Spatial and temporal relationships of electrocorticographic alpha and gamma activity during auditory processing

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ABSTRACT

Neuroimaging approaches have implicated multiple brain sites in musical perception, including the posterior part of the superior temporal gyrus and adjacent perisylvian areas. However, the detailed spatial and temporal relationship of neural signals that support auditory processing is largely unknown. In this study, we applied a novel inter-subject analysis approach to electrophysiological signals recorded from the surface of the brain (electrocorticography (ECoG)) in ten human subjects. This approach allowed us to reliably identify those ECoG features that were related to the processing of a complex auditory stimulus (i.e., continuous piece of music) and to investigate their spatial, temporal, and causal relationships. Our results identified stimulus-related modulations in the alpha (8–12 Hz) and high gamma (70–110 Hz) bands at neuroanatomical locations implicated in auditory processing. Specifically, we identified stimulus-related ECoG modulations in the alpha band in areas adjacent to primary auditory cortex, which are known to receive afferent auditory projections from the thalamus (80 of a total of 15,107 tested sites). In contrast, we identified stimulus-related ECoG modulations in the high gamma band not only in areas close to primary auditory cortex but also in other perisylvian areas known to be involved in higher-order auditory processing, and in superior premotor cortex (412/15,107 sites). Across all implicated areas, modulations in the high gamma band preceded those in the alpha band by 280 ms, and activity in the high gamma band causally predicted alpha activity, but not vice versa (Granger causality, $p < 1e^{-8}$). Additionally, detailed analyses using Granger causality identified causal relationships of high gamma activity between distinct locations in early auditory pathways within superior temporal gyrus (STG) and posterior STG, between posterior STG and inferior frontal cortex, and between STG and premotor cortex. Evidence suggests that these relationships reflect direct cortico-cortical connections rather than common driving input from subcortical structures such as the thalamus. In summary, our inter-subject analyses defined the spatial and temporal relationships between music-related brain activity in the alpha and high gamma bands. They provide experimental evidence supporting current theories about the putative mechanisms of alpha and gamma activity, i.e., reflections of thalamo-cortical interactions and local cortical neural activity, respectively, and the results are also in agreement with existing functional models of auditory processing.

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Introduction

Music is a perceptual experience that engages many cognitive processes within different regions of the brain (Stewart et al., 2006). Over the past few decades, numerous studies using hemodynamic and electrophysiological imaging techniques (fMRI/PET and EEG/MEG, respectively) have attempted to uncover the neural underpinnings of music processing. For instance, a recent fMRI study by Alluri et al., 2012 investigated the BOLD responses related to the processing of timbre, rhythm, and tone while subjects listened to music. Other neuroimaging studies investigated the relationship between sound intensity and brain activity in auditory cortex (Brechmann et al., 2002; Hart et al., 2003; Mulert et al., 2005; Tanji et al., 2010; Thaerig et al., 2008; Yetkin et al., 2004), and EEG studies determined relationships between rhythm and pitch and EEG components during listening and imagination of melodies (Schaefer et al., 2009).

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These and other studies have made important progress in identifying those brain regions whose activity changes with the perception of different individual musical features (e.g., sound intensity, rhythm, pitch), but most of them have been constrained to highly controlled experiments using artificial stimuli (e.g., presenting tones at different intensities or pitches). This is unfortunate, because cortical processing of artificial stimuli may differ in important ways from the processing of complex natural stimuli (such as music), and because evidence suggests that the brain employs general principles that govern the processing of complex natural stimuli (Hasson et al., 2004, 2010). In addition to experimental constraints, methodological limitations have not allowed to simultaneously evaluate the temporal and spatial dynamics related to music processing. For instance, fMRI and PET measure brain metabolic activity with excellent spatial but reduced temporal resolution (several seconds). Thus, they cannot track the rapid moment-to-moment variations related to processing of continuous music. Conversely, EEG and MEG measure brain electrical activity with excellent temporal resolution but poor spatial resolution (several centimeters) and cannot reliably ascribe activity changes to particular brain areas.

Electrocorticographic (ECoG) recordings from the surface of the brain have recently been used to study the neural dynamics during processing of complex sounds, in particular speech (Edwards et al., 2009; Lachaux et al., 2007; Pasley et al., 2012; Sinai et al., 2009). This relatively new imaging technique combines high temporal resolution with high spatial resolution and coverage. It can also detect different neurophysiological processes that subserve sensory, motor/language, or cognitive functions (Crone et al., 1998; Hermes et al., 2012). These processes include ECoG modulations in the alpha (8–12 Hz) and high gamma (70–110 Hz) frequency bands. Activity in the alpha band seems to reflect interactions between the thalamus and the cortex (Lopes Da Silva, 1991; Steriade et al., 1990; Zhang et al., 2004), and may facilitate information transfer to task-related cortical areas by inhibiting neural activity in task-unrelated areas (Jensen and Mazaheri, 2010). On the other hand, activity in the high gamma band seems to reflect task-related activity of neural populations directly underneath the electrodes (Crone et al., 1998, 2001; Miller et al., 2007, 2009; Schalk et al., 2007).

Despite this body of work, the most salient spatial and temporal relationships of these neural processes during processing of a complex natural auditory stimulus remain undefined. To address this issue, we recorded electrical activity from electrodes implanted on the brain's surface of ten human subjects while they were listening to music. We used these data to define the cortical locations that modulate their alpha or gamma activity during auditory processing and to define their temporal and causal relationships. Our results implicate perisylvian structures as well as superior premotor cortex, and establish the differing spatial and temporal contributions of alpha and gamma activity.

Materials and methods

Subjects and data collection

We recorded electrical activity from intracranial electrodes of ten subjects (4 men, 6 women) with intractable epilepsy who were listening to a complex natural auditory stimulus (the song "Another Brick in the Wall — Part 1" (Pink Floyd, Columbia Records, 1979)). These subjects underwent temporary implantation of subdural electrode arrays to localize the epileptogenic focus and to delineate it from eloquent (i.e., functional) cortical areas prior to brain resection. Table 1 summarizes the subjects' clinical profiles. All of the subjects gave informed consent to participate in the study, which was approved by the Institutional Review Board of Albany Medical College. None of the subjects had a history of hearing impairment. The implanted electrode grids consisted of platinum-iridium electrodes that were 4 mm in diameter (2.3–3 mm exposed) and spaced with an inter-electrode distance of 0.6 or 1 cm. The total numbers of implanted electrodes were 96, 83, 109, 58, 120,

Table 1
Clinical profiles of the subjects that participated in the study. All of the subjects had normal cognitive capacity and were functionally independent.

| Subject	Age	Sex	Handedness	Seizure Focus	# of Elec.
A	29	F	R	Left temporal	86
B	30	M	R	Left temporal	82
C	26	F	R	Left temporal	103
D	45	M	R	Left temporal	56
E	29	F	R	Left temporal	108
F	45	F	L	Left temporal	57
G	60	M	R	Left temporal	53
H	17	F	L	Left temporal	93
I	28	M	R	Left temporal	110
J	25	F	R	Left temporal	92

58, 59, 98, 134, and 98 for the different subjects, respectively. Electrodes were implanted on the left hemisphere for all subjects (see Fig. 1 for electrode coverage). ECoG signals were digitized at 1200 Hz, synchronized with stimulus presentation, and stored using the BCI2000 software platform (Schalk and Mellinger, 2010; Schalk et al., 2004). ECoG signals were recorded while the subjects were listening to the song, which was 3:00 min long, digitized at 44.1 kHz in waveform mono audio file format, and binaurally presented to each subject using in-ear monitoring earphones. In addition, we recorded the same amount of ECoG signals while subjects were at rest with eyes open. We visually inspected the recordings and removed those electrodes that did not contain clean ECoG signals or had interictal activity, which left 86, 82, 103, 56, 108, 57, 53, 93, 110, and 92 electrodes for the different subjects.

Cortical mapping

We defined the brain anatomy of each subject using pre-operative magnetic resonance imaging (MRI) scans, and the location of the electrodes using post-operative computer tomography (CT) imaging. We then created a 3D surface model of each subject's cortex from the MRI images, co-registered it with the location of the electrodes given by the CT images using Curry Software (Compumedics NeuroScan), and transformed the 3D model and electrode locations into Talairach space (see Fig. 1).

Extraction of ECoG and sound features

To extract the time course of alpha and high gamma activity, we first filtered ECoG signals from each electrode at each specific frequency band (i.e., 8–12 Hz and 70–110 Hz) using an IIR band-pass filter and removed spatially distributed noise common to all ECoG electrodes using a common average reference (CAR) spatial filter. We then computed the envelope of the ECoG signal (i.e., the magnitude of the analytic signal) in each frequency band. Finally, we computed the natural logarithm of the envelope power (i.e., squaring each element of the envelope and then computing the natural logarithm) and resampled the result to 10 Hz. To extract the song's sound intensity, we computed the average power derived from non-overlapping 10 ms segments of the song. We then smoothed the sound intensity by applying a low pass IIR filter at 5 Hz and resampled the result to 10 Hz. The total length of the alpha, high gamma, and sound intensity time courses are 1800 samples each. All filtering operations were performed forwards and then backwards (using Matlab's filtfilt command) to avoid an introduction of a group delay. The following analyses then determined those locations or interactions across locations that contained alpha or gamma activity that was related to auditory processing.
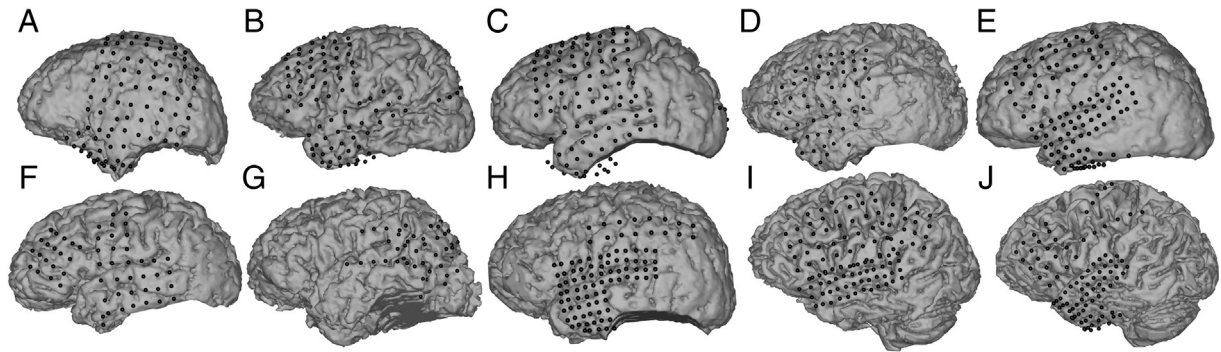
Fig. 1. Subject-specific brain models and locations of implanted and analyzed electrodes. The brain model template marked with a star shows the approximate location of implanted electrodes from all subjects.

Intersubject correlation (ISC) analysis

Identifying task-related neural signals is typically accomplished by comparing brain activity during two conditions (e.g., task vs. baseline) or by correlating brain activity to a particular aspect of the task (e.g., time course of sound intensity as in Potes et al., 2012). However, these approaches either require many repetitions of task and rest periods (to minimize the effect of spontaneous brain activity changes that are not related to the task) or a very specific hypothesis about what aspect of the task may be reflected in brain signals. Thus, these approaches are not amenable to identifying the most relevant neural processes related to processing of a continuos piece of music. However, recent research (Hasson et al., 2004, 2010) has established that it is possible to identify such processes by studying brain signals exclusively across (rather than within) subjects.

Based on this idea, we identified task-related neural signals as those that were correlated across subjects. This approach ensured that all neural signals identified with this procedure are related to the processing of music since ECoG modulations resulting from the presentation of music were the only aspect that linked neural signals from one subject to neural signals from another subject. It also ensured that the results represented only task-related neural signals that were common across subjects. Because the location of the electrodes varied across subjects, we could not compare activity changes at the identical location across subjects. Instead, we identified, for each electrode location in each subject, all electrodes from all other subjects that were in close proximity (<1 cm) to that electrode. This permitted comparison of brain activity from one individual to brain activity from other subjects. For each such pair of electrodes, we computed the average Talairach coordinate, which resulted in a total of 15,107 locations (336 ± 210 per subject combination) that formed the basis for our analyses. For each of these locations/electrode pairs, and separately for ECoG activity in the alpha and high gamma bands, we computed the pairwise Spearman correlation coefficient (intersubject correlation (ISC) r) and determined its significance (i.e., p-value). The statistical significance of the resulting correlation coefficients was computed using a bootstrapping randomization test in which the envelope samples for each frequency band and for each channel were randomly scrambled (i.e., 1000 times) across time. We repeated the same procedure for all locations and all combinations of subjects (i.e., $\binom{10}{2} = 45$ combinations).

Next, we determined all locations whose p-values were significantly different than chance after Bonferroni correction for 15,107 locations (i.e., $p < \frac{0.01}{15107} = 6.6e^{-7}$), and projected the negative logarithm of the corrected p-values ($-log_{10}(p)$) for each electrode on to the 3D brain cortical template provided by the Montreal Neurological Institute (MNI).

To determine causal relationships between the time course of average alpha activity (calculated across all locations implicated by our analyses) and the time course of average gamma activity, we calculated Granger causality (Granger, 1969) using a model order of 10, suggested by the Bayesian information criterion (BIC) (Schwarz, 1978). Finally, we determined the lag between brain activity in these two time courses by identifying the time of the peak of the cross-correlation function.

Intersubject Granger causality (ISG) analysis

We then established those pairs of locations whose activity time course were related to each other causally and were also related to auditory processing. To do this, we estimated causal interactions between different recording sites across subjects at alpha and high gamma frequencies using bivariate Granger causality. We considered Granger causality from X to Y (i.e., $X \rightarrow Y$) if adding past values of X and Y (i.e., full model) provide more information about future values of Y compared to when only past values of Y (i.e., restricted model) are considered. In this analysis, X or Y are time series representing alpha or high gamma activity in a particular electrode location and subject. Unlike previous ECoG studies (Korzeniewska et al., 2011), our Granger causality analysis is set to predict the power instead of the amplitude of the ECoG signal in a particular frequency band. For our visualization of causal interactions identified with our Granger causality analyses, we used directed arrows that connected two specific locations on an MNI brain. In our analyses, we considered all possible (630,800) pairs of electrode locations across subjects.

To select the best model order for Granger causality, we computed the Bayesian information criterion (BIC) (Schwarz, 1978) across all pairs of electrodes, which resulted in a model order of 10. To validate the goodness-of-fit of each autoregressive (AR) model, we checked whether the residuals (i.e., the errors) were serially uncorrelated using the Durbin–Watson test (Durbin and Watson, 1950) and examined the consistency of the model (Ding et al., 2000) and the adjusted coefficient of determination (R^2) (Cameron and Windmeijer, 1997). All significant Granger causality connections had consistency and R^2 values greater than 80%, and all the residuals passed the Durbin–Watson test.

To assess the statistical significance (i.e., p-value) of the Granger causality between two locations $X \rightarrow Y$, we tested the null hypothesis (i.e., the full model does not fit the data better than the restricted model) using the F-statistic $\mathbf{F} = \frac{(\text{RSS}_F - \text{RSS}_R)(n - 3k)}{\text{RSS}_R(k)}$, where RSS_F and RSS_R were the residual sum of squares of the full and restricted model, respectively, k was the model order (i.e., k = 10), and n was the number of observations (i.e., 1800). To determine statistical significance (i.e., a p-value), we compared the F-statistic to an F-distribution with (k, $n - 3k$) degrees of freedom. The null hypothesis was rejected if the p-value was less than $1.58e^{-8}$ after Bonferroni correction for all possible connections (i.e., p-value $< \frac{0.01}{630800} = 1.58e^{-8}$).

The critical value of the F-distribution with (10,1170) degrees of freedom was 0.0145.

Application of bivariate Granger causality is known to be susceptible to spurious connections (i.e., connections that are either mediated or confounded by another time series, e.g., alpha or high gamma activity in a particular channel and subject). To account for this known potential confound, we removed all spurious connections from the resulting set of statistically significant causal interactions using the approach described in (Hedlin et al., 2010). To display only large cortical networks, we removed short connections (i.e., those with a distance less than 1 cm), and then selected the most significant one from the connections that were in close proximity (i.e., connections whose start or end points were in a distance less than 1 cm).

Results

Spatial relationship

We first investigated the spatial relationship of locations whose alpha or high gamma activity was related to music processing. Specifically, the results shown in Fig. 2a highlight those locations whose alpha (upper panel) or gamma (lower panel) activity was significantly related to music processing (left panels) as opposed to the rest condition (i.e., relaxing on a bed with eyes open, right panels). The black dots and colored areas in the brain figures identify these

locations and their corresponding accumulated $-log_{10}(p)$ values. There were a total of 500 significant locations across all subjects, the two frequency bands, and the task and rest conditions. Specifically, for the ECoG recordings during the task condition, 80 locations had significant alpha-ISC values (mean correlation $\pm$ standard deviation across the 80 locations: $r = 0.13 \pm 0.02$, max $r = 0.19$) and were primarily located in areas close to primary auditory cortex (Fig. 2a, top-left). Moreover, 412 locations had significant gamma-ISC values ($r = 0.15 \pm 0.03$, max $r = 0.27$) and were not only located in areas close to primary auditory cortex but also over auditory association areas as well as in premotor cortex (Fig. 2a, bottom-left). Premotor cortex has been shown to be engaged in processing of sequential sounds (Platel et al., 1997), chords (Maess et al., 2001), rhythms, and in prediction of pitch (Schubotz and von Cramon, 2002; Schubotz et al., 2000). In contrast, for the ECoG recordings during rest, only 8 (Fig. 2a, top-right) (mean correlation $\pm$ standard deviation across the 8 locations: $r = 0.001 \pm 0.13$, max $r = 0.14$) and 0 (Fig. 2a, bottom-right) locations had significant alpha-ISC and gamma-ISC values, respectively. The number of locations with significant alpha- and gamma-ISC values during the task was larger than those during rest (Fisher's exact probability test, two-tail, $p = 4.51e-7$ for alpha, $p = 1.88e-75$ for gamma). These results are summarized in Fig. 2b. While ECoG activity during the task was correlated across subjects in the alpha and high gamma bands, this was not the case for the beta (12–30 Hz, 1 location) and low gamma (35–50 Hz, 17) frequency
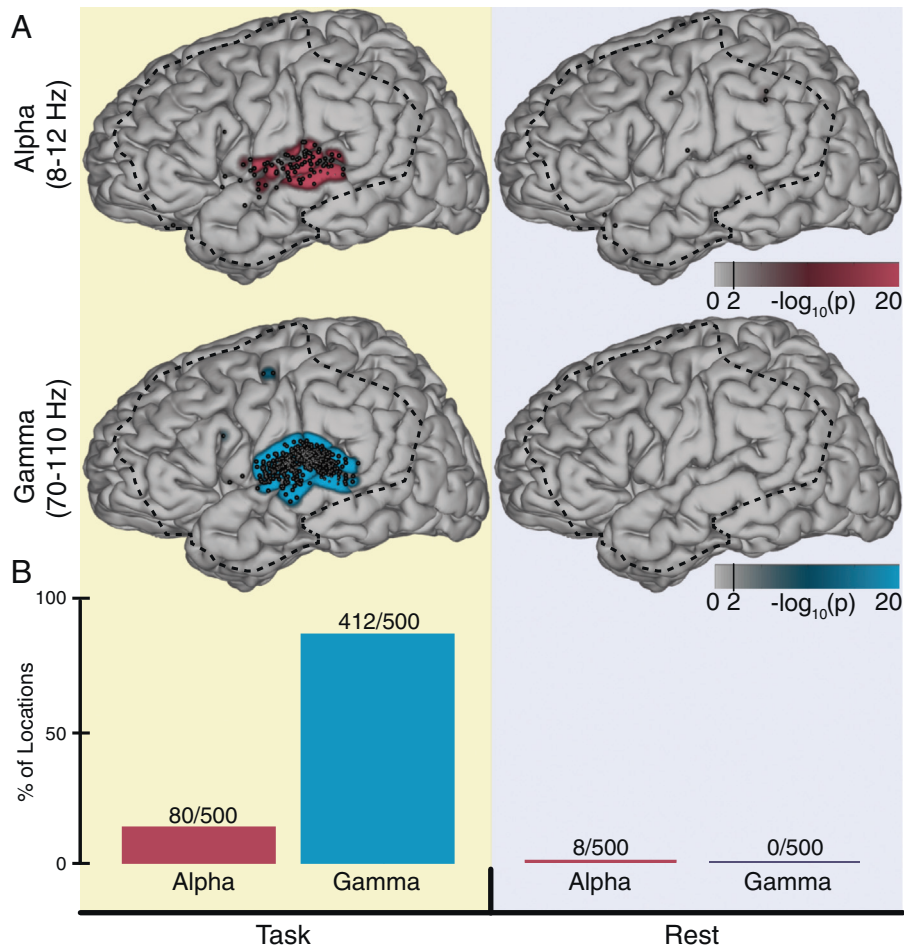
Fig. 2. Intersubject correlation analysis. (A) Topographical distribution of accumulated negative log of the significance of the ISC values during the task (left panels) and rest (right panels) conditions for ECoG activity in the alpha (top row) and high gamma (bottom row) bands. Values larger than 2 are statistically significant at a confidence level of 99% (see vertical line in color bars). (B) Number of locations with significant ISC values at each frequency band and for task (left) and rest (right) and the total number of significant locations (277). The dashed lines on the brain topographies outline the spatial coverage of our intersubject analyses.

bands (see Suppl. Fig. S1.) It is important to note that our results only minimally depend on the specific metric (i.e., correlation) used here as we obtained very similar results when we used the mutual information metric instead of the correlation metric.

Temporal relationship

In addition to investigating the spatial relationship of locations whose alpha or high gamma activity was related to auditory processing, we also established the temporal relationship across alpha activity, high gamma activity, and the song's sound intensity. For this, we first averaged the time courses of alpha and high gamma activity across all locations where activity was significantly correlated across individuals. Then, we correlated the three averaged time courses of alpha activity, high gamma activity, and the song's sound intensity with each other. The results are shown in Fig. 3 and reveal a significant negative correlation between alpha and high gamma activity ($r = -0.52$), indicating that high gamma activity augmentation in auditory cortical areas during auditory processing is accompanied by alpha activity suppression (see also Crone et al., 2001). We also found significant positive correlation between high gamma activity and sound intensity ($r = 0.37$), in line with our previous findings (Potes et al., 2012), as well as significant negative correlation between alpha activity and sound intensity ($r = -0.3$). ($p < 0.0001$, Spearman's correlation, n = 1800.) The scatter plots shown in Fig. 3b further illustrate these relationships. Importantly, Granger causality analyses revealed that high gamma activity predicted alpha activity ($p << 1e^{-8}$), but not vice versa, and cross-correlation analysis indicated that the onset of high gamma activity preceded alpha activity by 280 ms.

Causal relationships

Finally, we tested all possible combinations of locations across subjects (i.e., 630,800) for causal relationship in the alpha and high gamma frequency bands. This analysis did not identify any significant connection for either the task or the rest conditions in the alpha frequency band, nor for the rest condition in the high gamma frequency band. Yet, it identified 68 significant connections for the task condition in the high gamma frequency band (Fig. 5a). After removing spurious connections and identifying the most salient connections, these results were reduced to 10 connections (Fig. 5b). We did not identify any significant connection for the task or rest condition in any of the other frequency bands (ie beta and low gamma) (See Suppl. Fig. S2). It is

remarkable that out of 630,800 possible connections, the 10 statistically significant connections are all in line with current understanding of cortical auditory processing. Furthermore, the negative results in the rest conditions suggest that our results reflect a highly robust account of the most salient causal relationships between different brain regions involved in auditory processing. Our final results suggested causal relationships of high gamma activity between distinct locations in early auditory pathways within superior temporal gyrus (STG) and posterior STG, between posterior STG and inferior frontal cortex, and between STG and premotor cortex (Fig. 5b). Thus, our results provide electrophysiological verification of long-standing hypotheses about the key functional connections related to auditory processing. At the same time, they also highlight functional connection directly from areas close to early auditory cortex to a distinct location in superior parts of premotor cortex, which have been suggested in fMRI studies (Grahn and Rowe, 2009). Because our results did not reveal music-related alpha activity in the same location, they suggest that that functional connection may be realized by cortico-cortical projections rather than common driving input from subcortical structures such as the thalamus.

Discussion

The role of alpha and high gamma activity in auditory processing

In the present study, we identified the ECoG activity in the alpha and high gamma band that is related to auditory processing of a complex natural auditory stimulus. We also characterized their spatial, temporal, and causal relationships, and related the results to established understanding of the physiological origin of alpha and gamma activity, and current understanding of central auditory processing. From an anatomical perspective, recent animal and human research suggests that signals related to auditory input are relayed from the medial geniculate nucleus of the thalamus to auditory core areas that include primary auditory cortex and adjacent areas where they are processed to extract low-level aspects of auditory stimuli (e.g., sound intensity). Auditory signals then travel from core areas to higher-order areas (e.g., anterior and posterior parts of the STG) to process more complex aspects of auditory stimuli (e.g., timbre, pitch, or melody).

From a functional perspective, there is substantial evidence that brain oscillations in the alpha band might reflect neural interactions between the thalamus and the cortex (Fig. 4a) (Hughes and Crunelli, 2005; Lopes Da Silva, 1991; Lopes Da Silva et al., 1973), and recent
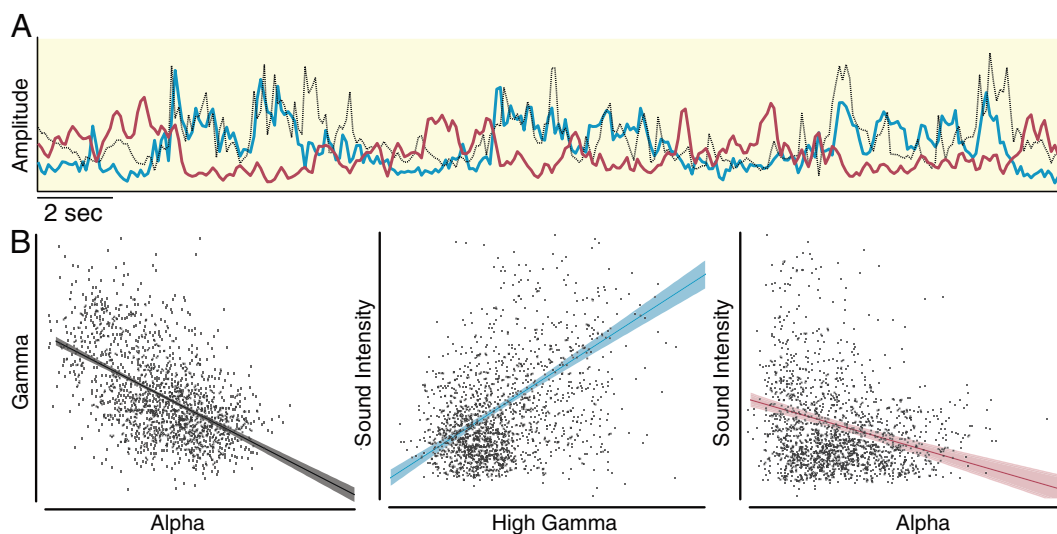
Fig. 3. Temporal relationship between alpha, high gamma, and sound intensity. (A) Representative part of the time course of the sound intensity (black trace) and the average time course of ECoG gamma (blue trace) and alpha (red trace) activity. (B) Scatter plots illustrate the relationship between these three variables for all data points, as well as regression lines and their 95% confidence bands.
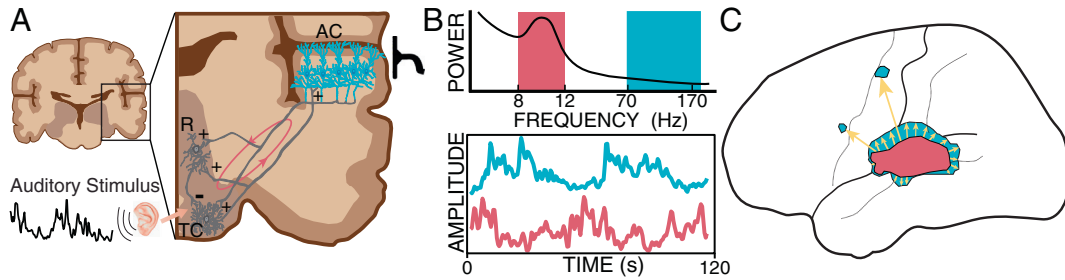
Fig. 4. Relationship between anatomy of auditory processing, current understanding of ECoG physiology, and our results. (A) Auditory pathways between the medial geniculate nucleus of the thalamus and primary auditory cortex. Thalamic neurons (i.e., thalamo-cortical (TC) and reticular (R) neurons) are shown in gray, auditory cortex (AC) neurons are shown in blue, and their interactions are shown in red. (B) Top: Exemplary illustration of typical power spectral density of ECoG signals. Activity in the alpha (8–12 Hz) band, indicated by the red band, reflects thalamocortical interactions. Activity in the gamma (70–110 Hz) band, indicated by the blue band, indexes activity of local populations of neurons. Bottom: Average time course of the first 120 sec of ECoG activity. The blue trace gives gamma activity — the red trace gives alpha activity. (C) Outline of areas with significant ISC values in the alpha and gamma ECoG amplitudes given by the results in Fig. 2. Taken together, our results are consistent with the hypothesis that auditory information reaches the cortex in areas close to auditory cortex, from where they are communicated to peri-sylvian and distinct frontal cortical locations (see illustrative yellow arrows).

experimental evidence in animals is beginning to confirm the important role of thalamic modulation of cortical activity (Haegens et al., 2011; Saalmann et al., 2012). This modulation of the cortex, reflected by augmentation or suppression of the power in the alpha band (van Dijk et al., 2010), might be the mechanism that facilitates transfer of information to task-related brain areas by inhibiting neural activity in task-unrelated areas. Other studies have suggested that brain activity in the high gamma band reflects the firing rate of the cortical neuronal population beneath each electrode (Cardin et al., 2009; Miller, 2010; Miller et al., 2009; Ray and Maunsell, 2011). This view is supported by many studies that have defined strong temporal or spatial relationships of gamma activity recorded at specific locations with specific aspects of motor, perceptual, or cognitive function (Crone et al., 1998, 2001; Kub'anek et al., 2009; Potes et al., 2012; Schalk et al., 2007).

Integrating this anatomical and functional evidence, one may expect to find task-related activity in the alpha band only close to core areas (i.e., areas that have thalamo-cortical connections), and task-related activity in the high gamma band not only in core areas but also in higher-order areas (because all those cortical areas are presumed to be involved in auditory processing). Similarly, causal interactions between different cortical sites should be identified primarily between the gamma band and not the other frequency bands. Our results provide the first direct electrophysiological confirmation of these expectations.

The locations of significant alpha-ISC values highlighted core areas (Fig. 4c), whereas the locations of significant gamma-ISC values highlighted not only core areas but also other cortical areas that have been proposed to be activated in established cortical auditory models (Griffiths and Warren, 2002; Hackett, 2008; Kaas and Hackett, 1999; Zatorre and Belin, 2001; Zatorre et al., 2002, 2007). Our functional connectivity analyses identified significant causal interactions exclusively at high gamma but not at other frequencies. Cortical interactions at high gamma (see Fig. 5) were generally consistent with current understanding of cortical auditory processing. Our results are consistent with the hypothesis that thalamo-cortical projections transmit auditory information from the thalamus to early auditory cortex, from where cortico-cortical projections relay the results to other perisylvian areas to extract complex auditory features (Kumar et al., 2007; Zatorre et al., 2007; Zhang et al., 2004). Specifically, previous studies have shown that neurons in the medial geniculate nucleus of the thalamus send auditory information to the cortex through projections that terminate in primary auditory cortex (Steriade et al., 1990). In addition, neurons in auditory cortex have projections back to the thalamus. Our results identified significant alpha-ISC values only in locations close to primary auditory cortex, and thereby link anatomical structures with thalamocortical connections to oscillatory electrophysiological activity and its hypothesized originating mechanism (Figs. 4b, c). In addition, our results identified significant gamma-ISC values in larger perisylvian areas that have previously been implicated in auditory processing (Alluri et al., 2012; Griffiths and Warren, 2002; Hackett, 2008; Zatorre and Belin, 2001; Zatorre et al., 2002, 2004, 2007). Together with our findings that high gamma and alpha activity are negatively correlated, and that high gamma activity predicts alpha activity, our results support the hypothesis that activity in the alpha band reflects interactions between the thalamus and the cortex (Hackett, 2008; Saalmann et al., 2012; Zatorre et al., 2007), and that these interactions are driven by local neuronal activity in early auditory cortex.

Implications

The present results advocate the use of ECoG and more natural paradigms to obtain a comprehensive picture of auditory processing. First, our approach provides a novel, robust, and very specific method to identify the most common aspects of task-related brain activity, which is currently typically evaluated within subjects by either comparing brain activity during a task to brain activity during rest, or by relating
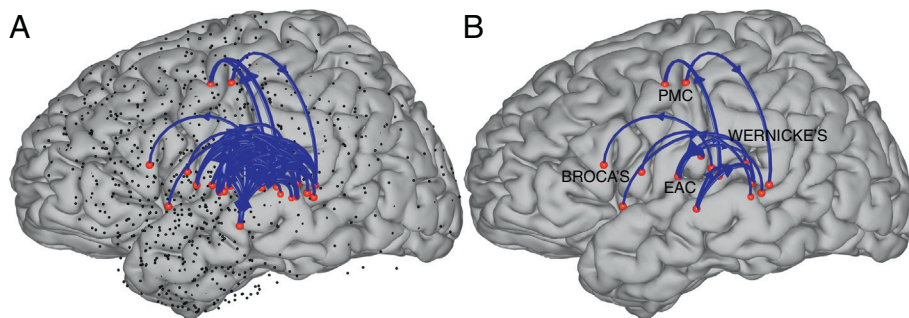
Fig. 5. Intersubject Granger causality analysis. Causal relationships of activity in the high gamma band recorded during listening to music and between different pairs of electrode locations. Across all possible 630,800 electrode combinations, only 68 connections were significant at $\alpha = 1.58e^{-8}$ after Bonferroni correction (A). These connections were further reduced to the ten most salient 10 connections (B). See text for details.

brain activity to a specific aspect of the task (e.g., sound intensity, kinematic parameter). Second, the approach implemented here provides the basis for functional rather than anatomical co-registration of brains of different individuals of the same or even different species (Mantini et al., 2012). Third, our results suggest that high gamma activity and alpha activity are negatively correlated, and that high gamma activity predicted alpha activity and preceded it by 280 ms. Hence, higher gamma amplitudes, which have been shown to be related to higher stimulus intensity (Potes et al., 2012), lead to decrease in alpha amplitudes presumably related to an increase in cortical excitability. This evidence provides a link between higher stimulus intensity and a resulting higher cortical excitability. The significant correlation between high gamma activity and sound intensity (i.e., $r = 0.37$), and between alpha activity and sound intensity (i.e., $r = -0.3$) suggests that low-level perceptual mechanisms, such as those involved in processing sound intensity, might be the common source across subjects. This notion of a universal brain representation for a specific auditory stimulus has also been demonstrated in the EEG literature (Schaefer et al., 2011).

Current experimental limitations

The results presented here are encouraging and could not be readily derived with other neuroimaging or processing techniques. However, our results do rely on electrode grids that have been implanted for the localization of epileptic foci, which typically originate from a single hemisphere. Thus, grid coverage is incomplete and variable across subjects. Hence, we could not investigate brain lateralization of acoustic processing. We also acknowledge that there are some interpersonal differences in the ECoG responses that could be related to the patients' clinical and cognitive states as well as the patients' music preference, cultural background, and musical training. Despite these notable issues and interpersonal differences, the results presented here or in similar ECoG-based studies are usually consistent with expectations based on the neuroanatomy or on results from other imaging modalities.

Future research questions

The present study provides new information about the neural mechanisms engaged in music processing, but also raises a number of important questions. Our results suggest an important interplay between cortical and thalamic activity. Investigation of this interplay would necessitate simultaneous recordings from the thalamus and from different areas of the cortex, and experimental manipulations that modify external or internal parameters (e.g., stimulus intensity, stimulus modality, or attention). Our data-driven results determined the cortical locations involved in auditory processing. However, their functional relevance, in particular regarding the location in superior premotor cortex, is currently unclear. The functional relevance of the causal relationships between different brain areas is currently largely undefined. For example, it is possible that the functional connection between auditory cortex, Broca's area, Wernicke's area, and premotor cortex (Fig. 5b) may be related to the processing of lyrics in the music. As another example, it is possible that the functional connection between STG and premotor cortex may be related to the perception of beat, as shown by Grahn and Rowe (2009). Finally, our methods transform multi-subject data into common and readily interpretable representations using a rigorous processing and statistical framework. Thus, this approach could form the basis for studies addressing questions that could not be answered with previous subject-specific analytic methods.

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