., 2009) and inverse modeling (Pantev et al., 1993, 1996b) in humans confirm that the principal generators of the 40-Hz ASSR lie in posterior-medial Heschl's gyrus (HG) where A1 is found. Local field potentials (LFPs) recorded from electrodes inserted into human posterior-medial HG reliably track click trains over the frequency range 25–200 Hz with a maximum tracking at rates near 50 Hz, whereas LFPs recorded from anterolateral HG (a putative belt region of auditory cortex) show only a weak or nonexistent frequency-following response over this range (Brugge et al., 2009). Gutschalk et al. (1999) used a multiple source model to deconvolve ASSR source waveforms from ASSRS recorded at AM rates from 32.2 Hz to 52.6 Hz. With this procedure they found evidence for a weak generator in ~50% of hemispheres, which localized ~10 mm lateral to and responded ~5 ms after a stronger ASSR source that was present more medially in the region of HG in all hemispheres. It was suggested that this second source may be sensitive to attention. If a second source in anterolateral HG was activated by attention in our study, an anterolateral shift in 3D source location and a phase lag in the ASSR would have been expected when the T^R task was introduced in Experiment 1. Neither effect was found in Group E ($n = 31$ participants), indicating that the underlying source configuration was stable between conditions. This was not true, however, for the cortical sources of N1 and P2, which localized to the region of A2 and shifted to more posterior regions with attention. As far as we are aware the latter effect has not previously been reported. Cortical sources for N1 and P2 may shift their centers of activation under attention when auditory association areas that integrate spectrotemporal and auditory spatial information with multisensory and top–down information are activated. In contrast, ASSRs arise from sources restricted to A1 that may serve mainly to code information about the elementary features of environmental sounds.

Although the principal effect of auditory attention in our studies was an increase in ASSR amplitude, other results indicate that ASSR amplitude is not always increased by attention. As discussed above, Experiments 1 and 2 of the current study and the dual-modality study of Gander et al. (2010) found robust amplitude enhancements by auditory attention ($P < 0.008$ or better) when a single carrier frequency was present in the baseline and attended stages. However, a second study by Gander et al. (2010) found no increase from baseline ($n = 39$ participants, $P > 0.75$) when *two* AM sounds were present during the baseline and attend stages, even though the two nonharmonic carriers were separated by more than four octaves and their cortical sources were tonotopically resolved by inverse modeling. This suggests that when two or more sounds are present, competitive interactions among auditory representations may normalize representational maps in A1, such that global activity is constrained. Consequently, the principal effect of auditory attention may be not to increase global neural activity in A1 (although that can happen), but to broaden the tuning bandwidth of excitatory and inhibitory neurons in multiple feature maps that have been described in A1 (Cheung et al., 2001; Schreiner and Winer, 2007) and within which neural representations for environmental sounds are formed.

4.2. Effects of auditory experience on ASSR phase

When carrier frequencies are AM at 40 Hz and presented continuously for several minutes one carrier frequency at a time, a relationship between ASSR phase and carrier frequency is observed that reflects transit times for the traveling wave on the basilar membrane measured from auditory nerve fibers (Ross et al., 2000; Ruggero and Rich, 1987; see Greenberg et al., 1998 for a review). However, while the ordering of phase with respect to carrier frequency is determined by basilar membrane mechanics, the slope of its relation to carrier frequency is not fixed but can rescale by as much as 2.8 depending on stimulus and task conditions (Bosnyak et al., 2007; Patel and Balaban, 2004). The present findings support the view that ASSR phase is a dynamic variable, expressing in our studies remodeling by auditory experience of the temporal properties of population activity in A1 or in subcortical nuclei projecting to this region when carrier frequency is held constant. Although we cannot identify the mechanisms underlying this neuroplastic effect or their precise site of action, constraints on these mechanisms can be proposed. In particular, it is unlikely that modulation of the traveling wave by olivocochlear feedback to outer hair cells is responsible. Modulation of traveling delays caused by such feedback would disrupt place coding by auditory neurons, which is a fundamental principle of coding in the auditory system. Enhancement of cortical excitability by the BF attention system or a similar attention mechanism also appears unable to explain the phase advance. Attention had no detectable effect on ASSR phase in our studies, even though ASSR amplitude (which is

sensitive to the number of neurons depolarizing synchronously in the auditory cortex) was strongly modulated by task attention.

There are, however, several other mechanisms that may have contributed to the experience-induced changes found in our experiments. Activity-dependent mechanisms that underlie non-associative long-term potentiation (LTP) are one possibility. Non-associative LTP consolidates over a retention interval in the range of hours and is disrupted if regulatory genes involved in protein synthesis are suppressed by molecular blockade or removed by genetic engineering (Bramham et al., 2010). In our studies significant between-session changes without within-session changes were observed for ASSR phase in Experiment 1 and for P2 amplitude in both experiments, corroborating for P2 earlier reports by Atienza et al. (2002), Ross and Tremblay (2009), and Sheehan et al. (2005). These findings could reflect a consolidating process (Galvan and Weinberger, 2002), although other explanations such as a release from within-session adaptation could be proposed. It should be noted that in Experiment 2 within-session advances predominated for ASSR phase dissociating it from P2, possibly because the continuous performance task of this study (which compared to the 2IFC procedure of Experiment 1 required a more rapid rate of behavioural responding but not a comparison of stimuli) accelerated remodeling of neural networks contributing to ASSR phase. Spike-timing plasticity, in which neurons compete for control of postsynaptic targets on the basis of their temporal relations (Markram et al., 1997), is another mechanism that may have contributed to remodeling of ASSR phase. Because spiking in auditory cortical neurons tracks AM rates up to about 60 Hz (Lu et al., 2001), this mechanism could have recruited cortical neurons with fast inputs into a distinctive temporal representation, yielding a phase advance the magnitude of which could have been attenuated in the population average (Song et al., 2000). This mechanism could have sculpted a neural representation for trained sound on the basis of phase locking within cortical or subcortical networks without requiring an increased tonotopic representation that would have been expected to affect ASSR amplitude. An alternative mechanism that may have contributed to remodeling of ASSR phase consists of processes that are known to modify the input–output functions of subcortical neurons to reflect the statistics of stimulus input (Garcia-Lazaro et al., 2007; Lundstrom et al., 2008). For example, neurons in the rat inferior colliculus have been found to adjust their transfer functions to reflect the dominant intensity in a distribution of applied intensities (Dean et al., 2005). If exposure to AM sounds by our training procedure progressively lowered the threshold of a population of neurons to reflect the dominant intensity in the AM train (60 dB SPL), a phase advance could have been observed when neurons depolarized earlier in the AM cycle. Although remodeling of neuron transfer functions is known to occur within seconds or minutes (Dean et al., 2005) compared to the ASSR phase advance which increased progressively over days, changes in transfer functions over days have not been studied in animal models. It should be noted that ABRs and FFRs that are generated by subcortical nuclei during early auditory processing also appear to be neuroplastic (Musacchia et al., 2008; Song et al., 2008). Whether modification of these early responses contributed to the phase advance expressed in the cortically generated ASSR is not known and remains a question for further research.

Regardless of its specific mechanism, the phase advance induced by auditory experience in our experiments appeared early in the stream of auditory processing. It was observed throughout the duration of the stimulus and was not modulated by the delivery of auditory targets in the second half of the stimulus period, although ASSR amplitude was modulated by this task feature. The phase advance tracked changes in detection thresholds and the slope of psychophysical functions over training sessions within subjects and appeared to be greater on trials on which targets were detected than on trials where targets were missed. Because the phase advance was expressed at ASSR onset it does not appear to reflect re-entrant feedback to the auditory core region from P2 or other later brain sources, but is rather an antedating brain event. On the other hand ASSR amplitude appeared to be more resistant to change in the present experiments and did not closely track ASSR phase shifts or perception although an enhancement was eventually detected when training was extended to 10 sessions. In a previous study ASSR amplitude did not change over 15 training sessions when discrimination among several carrier frequencies was required (Bosnyak et al., 2004), possibly because competitive interactions in A1 may have obstructed a tonotopic map expansion for the trained sounds under this condition (a phase shift and P2 amplitude enhancement were, however, observed). These observations taken in conjunction with the present literature suggest the tentative principle that remodeling of sensory representations may be more readily expressed in the temporal properties of AEPs with latencies below or near about ~100 ms, whereas amplitude enhancements are observed mainly for AEPs with longer latencies [in order of increasing latency Ta ~120 ms: Alain et al. (2007); N1c ~135 ms: Bosnyak et al. (2004), Shahin et al. (2003); P2~190 ms: Atienza et al. (2002), Bosnyak et al. (2004), Reinke et al. (2003), Sheehan et al. (2005), Ross and Tremblay (2009), Tremblay et al. (2001); N2: Fujioka et al. (2006); frontotemporal brain activity: Shahin et al. (2007, 2008), van Wassenhove and Nagarajan (2007)]. The latter AEPs appear to reflect brain communication involving auditory association areas where the affected neural populations are large and where reciprocal inhibitory interactions may be weaker.

In our studies neither the ASSR phase advance nor the P2 amplitude enhancement produced by auditory experience were gated by explicit auditory attention. This independence was most evident in Experiment 1 where changes in ASSR phase and P2 amplitude occurred equally in a group that received explicit training on day 1 and in a control group that viewed a silent video during auditory exposure without knowledge of auditory task structure. P2 amplitude enhancements reported by Sheehan et al. (2005) and by Ross and Tremblay (2009) also occurred in the absence of explicit auditory training, although in these studies participants were tested for auditory discrimination without knowledge of results between the sessions in which brain responses were measured (a practice that was omitted in the experiments reported here). These findings suggest that passive exposure to background sounds can be sufficient to remodel AEPs in adult humans. They also concur with animal studies suggesting that stimulus-driven mechanisms in the immature brain that tune auditory neurons to represent environmental sounds (de Villers-Sidani et al., 2008; Zhang et al., 2001) continue to operate in the adult organism (Pienkowski and Eggermont, 2009; Stanton and Harrison, 1996) even when the sounds have no behavioural relevance. The findings do not, however, rule out a role for attention in auditory remodeling. If auditory stimuli are sufficiently salient, bottom–up sensory input acting through extralemniscal pathways may be sufficient to bring the BF attention system under stimulus control (Weinberger, 2007) or to activate top–down mechanisms (Sarter et al., 2005) that may influence the course of changes induced by auditory experience (Seitz and Dinse, 2007).

5. Summary and conclusion

The two experiments reported in this paper used the 40-Hz auditory steady-state response (ASSR) localizing tonotopically to sources in primary auditory cortex (A1) to investigate neural

plasticity in early stages of auditory information processing. We found that exposure to 40-Hz AM sounds advanced the phase of the ASSR independently of task attention. In Experiment 1 the phase advance appeared abruptly between sessions separated by an interval of 24–72 h and was not accompanied by a change in ASSR amplitude over this interval. Extended training in Experiment 2 with the same stimuli led to further advances in ASSR phase and also to an increase in ASSR amplitude, but the training effect on phase preceded that on amplitude by several sessions and correlated more closely with auditory perception than did the amplitude change. A single session of sound exposure was sufficient to yield a phase advance in a control group tested about 6 weeks later, suggesting a persistent modification of temporal processing expressed in A1. In both experiments ASSR amplitude was increased by auditory attention, but attention had no effect on ASSR phase. These results suggest that ASSR amplitude and ASSR phase reflect fundamentally different aspects of auditory information processing. They also indicate that experience with AM sounds modifies early neural processing in the region of A1, or in subcortical nuclei projecting to this region, and that this effect is expressed preferentially in ASSR phase.

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References

Alain, C., Snyder, J.S., He, Y., Reinke, K.S., 2007. Changes in auditory cortex parallel rapid perceptual learning. Cereb. Cortex 17, 1074–1084.

Atienza, M., Cantero, J.L., Dominguez-Marin, E., 2002. The time course of neural changes underlying auditory perceptual learning. Learn. Mem. 9, 138–150.

Ahveninen, J., Jääskeläinen, I.P., Kaakkola, S., Tiitinen, H., Pekkonen, E., 2002. Aging and cholinergic modulation of the transient magnetic 40-Hz auditory response. Neuroimage 15, 153–158.

Bidet-Caulet, A., Fischer, C., Besle, J., Aguera, P.E., Giard, M.H., Bertrand, O., 2007. Effects of selective attention on the electrophysiological representation of concurrent sounds in the human auditory cortex. J. Neurosci. 27, 9252–9261.

Bigl, V., Woolf, N.J., Butcher, L.L., 1982. Cholinergic projections from the basal forebrain to frontal, parietal, temporal, occipital, and cingulate cortices: a combined fluorescent tracer and acetylcholinesterase analysis. Brain Res. Bull. 8, 727–749.

Blake, D.T., Strata, F., Churchland, A.K., Merzenich, M.M., 2002. Neural correlates of instrumental learning in primary auditory cortex. Proc. Natl. Acad. Sci. USA 99, 10114–10119.

Bosnyak, D.J., Roberts, L.E., 2001. An Analysis of Swept-Rate Auditory Stimulation Using Temporal Deconvolution Reveals no Departure From Linear Summation Hypothesis. Society for Neuroscience, San Diego.

Bosnyak, D.J., Eaton, R.A., Roberts, L.E., 2004. Distributed auditory cortical representations are modified when non-musicians are trained at pitch discrimination with 40 Hz amplitude modulated tones. Cereb. Cortex 14, 1088–1099.

Bosnyak, D.J., Stevens, S., Gander, P.E., Roberts, L.E., 2007. Phase dynamics in the 40 Hz auditory steady state response. In: Cheyne, D., Ross, B., Stroink, G., Weinberg, H. (Eds.), New Frontiers in Biomagnetism. International Congress Series. Elsevier, Amsterdam, pp. 29–32.

Bramham, C.R., Alme, M.N., Bittins, M., Kuipers, S.D., Nair, R.R., Pai, B., Panja, D., Schubert, M., Soule, J., Tiron, A., Wibrand, K., 2010. The arc or synaptic memory. Exp. Brain Res. 200, 125–140.

Brown, M., Irvine, D.R., Park, V.N., 2004. Perceptual learning on an auditory frequency discrimination task by cats: association with changes in primary auditory cortex. Cereb. Cortex 14, 952–965.

Brugge, J.F., Nourski, K.V., Oya, H., Reale, R.A., Kawasaki, H., Steinschneider, M., Howard, M.A., 2009. Coding of repetitive transients by auditory cortex on Heschl's gyrus. J. Neurophysiol. 102, 2358–2374.

Campbell, K.A., Kalmbacher, C.E., Specht, C.D., Gregg, T.R., 1995. Dependence of rat vertex auditory evoked potentials on central muscarinic receptor activation. Brain Res. 702, 110–116.

Cheung, S.W., Bedenbaugh, P.H., Nagarajan, S.S., Schreiner, C.E., 2001. Functional organization of squirrel monkey primary auditory cortex: responses to pure tones. J. Neurophysiol. 85, 1732–1749.

de Villers-Sidani, E., Simpson, K.L., Lu, Y.F., Lin, R.C., Merzenich, M.M., 2008. Manipulating critical period closure across different sectors of the primary auditory cortex. Nat. Neurosci. 11, 957–965.

Dean, I., Harper, N.S., McAlpine, D., 2005. Neural population coding of sound level adapts to stimulus statistics. Nat. Neurosci. 8, 1684–1689.

Dickerson, L.W., Buchwald, J.S., 1991. Midlatency auditory-evoked responses: effect of scopolamine in the cat and implications for brain stem cholinergic mechanisms. Exp. Neurol. 112, 229–239.

Formisano, E., Kim, D.S., Di Salle, F., van de Moortele, P.F., Ugurbil, K., Goebel, R., 2003. Mirror-symmetric tonotopic maps in human primary auditory cortex. Neuron 40, 859–869.

Freund, T.F., Meskenaite, V., 1992. γ-Aminobutyric acid-containing basal forebrain neurons innervate inhibitory interneurons in the neocortex. Proc. Natl. Acad. Sci. USA 89, 738–742.

Fritz, J., Elhilali, M., Shamma, S., 2005. Active listening: task-dependent plasticity of spectrotemporal receptive fields in primary auditory cortex. Hear. Res. 206, 159–176.

Fujioka, T., Ross, B., Kakigi, R., Pantev, C., Trainor, L.J., 2006. One year of musical training affects development of auditory cortical-evoked fields in young children. Brain 129, 2593–2608.

Galvan, V.V., Weinberger, N.M., 2002. Long-term consolidation and retention of learning-induced tuning plasticity in the auditory cortex of the guinea pig. Neurobiol. Learn. Mem. 77, 78–108.

Gander, P.E., Bosnyak, D.J., Wolek, R., Roberts, L.E., 2007. Modulation of the 40-Hz auditory steady state response by attention during acoustic training. In: Cheyne, D., Ross, B., Stroink, G., Weinberg, H. (Eds.), New Frontiers in Biomagnetism. International Congress Series. Elsevier, Amsterdam, pp. 37–40.

Gander, P.E., Bosnyak, D.J., Roberts, L.E., 2010. Evidence for modality-specific but not frequency-specific modulation of human primary auditory cortex by attention. Hear. Res., (epub ahead of print).

Garcia-Lazaro, J.A., Ho, S.S., Nair, A., Schnupp, J.W., 2007. Shifting and scaling adaptation to dynamic stimuli in somatosensory cortex. Eur. J. Neurosci. 26, 2359–2368.

Godey, B., Schwartz, D., de Graaf, J.B., Chauvel, P., Liegeois-Chauvel, C., 2001. Neuromagnetic source localization of auditory evoked fields and intracerebral evoked potentials: a comparison of data in the same patients. Clin. Neurophysiol. 112, 1850–1859.

Greenberg, S., Poeppel, D., Roberts, T., 1998. A space–time theory of pitch and timbre based on cortical expansion of the cochlear traveling wave delay. In: Palmer, A., Rees, A., Summerfield, Q., Meddis, R. (Eds.), Psychophysical and Physiological Advances in Hearing. Whurr, London, pp. 293–300.

Gutschalk, A., Mase, R., Roth, R., Ille, N., Rupp, A., Hähnel, S., Picton, T.W., Scherg, M., 1999. Deconvolution of 40 Hz steady-state fields reveals two overlapping source activities of the human auditory cortex. Clin. Neurophysiol. 110, 856–868.

Jääskeläinen, I.P., Hirvonen, J., Huttunen, J., Kaakkola, S., Pekkonen, E., 1999. Scopolamine enhances middle latency auditory evoked magnetic fields. Neurosci. Lett. 259, 41–44.

Kaas, J.H., Hackett, T.A., 2000. Subdivisions of auditory cortex and processing streams in primates. Proc. Natl. Acad. Sci. USA 97, 11793–11799.

Kilgard, M.P., Merzenich, M.M., 2002. Order-sensitive plasticity in adult primary auditory cortex. Proc. Natl. Acad. Sci. USA 99, 3205–3209.

Kilgard, M.P., Pandya, P.K., Vazquez, J., Gehi, A., Schreiner, C.E., Merzenich, M.M., 2001. Sensory input directs spatial and temporal plasticity in primary auditory cortex. J. Neurophysiol. 86, 326–338.

Krishnan, A., Gandour, J.T., Bidelman, G.M., Swaminathan, J., 2009. Experience-dependent neural representation of dynamic pitch in the brainstem. Neuroreport 20, 408–413.

Kuriki, S., Kanda, S., Hirata, Y., 2006. Effects of musical experience on different components of MEG responses elicited by sequential piano-tones and chords. J. Neurosci. 26, 4046–4053.

Lu, T., Liang, L., Wang, X., 2001. Temporal and rate representations of time-varying signals in the auditory cortex of awake primates. Nat. Neurosci. 4, 1131–1138.

Lundstrom, B.N., Higgs, M.H., Spain, W.J., Fairhall, A.L., 2008. Fractional differentiation by neocortical pyramidal neurons. Nat. Neurosci. 11, 1335–1342.

Markram, H., Lubke, J., Frotscher, M., Sakmann, B., 1997. Regulation of synaptic efficacy by coincidence of postsynaptic APs and EPSPs. Science 275, 213–215.

Menning, H., Roberts, L.E., Pantev, C., 2000. Plastic changes in the auditory cortex induced by intensive frequency discrimination training. Neuroreport 11, 817–822.

Metherate, R., Ashe, J.H., 1993. Nucleus basalis stimulation facilitates thalamocortical synaptic transmission in the rat auditory cortex. Synapse 14, 132–143.

Musacchia, G., Strait, D., Kraus, N., 2008. Relationships between behavior, brainstem and cortical encoding of seen and heard speech in musicians and non-musicians. Hear Res. 241, 34–42.

Näätänen, R., Picton, T., 1987. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 24, 375–425.

Pantev, C., Elbert, T., Makeig, S., Hampson, S., Eulitz, C., Hoke, M., 1993. Relationship of transient and steady-state auditory evoked fields. Electroencephalogr. Clin. Neurophysiol. 88, 389–396.

Pantev, C., Eulitz, C., Hampson, S., Ross, B., Roberts, L.E., 1996a. The auditory evoked "off" response: sources and comparison with the "on" and the "sustained" responses. Ear Hear. 17, 255–265.

Pantev, C., Roberts, L.E., Elbert, T., Ross, B., Wienbruch, C., 1996b. Tonotopic organization of the sources of human auditory steady-state responses. Hear. Res. 101, 62–74.

Patel, A.D., Balaban, E., 2004. Human auditory cortical dynamics during perception of long acoustic sequences: phase tracking of carrier frequency by the auditory steady-state response. Cereb. Cortex 14, 35–46.
Petkov, C.I., Kang, X., Alho, K., Bertrand, O., Yund, E.W., Woods, D.L., 2004. Attentional modulation of human auditory cortex. Nat. Neurosci. 7, 658–663.
Picton, T.W., Alain, C., Woods, D.L., John, M.S., Scherg, M., Valdes-Sosa, P., Bosch-Bayard, J., Trujillo, N.J., 1999. Intracerebral sources of human auditory-evoked potentials. Audiol. Neurootol. 4, 64–79.
Pienkowski, M., Eggermont, J.J., 2009. Long-term, partially-reversible reorganization of frequency tuning in mature cat primary auditory cortex can be induced by passive exposure to moderate-level sounds. Hear. Res. 257, 24–40.
Poghosyan, V., Ioannides, A.A., 2008. Attention modulates earliest responses in the primary auditory and visual cortices. Neuron 58, 802–813.
Recanzone, G.H., Schreiner, C.E., Merzenich, M.M., 1993. Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. J. Neurosci. 13, 87–103.
Reinke, K.S., He, Y., Wang, C., Alain, C., 2003. Perceptual learning modulates sensory evoked response during vowel segregation. Cogn. Brain Res. 17, 781–791.
Rigdon, G.C., Pirch, J.H., 1986. Nucleus basalis involvement in conditioned neuronal responses in the rat frontal cortex. J. Neurosci. 6, 2535–2542.
Ross, B., Borgmann, C., Draganova, R., Roberts, L.E., Pantev, C., 2000. A high-precision magnetoencephalographic study of human auditory steady-state responses to amplitude-modulated tones. J. Acoust. Soc. Am. 108, 679–691.
Ross, B., Tremblay, K., 2009. Stimulus experience modifies auditory neuromagnetic responses in young and older listeners. Hear. Res. 248, 48–59.
Ruggero, M.A., Rich, N.C., 1987. Timing of spike initiation in cochlear afferents: dependence on site of innervation. J. Neurophysiol. 58, 379–403.
Sarter, M., Hasselmo, M.E., Bruno, J.P., Givens, B., 2005. Unraveling the attentional functions of cortical cholinergic inputs: interactions between signal-driven and cognitive modulation of signal detection. Brain Res. Rev. 48, 98–111.
Schreiner, C.E., Winer, J.A., 2007. Auditory cortex mapmaking: principles, projections, and plasticity. Neuron 56, 356–365.
Seitz, A.R., Dinse, H.R., 2007. A common framework for perceptual learning. Curr. Opin. Neurobiol. 17, 148–153.
Shahin, A., Bosnyak, D.J., Trainor, L.J., Roberts, L.E., 2003. Enhancement of neuroplastic P2 and N1c auditory evoked potentials in musicians. J. Neurosci. 23, 5545–5552.
Shahin, A., Roberts, L.E., Trainor, L.J., 2004. Enhancement of auditory cortical development by musical experience in children. Neuroreport 15, 1917–1921.
Shahin, A.J., Roberts, L.E., Pantev, C., Aziz, M., Picton, T.W., 2007. Enhanced anterior-temporal processing for complex tones in musicians. Clin. Neurophysiol. 118, 209–220.
Shahin, A.J., Roberts, L.E., Chau, W., Trainor, L.J., Miller, L.M., 2008. Music training leads to the development of timbre-specific gamma band activity. Neuroimage 41, 113–122.
Sheehan, K.A., McArthur, G.M., Bishop, D.V., 2005. Is discrimination training necessary to cause changes in the P2 auditory event-related brain potential to speech sounds? Cogn. Brain Res. 25, 547–553.
Song, S., Miller, K.D., Abbott, L.F., 2000. Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. Nat. Neurosci. 3, 919–926.
Song, J.H., Skoe, E., Wong, P.C.M., Kraus, N., 2008. Plasticity in the adult human auditory brainstem following short-term linguistic learning. J. Cog. Neurosci. 20, 1892–1902.
Stanton, S.G., Harrison, R.V., 1996. Abnormal cochleotopic organization in the auditory cortex of cats reared in a frequency augmented environment. Aud. Neurosci. 2, 97–107.
Tremblay, K., Kraus, N., McGee, T., Ponton, C., Otis, B., 2001. Central auditory plasticity: changes in the N1–P2 complex after speech-sound training. Ear Hear. 22, 79–90.
van Wassenhove, V., Nagarajan, S., 2007. Auditory cortical plasticity in learning to discriminate modulation rate. J. Neurosci. 27, 2663–2672.
Weinberger, N.M., 2004. Specific long-term memory traces in primary auditory cortex. Nat. Rev. Neurosci. 5, 279–290.
Weinberger, N.M., 2007. Auditory associative memory and representational plasticity in the primary auditory cortex. Hear. Res. 229, 54–68.
Wienbruch, C., Paul, I., Weisz, N., Elbert, T., Roberts, L.E., 2006. Frequency organization of the 40-Hz auditory steady-state response in normal hearing and in tinnitus. Neuroimage 33, 180–194.
Zhang,,, L.I., Bao, S., Merzenich, M.M., 2001. Persistent and specific influences of early acoustic environments on primary auditory cortex. Nat. Neurosci. 4, 1123–1130.