



Human pitch perception is reflected in the timing of stimulus-related cortical activity

Aniruddh D. Patel¹ and Evan Balaban^{1,2}

¹ The Neurosciences Institute, 10640 John Jay Hopkins Drive, San Diego, California 92121, USA

² Present address: Program in Neuroscience, CUNY College of Staten Island, 2800 Victory Boulevard, Staten Island, New York 10314, USA

The authors contributed equally to this work

Correspondence should be addressed to A.D.P. (apatel@nsi.edu) or E.B. (balaban@postbox.csi.cuny.edu)

'Pitch' refers to a sound's subjective highness or lowness, as distinct from 'frequency,' which refers to a sound's physical structure. In speech, music and other natural contexts, complex tones are often perceived with a single pitch. Using whole-head magnetoencephalography (MEG) and stimuli that dissociate pitch from frequency, we studied cortical dynamics in normal individuals who extracted different pitches from the same tone complexes. Whereas all subjects showed similar spatial distributions in the magnitude of their brain responses to the stimuli, subjects who heard different pitches exhibited contrasting temporal patterns of brain activity in their right but not their left hemispheres. These data demonstrate a specific relationship between pitch perception and the timing (phase) of dynamic patterns of cortical activity.

In speech and music, complexes of tones are perceived as having a single 'pitch,' a term referring to the subjective highness or lowness of sound. Pitch extraction is crucial in the perception of speech intonation and musical melody, and has long attracted interest as a form of central auditory processing amenable to quantitative investigation and modeling^{1–3}. The role of temporal patterns of neural activity in pitch processing has long been a subject of contention (for review, see ref. 4). One view is that the auditory system extracts pitch from complex sounds by deriving a spectral profile from frequency-specific (tonotopic) auditory input, followed by pattern-matching mechanisms^{5,6}. In contrast, others have proposed mechanisms based on the timing of auditory nerve fiber activity irrespective of frequency organization^{7,8}. Independent of these mechanisms, it is debated whether pitch is reflected at the cortical level in the overall rate/amount of neural activity at different locations in spatial maps, and/or by temporally different patterns of neural activity⁹. Our study addresses this latter question by examining the amount and timing of stimulus-related cortical activity during complex pitch perception.

A classic example of complex pitch processing involves the perception of a low pitch corresponding to a frequency not physically present in the acoustic spectrum of a tone complex, known as the 'missing fundamental' (MF). We exploit natural variation in MF perception to study the neural correlates of pitch perception, by comparing cortical activity in normal individuals who do or do not hear the MF when exposed to the same acoustic stimulus.

RESULTS

Subjects, experimental design and stimuli

Neural activity was measured in 13 right-handed subjects (5 female) listening to sequences of alternating tones while brain signals were recorded with a 148-channel whole-head biomagne-

tometer (4-D Neuroimaging, San Diego, California). We studied stimulus-related cortical activity via the auditory steady-state response (aSSR), an ongoing oscillatory brain signal resulting from continuous amplitude modulation (AM) of an acoustic stimulus¹⁰. aSSR frequency equals the acoustic AM rate, and its power is greatest when AM is in the 40-Hz range^{11,12}. Localization studies suggest that the aSSR arises from sources in each primary auditory cortex^{12–14}. Whereas the exact mechanisms of aSSR generation remain unclear¹³, they are thought to include hair cell dynamics (modulation of auditory hair cell responses by the AM rate), cochlear mechanics (frequency-specific latencies of auditory hair cell responses) and some form of neural expansion of these latencies below and/or within auditory cortex^{16–18}. For our purposes, the crucial feature of the aSSR is that it is sensitive to aspects of the carrier signal. In particular, both the timing (phase)^{12,15,16} and magnitude^{10,12} of this brain signal vary systematically with the carrier frequency of the sound stimulus.

Following our previous work relating aSSR phase to tone-carrier frequency¹⁵, we sought to determine if aSSR phase was also influenced by the perception of pitch in tone complexes (Fig. 1). To dissociate pitch from frequency, we used tone complexes in which the direction of pitch change could be made independent of the direction of frequency change. We were particularly interested in contrasting tone complexes that do and do not generate a MF (Fig. 1a and b). If aSSR phase is only sensitive to carrier frequency, one would predict that the direction of phase change between tones 1 and 2 (Fig. 1a and b) would be the same, as all component frequencies increase in both cases. However, if aSSR phase is sensitive to pitch, then phase should change in opposite directions in these two cases for subjects who hear a MF (phase 'flipping'), because pitch increases from tone 1 to 2 in Fig. 1a, but decreases from tone 1 to 2 in Fig. 1b. In subjects that do not hear the MF, there should be no difference

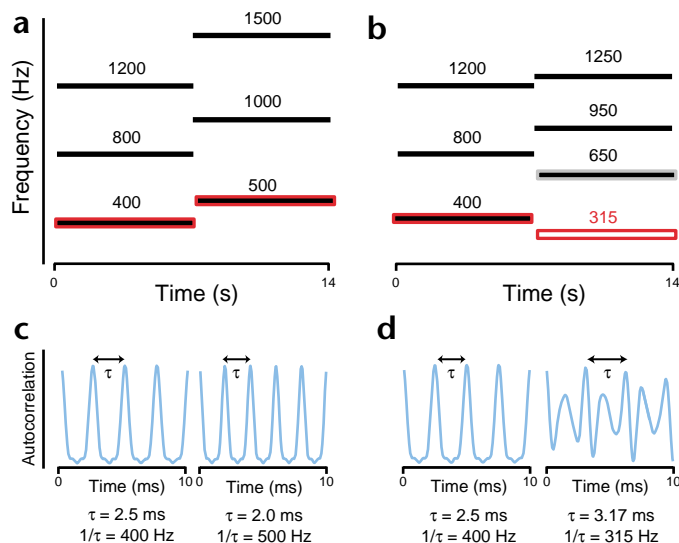


Fig. 1. Complex-tone stimuli with opposite directions of frequency and pitch change. (a, b) All frequencies (black lines; numerical values given above lines) increase from tone-complex 1 to 2, but in (a) the pitch (red box) increases while in (b) the pitch decreases, due to the perception of a MF. For subjects who do not hear the MF, the pitch in (b) increases (gray box). (c, d) Temporal correlate of pitch differences. Periodicity in the stimulus is shown by peaks in the correlation of the waveform against itself as a function of time (autocorrelation). The distance between highest peaks (τ) shortens between tone complexes 1 and 2 of (a), shown below in (c). Smaller τ corresponds to an increase in the apparent pitch of the sound. τ is lengthened between tone complexes 1 and 2 of (b), shown below in (d), due to the closer spacing of the frequency components of tone-complex 2 relative to 1. Longer τ corresponds to a decrease in the apparent pitch of the sound. For sound examples and details of the missing fundamental stimulus and its perception, see supplementary information.

in the direction of phase change in these two cases. The same reasoning applies to aSSR amplitude, and we applied the same analyses to aSSR magnitude to determine if pitch perception was reflected in magnitude flipping.

In the MF condition (Fig. 1b), tones of 400/800/1200 Hz alternated with tones of 650/950/1250 Hz. Whereas all frequency components increased from tone-complex 1 to 2, the frequency distance between components decreased, resulting in a lengthening of envelope period and a MF with lower pitch than tone-complex 1 (Fig. 1d). In the ‘complex tone up’ condition, 400/800/1200 Hz and 500/1000/1500 Hz tones alternated (Fig. 1a). Here, carrier frequencies and frequency distance increased between the tone complexes, leading to a perception of rising pitch (Fig. 1c). Two other conditions were included as controls: ‘pure tone up’ (tone 1, 400 Hz; tone 2, 500 Hz) and ‘pure tone down’ (tone 1, 400 Hz; tone 2, 325 Hz). These frequencies were chosen to mimic pitch alternation in the ‘complex tone up’ and ‘MF’ conditions, respectively. All sequences were 70 seconds long and consisted of 10 consecutive 7-second tones (five alternations between tone 1 and tone 2). Each subject heard five sequences per condition. To generate an auditory steady-state response, all sequences were given a constant 41.5-Hz amplitude modulation (AM).

Perceived pitch of the stimuli

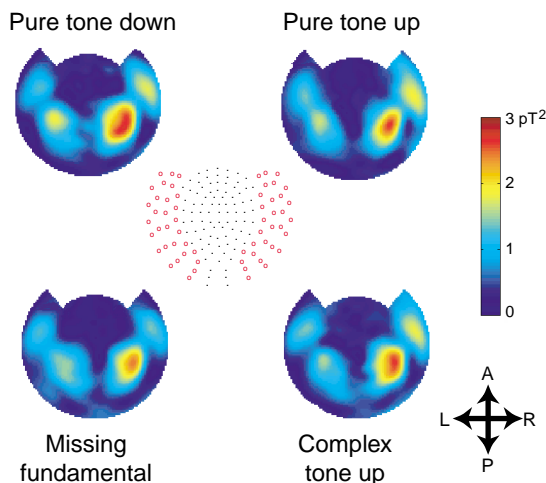
To ascertain the perceived pitch of the experimental stimuli, subjects adjusted the pitch of a pure tone to match the pitch of the amplitude-modulated tones used in the study. For the 650/950/1250 Hz (MF) stimuli, nine subjects heard a pitch of 334 ± 6 Hz (mean \pm s.e.m.; range, 320–378), and formed an ‘MF⁺’ group. One additional subject showed a bimodal response, reporting both a low pitch around 336 ± 8 Hz and a higher pitch

of 517 ± 21 Hz. Because this subject was clearly capable of hearing a MF, he was assigned to the MF⁺ group. Three additional subjects reported hearing only a higher pitch of 650 ± 0 Hz, with no trace of a MF. Additional tests revealed that these three subjects heard this high pitch even if the stimuli were not amplitude-modulated, and that their perception was never ambiguous. (See supplementary information, available on the *Nature Neuroscience* web site, http://neurosci.nature.com/web_specials.) These subjects formed an ‘MF⁻’ group, whose neural data could be compared with the MF⁺ group. All subjects agreed on the pitch of the 500/1000/1500 Hz tone (498 ± 4 Hz) and the pure tones (498 ± 4 Hz and 329 ± 6 Hz). The pitch of the 400/800/1200 Hz could be inferred as \sim 400 Hz (rather than 800 or 1200) from the fact that all subjects judged the tone-complex sequence in Fig. 1a as going up in pitch.

Power and distribution of the aSSR

Due to the AM of the stimuli, all subjects generated a robust aSSR at 41.5 Hz in each condition with similar spatial energy patterns. The grand average maps of aSSR energy for each condition are similar, with a broad maximum over the right posterior sensor quadrant, and subsidiary energy peaks in each sensor quadrant (Fig. 2). The geometry of this profile is consistent with sources in left and right auditory cortex, as suggested by localization studies of the aSSR^{12–14}. For each subject, the channels selected for dynamic analysis consisted of the union of channels over their energy peaks and a common bank of lateral channels illustrated in the figure inset (center, red zeros; see Methods).

Fig. 2. Power and spatial distribution of the aSSR in each of the four conditions (grand average across subjects). Each map represents the average spatial distribution of energy at 41.5 Hz (in picotesla squared, pT²) during 1 run of the given condition, computed using \sim 70 s-long Fourier transforms of data from each channel and plotted with spline interpolation. Each subject’s average energy map guided selection of channels for that subject: channels with energy greater than or equal to 1/4 of the maximum were included in the dynamic analyses. In addition, the lateral channels shown in the inset (center, red circles) were studied in all subjects, because aSSR phase responses in these regions are not necessarily predicted by the magnitude of the aSSR¹⁵. A, anterior; P, posterior; L, left; R, right.



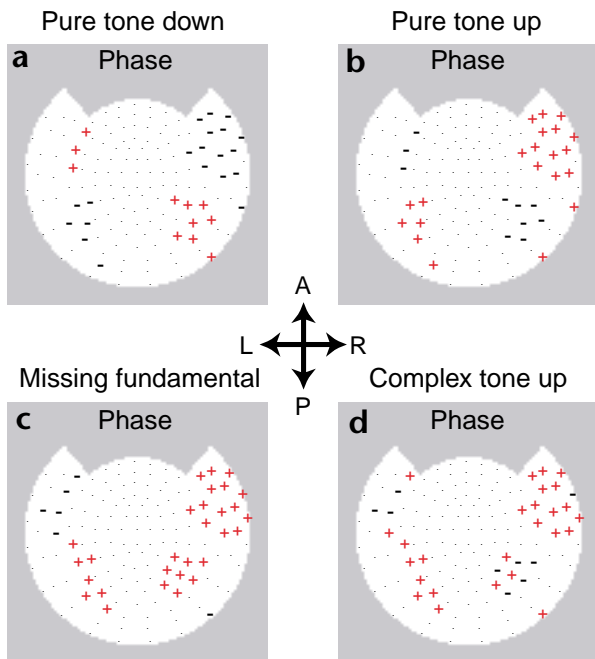


Fig. 3. Auditory steady state response phase is modulated by frequency and by pitch. Data are from one representative subject who heard the missing fundamental. (a, b) 'Pure tone down' and 'pure tone up' conditions, respectively. Red +, channels that showed a phase advance from tone 1 to tone 2; black -, channels that showed a phase delay. Direction of phase changes was almost completely reversed (that is, phase flipping occurred) from tone 1 (a) to tone 2 (b). (c, d) 'Missing fundamental' and 'complex tone up' conditions. Phase flipping is evident at several channels. A, anterior; P, posterior; L, left; R, right.

Dynamic measures of the aSSR

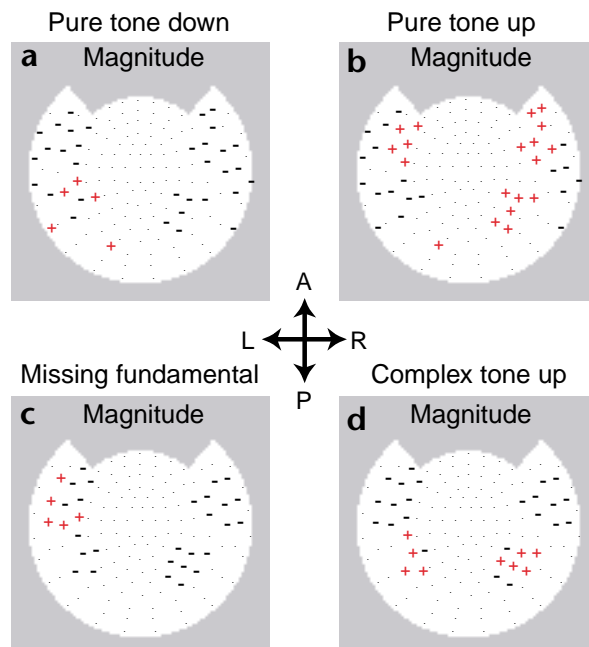
The primary motivation for this study was to determine if cortical dynamics are influenced by pitch as opposed to frequency. To accomplish this, we compared aSSR dynamics in pure- and complex-tone sequences. During pure-tone sequences, changes in frequency and pitch are correlated for all subjects. In both complex-tone conditions, all carrier frequencies increase from tone 1 to 2, but pitch increases in the 'complex tone up' condition and decreases in the MF condition only for subjects who hear the MF. These differences were used to ascertain any relationship between dynamic changes in cortical signal production and the perception of pitch.

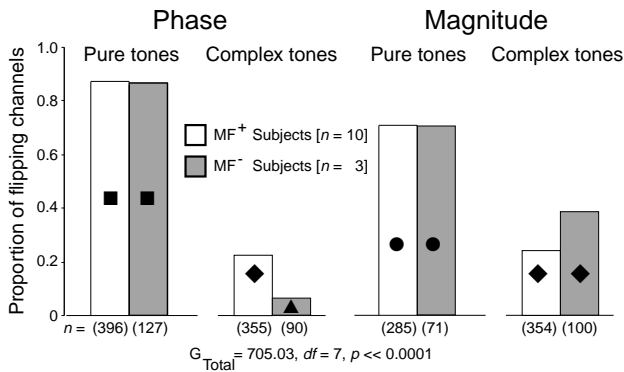
For each subject, we took sequential fast Fourier transforms (FFTs) of MEG data measured during each sequence, and extracted the magnitude and phase at 41.5 Hz to determine if these parameters increased or decreased from tone 1 to tone 2. Data from all five sequences of a given condition were combined, and pure and complex stimulus trials were examined separately. In the pure-tone conditions, neural data were analyzed at 21 different FFT lengths and those sensors showing significant phase differences between tones 1 and 2 at eleven or more of these different FFT lengths across the two conditions were selected for analysis as 'passing phase channels' (see Methods). The same criteria were applied independently to FFT magnitudes, leading to selection of 'passing magnitude channels.' Phase results for pure tones are shown for a representative subject in Fig. 3a and b. Red (+) channels show an aSSR phase advance from tone 1 to tone 2, while black (-) channels show a phase delay. Neural data from complex tone sequences were analyzed in exactly the same way (Fig. 3c and d, results for the same subject, who heard the MF).

Fig. 4. Auditory steady state response magnitude modulations. Data are from the same subject shown in Fig. 3. (a, b) 'Pure tone down' and 'pure tone up' conditions. Red +, channels that showed a magnitude increase from tone 1 to tone 2; black -, channels that showed a magnitude decrease. (c, d) 'Missing fundamental' and 'complex tone up' conditions. A, anterior; P, posterior; L, left; R, right.

Focusing on the pure tone 'down' condition (Fig. 3a), we observed a spatially segregated and anti-symmetrical pattern of phase advances and delays in each hemisphere, consistent with two or more sources in each auditory cortex^{14,19}. The present study was not designed to localize sources, but rather to examine the influence of frequency/pitch on aSSR dynamics. For this reason, the essential information is not the absolute direction of a channel's phase change in the 'up' or 'down' conditions, but the reversal of this direction of change between these two conditions, or phase flipping. This is represented by a change in sign/color for a given channel in Fig. 3a versus Fig. 3b. In the complex-tone conditions (Fig. 3c and d), phase flipping occurred at a smaller number of passing channels than in the pure tone conditions, suggesting that most cells generating the aSSR were driven by frequency rather than pitch. The spatial pattern of channels showing phase advances and delays also no longer had the simple configuration seen in Fig. 3a and b. This could occur if some aSSR sources were responding to frequency and others to pitch.

Magnitude flipping was evident in both the pure and complex tone conditions, suggesting that both phase and magnitude of the aSSR could reflect pitch perception (Fig. 4). Alternatively, flipping in either signal could reflect other perceptual or physical differences between the tones. Comparison of data between subjects who did and did not hear the MF was used to determine if either correlate had a special relationship to pitch perception.





Differences in aSSR dynamics between subject groups

For each subject, we quantified the number of passing channels that did and did not flip between conditions for both pure and complex tones. For example, the subject shown in Fig. 3a and b had 9 passing phase channels on the left, all of which flipped, and 22 passing phase channels on the right, 21 of which flipped. The subject whose data is shown in Fig. 4a and b had 19 passing magnitude channels on the left, 9 of which flipped, and 19 passing magnitude channels on the right, 13 of which flipped (summed data for all subjects, Fig. 5). To avoid statistical problems with multiple comparisons, we analyzed these data using a simultaneous unplanned test procedure for homogeneity of frequencies²⁰.

The G-statistic²⁰ (Fig. 5) indicates highly significant heterogeneity of frequencies among the different groups and conditions. During pure tone sequences, MF⁺ and MF⁻ subjects had similar proportions of passing channels that flipped in both phase (~90%) and magnitude (~70%). Both groups of subjects showed a substantial reduction in the proportion of passing channels that flipped in the complex-tone conditions in both phase and magnitude (on average, 1/3 of the proportion of flipping channels in the pure tone condition). Complex-tone magnitude flips had statistically indistinguishable proportions in MF⁺ and MF⁻ subjects. However, the proportion of passing channels exhibiting complex-tone phase flips were significantly reduced in MF⁻ subjects as compared with MF⁺ subjects (Fig. 5), suggesting a relationship between phase flipping and pitch perception.

MF⁺ and MF⁻ subjects showed comparable proportions of phase flipping in the left and right hemisphere for pure tones (~90%; Fig. 6). For complex tones, MF⁺ subjects show phase flipping at ~25% of passing channels in each hemisphere, whereas MF⁻ subjects showed a similar response in the left hemisphere only. Complex-tone phase flipping was virtually absent on the right in the MF⁻ subjects (who did not perceive a change in pitch direction between the up and down conditions), despite a large number of right hemisphere passing channels (67, Fig. 6). This markedly differed from the pattern of right hemisphere phase

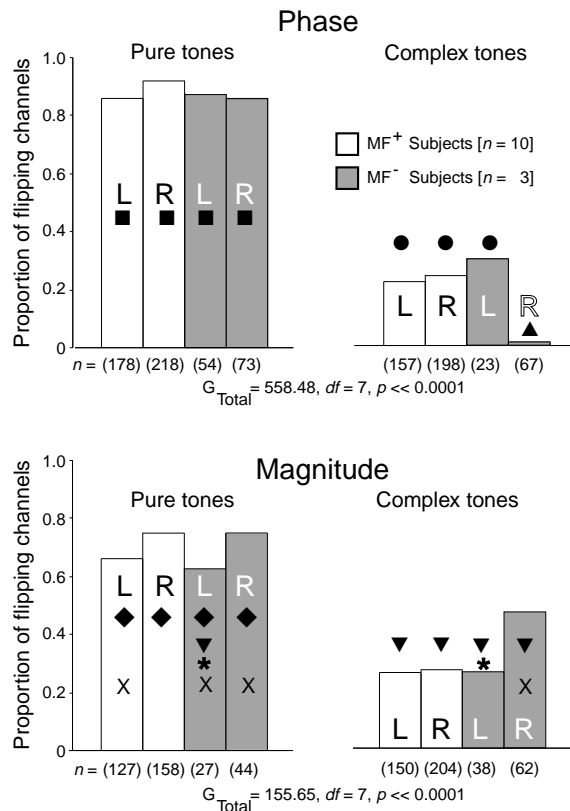
Fig. 6. Spatial organization of passing channels exhibiting phase and magnitude flipping. Bars and analyses as in Fig. 5. Responses are separated according to whether passing channels occurred in the right or left hemisphere of the brain. The shapes (square, circle, triangle, diamond, inverted triangle, asterisk, cross) indicate the results of simultaneous unplanned comparison tests. Groups with the same shapes are not significantly different from each other; groups with different shapes are significantly different at or below the $p < 0.05$ level. Numbers below the bars represent the total number of passing channels in each category. Top, phase results; bottom, magnitude results. The value of the overall G-test for heterogeneity in frequencies is also given for each set of graphs.

Fig. 5. Passing channels exhibiting phase and magnitude flipping. Bars represent the proportion of passing phase and magnitude channels exhibiting phase- (left) or magnitude- (right) flipping between the up and down conditions. White bars, MF⁺ subjects; gray bars, MF⁻ subjects. Shapes (square, circle, diamond, triangle) indicate results of simultaneous unplanned comparison tests. Groups with the same shapes are not significantly different from each other, and groups with different shapes are significantly different at or below the $p < 0.05$ level. Numbers under each bar represent the total number of passing channels in each category. The value of the overall G-test for heterogeneity in frequencies is also given.

flipping to pure tones in these same subjects, and to the right hemisphere phase flipping to tone complexes in MF⁺ subjects.

The magnitude data exhibited no significant differences between groups for flips in either hemisphere (Fig. 6). Thus, the only pitch-related difference seen in dynamic patterns of cortical activity was for phase flips in the right hemispheres of MF⁺ and MF⁻ subjects, and this was only seen in the complex tone conditions. This difference was specific to the temporal (phase) aspect of brain signals, and was not reflected in changes in the amount of signal (magnitude).

Statistical comparisons at the level of subjects gave the same results. In the complex-tone conditions, 10 of 10 MF⁺ subjects showed phase flips in the right hemisphere, and only 1 of 3 MF⁻ subjects showed phase flips on the right. This difference in proportions was statistically significant ($p = 0.0385$, Fisher Exact Test). In the left hemisphere, 8 of 10 MF⁺ subjects and 3 of 3 MF⁻ subjects showed phase flips, proportions that are not significantly different ($p > 0.99$, Fisher Exact Test). Similarly, subject groups did not show any differential representation of magnitude flips in the two hemispheres during the complex-tone conditions (right, 9/10 MF⁺ and 3/3 MF⁻ subjects; left, 8/10 MF⁺ and 2/3 MF⁻ subjects, both $p > 0.99$, Fisher Exact Test). Together with the evidence





reviewed above, these data suggest that complex-tone pitch perception has a special relationship with dynamic timing patterns of neural activity in the right hemisphere.

DISCUSSION

Stimulus-related cortical activity was studied in normal individuals who experienced different pitch percepts when exposed to the same stimuli, to determine if pitch perception was reflected in the amount (magnitude) and/or timing (phase) of neural activity. Using complex tones that generated a MF, we found that neural response magnitude was similar across subjects and hemispheres, consistent with previous imaging work^{21–23}. We also found that dynamic patterns of activity distinguish between subjects who do and who do not perceive a MF, and that these differences were manifested in the right hemisphere.

The present study was not designed to settle the long-standing argument between advocates of spectral^{5,6} and temporal^{7,8} pitch-extraction models. Because of frequency-dependent time delays in the cochlea^{16,18}, either method of extraction (or a mixed method) could contribute to cortical activity in which the timing varies with the perceived pitch of the stimulus. These findings also do not rule out subtle spatial changes in the magnitude of cortical activity during pitch perception, because these may be reflected in aspects of the brain signal that our study was not designed to detect. The extent to which the mechanisms generating the observed aSSR phase changes make use of spectral and/or temporal aspects of the stimulus, and the possibility of small parallel changes in cortical signal location remain open questions for future research.

The observed hemispheric difference is intriguing in light of a contradiction in the auditory literature. A previous study of MF perception in subjects with auditory cortical lesions²⁴, as well as lesion²⁵, imaging²⁶ and animal²⁷ studies using other (non-MF) stimuli, has suggested that right auditory cortex plays a special functional role in complex pitch processing. In contrast, dynamic imaging studies using the missing fundamental^{21,22} have not found any consistent hemispheric difference in the amount of auditory cortical neural activation.

By focusing on phase changes in a band of activity that contains stimulus-related information, our data suggest a resolution to this discrepancy: missing fundamental sounds generate similar average amounts of neural activity in the two hemispheres, but this activity differs in its temporal dynamics on the two sides. These differences could result from the two auditory cortices performing different operations—the cortices may perform similar operations with differing temporal characteristics²⁸, or may receive inputs with different temporal patterns and/or time resolutions—or a combination of these possibilities. Relating information on cortical activity derived from MEG and fMRI to subcortical activity measured with EEG^{4,29} and fMRI³⁰ may help to resolve this issue.

What might explain the difference in right hemisphere temporal dynamics in MF⁺ and MF⁻ subjects when confronted with the same stimuli? Physiological recordings from animal⁸ and human⁴ subjects suggest that neural correlates of the periodicities of the missing fundamental and the three spectrally resolved, non-harmonically related tones in our stimuli should be present in the auditory brainstem of our subjects. If MF⁺ and MF⁻ subjects have the same neural correlates present in their brainstem responses, then cortical differences would imply selective amplification or suppression of different subsets of periodically firing auditory neurons between brainstem and cortex. To resolve whether such selective mechanisms exist, and how they develop

and operate, further studies should examine simultaneously measured brainstem and cortical responses in a large number of subjects showing individual variation in pitch perception.

If temporal dynamics recorded above the right auditory cortex reflect pitch processing (and perhaps other stimulus attributes as well), what correlates might be present in the signals recorded over left auditory cortex? MF⁺ and MF⁻ subjects both produced left-hemisphere phase flips to the complex stimuli in equal proportions (Fig. 6), even though MF⁻ subjects did not perceive the opposite directions of the pitch stimuli. This may reflect differences in the timbre or 'tone quality' between stimuli. The timbre of the missing fundamental stimulus was noticeably different from the preceding tone (and from the tones in the 'complex tone up' condition) to all subjects, whether they perceived the MF or not. Timbre differences among stimuli can potentially influence phase-flipping in both MF⁺ and MF⁻ subjects, because differences in timbre between the pure tone and complex tone stimuli were associated with a reduction in the proportion of passing channels showing phase-flipping (Fig. 6). The similar pattern of phase flipping seen in the left hemispheres of MF⁺ and MF⁻ subjects for the complex stimuli may indicate a common influence of timbre on left hemisphere cortical dynamics, a possibility meriting further investigation.

METHODS

Subjects and stimuli. The experimental protocol was approved by the Scripps/NSI Human Subjects Institutional Review Board. Subjects were right-handed individuals between the ages of 29 and 52 who passed an audiometric exam and gave informed consent. Tone sequences were created with Signal (Engineering Design, Belmont, Massachusetts). For the complex-tone sequences, the relative amplitude of the three component frequencies from lowest to highest was 1.75, 1.25 and 0.75. All tone sequences were amplitude-modulated at a rate of 41.5 Hz to a depth of 0.25 of maximum amplitude using a \cos^2 envelope. In the pitch-matching experiment, 2-s tones with 41.5 Hz AM were used, and subjects matched perceived pitch to pure tones (without AM) by numerically adjusting the frequency of a pure tone generator.

Magnetoencephalographic recording. Whole-head neuromagnetic signals were collected using a Magnes 2500WH MEG system (4-D Neuroimaging) in a magnetically shielded room. This system provides 148 magnetometer coils (1 cm in diameter) spaced 3 cm apart on an approximately ellipsoidal surface located ~3 cm from the scalp surface. Stimuli were delivered binaurally over non-magnetic ER30 tube-phones (Etymotic Research, Elk Grove, Illinois) at a comfortable level. Data were sampled at 678.17 Hz and band-pass filtered from 1–100 Hz online during data acquisition. Runs with magnetic flux jumps or excessive eye blinks were discarded and repeated.

Data preparation and analysis. Data were analyzed using Matlab (Mathworks, Natick, Massachusetts), Statview (SAS, Cary, North Carolina) and Biomstat (Exeter, Setauket, New York). Data from each MEG channel were digitally resampled (Resamp, Engineering Design) at 664 Hz before Fourier analysis in order to have 16 time points per 41.5 Hz cycle. This ensured that Fourier transforms that were integer multiples of 16 points in length had a bin precisely centered on 41.5 Hz, and also alleviated phase unwrapping problems¹⁵. For a given run for each subject, MEG data from the central 6 s of each 7 s tone were Fourier transformed, and the magnitudes and phases of the 41.5 Hz Fourier coefficients were extracted and labeled according to whether they occurred during tone 1 or tone 2. Magnitude and phase data from each successive pair of tones was zero-meaned to correct for possible drift. Data from all runs of a given condition were combined, and the mean phase of tones 1 and 2 were compared using Mann–Whitney U-tests³¹ to determine if phase advanced or delayed from tone 1 to tone 2. This analysis was conducted separately at 21 FFT lengths, from 160 points (~240 ms, 24 FFTs per tone) to 3360 points (~5 s, 1 FFT per tone). To be included in the analysis of 'pure tone up' versus 'pure tone down' stimuli, a channel had to show



nominally significant phase differences at the $p = 0.05$ level between tones 1 and 2 at 11 or more different FFT lengths across these 2 conditions. Channels passing this criterion (passing channels) were then plotted with the sign/color code in Fig. 3a and b and Fig. 4a and b, showing their direction of phase or magnitude difference between tones 1 and 2 in the two conditions (mean phase or magnitude averaged across all FFT lengths). Phase flipping was analyzed by counting the number of channels that reversed the direction of their phase change between up and down conditions (Fig. 3a and b); magnitude flipping was analyzed in the same way (Fig. 4a and b). These same procedures and criteria were used for the complex-tone conditions. Data were compiled across subjects by counting the number of passing channels that did and did not show flipping in the pure- and complex-tone conditions.

Statistical analyses of frequency data used the simultaneous unplanned test procedure for homogeneity of frequencies²⁰, as implemented in the Biomstat computer program, using a *post hoc* test p -value of 0.05.

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