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Understanding the functional connectivity of the brain is of substantial importance for basic and translational neuroscience, but existing techniques to derive this functional connectivity have important limitations. The goal of this proposed project is to develop methods that support direct and objective assessment of functional connectivity in high-resolution electrophysiological brain signals. The objective is to provide the methodological basis for construction of the most detailed functional connectivity maps generated to date.

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Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):	0.00
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Project Abstract (from application)

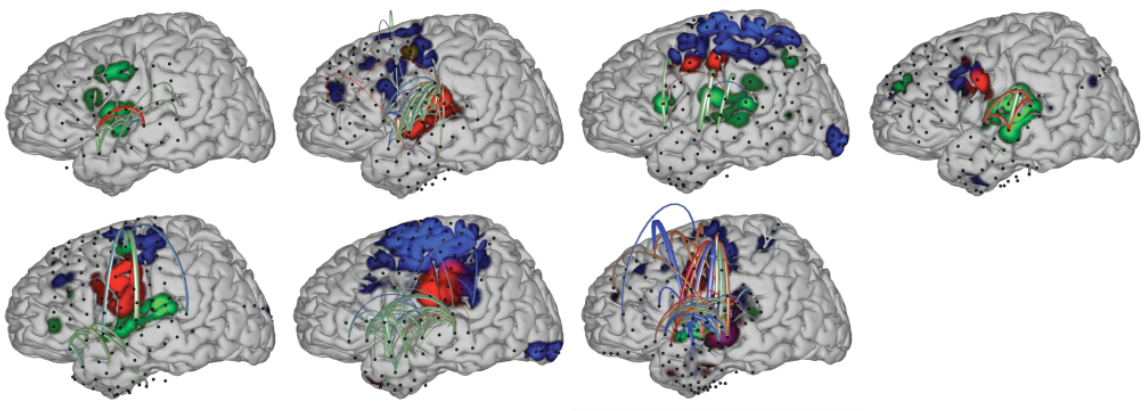
Understanding the functional connectivity of the brain is of substantial importance for basic and translational neuroscience, but existing techniques to derive this functional connectivity have important limitations. The goal of this proposed project is to develop methods that support direct and objective assessment of functional connectivity in high-resolution electrophysiological brain signals. The objective is to provide the methodological basis for construction of the most detailed functional connectivity maps generated to date.

Project Summary

Our entry point to the project was a dataset of electrocorticographic (ECoG) activity that were recorded while seven people listened to music, a complex auditory stimulus. We set out to develop methods that could accurately establish those functional brain connections that were related to processing of the auditory stimulus.

For a particular set of two brain signal features, functional connectivity can in principle be readily established using existing techniques such as Granger causality. These techniques then need to be applied to all combinations of brain signal features. Because there are usually thousands of such combinations of brain signal features, this raises significant problems of with multiple comparisons. Moreover, extraction of ECoG features and application of Granger causality itself depends on a number of assumptions that are usually violated with brain signals. While all of these issues are well known in their respective fields of statistics and modeling, they are not usually considered in neuroscience. Thus, our initial work included a careful analysis of these assumptions, and the design of analytic procedures that would not violate these assumptions.

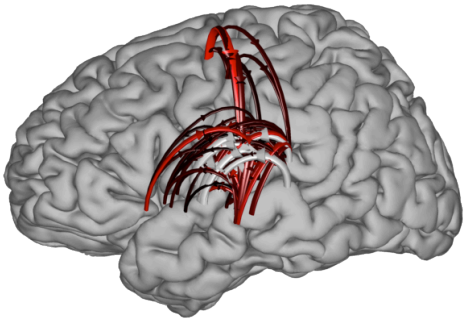
The next step was to establish procedures that can determine that subset of functional connectivity that is in fact related to the task. We began by designing procedures that would establish such task-related functional connectivity by evaluating functional connectivity in relatively short time windows (e.g., 1-sec) and then determining the statistical difference between functional connectivity metrics during the task and during rest, i.e., a within-subject analysis.



The figure on the previous page shows, for each of the seven subjects, those functional connections in ECoG gamma activity (shown in colored arrows) that were statistically different between the task and rest condition. They also highlight those cortical areas that were separately identified as being related to auditory, face motor, or hand motor function (green, red, or blue shading, respectively). Thus, this work produced the first comprehensive analysis of ECoG functional connectivity related to auditory processing. While the results are largely consistent with expectations given by current understanding in functional neuroanatomy, this was not always the case (e.g., the highly statistically significant (blue) connection from temporal to superior prefrontal cortex in the last subject). Careful analyses determined that the likely cause for such potentially incorrect result is the fundamental assumption made by almost all task-related analyses of brain signals that, with the exception of changes inducted by the particular task, the brain is in the same state during the task and during rest, which does not need to be the case.

Based on this consideration, we then evaluated a completely new technique to establish task-related brain signal activation and functional connectivity. This technique tests statistically whether a particular brain signal in one subject during task execution is similar to, or causally related to, a particular brain signal in a different subject. Thus, the only possibility for a brain signal in one subject to be similar to, or causally related to, a brain signal in a different subject is if they are both related to the task. This method had never before been applied to ECoG activity, and never before been applied to functional connectivity. The attached paper describes this method in detail, and applies it to determine task-related activation of ECoG activity. This paper is currently in submission with the Journal of Neuroscience, after favorable review of our presubmission inquiry.

Finally, we applied the same concept to Granger causality that is evaluated across subjects, i.e., asking the question whether one particular brain signal feature in one location in one subject is causally related to one particular brain signal feature in one location in a different subject. To date, this completely novel approach has produced extremely exciting results that we are currently working on summarizing in a journal paper. The figure below shows these results that were derived from all seven subjects. Each arrow indicates statistically significant causal relationship between two areas in the brain. The color/width of each arrow is proportional to the significance. All of these functional connections are in line with expectations based on current understanding of neurophysiology. However, this is the first time that such detailed and meaningful results have been derived directly and objectively directly from brain signals.



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Common Inter-individual Physiology During Processing of Complex Sounds

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Abstract

An enduring scientific and philosophical question has been to what extent the human brain functions similarly across individuals. Whether the electrical activity of neuronal populations at a particular brain location is similar across individuals performing the same task (e.g., listening to music), and how this activity is related to the underlying anatomy, are largely unknown. Here we demonstrate, using subdural cortical recordings in humans, that the instantaneous activity of both alpha (8-12 Hz) and high gamma (70-170 Hz) amplitudes was strongly correlated across individual subjects at neuroanatomical locations implicated in auditory processing. In particular, for ECoG amplitudes in the alpha band, we identified robust intersubject correlation (ISC) values only in areas adjacent to primary auditory cortex, which has been known to receive afferent auditory projections from the thalamus. In contrast, for ECoG power in the high gamma band, we identified robust ISC values not only in areas close to primary auditory cortex, but also in auditory association and premotor cortices, which have been shown to be involved in higher-order auditory processing. These results provide the first neurophysiological demonstration that neural activity associated with auditory processing is conserved across individuals and provide additional evidence for the distinct neurophysiological mechanisms of alpha and gamma activity.

Keywords: auditory processing, electrocorticography (ECoG), thalamo-cortical interactions, alpha and high gamma activity

1. Introduction

Korbinian Brodmann published a map of the human cortex in 1909 (Brodmann, 1909), which revealed that the brain's anatomical organization and cytoarchitecture share similarities across humans. Since then, a large number of studies have associated particular anatomical areas with particular functions. For instance, neuroimaging studies have demonstrated that brain metabolic activity detected over a period of several seconds during the presentation of sounds (Hejnar et al., 2007) and movies (Hasson et al., 2004) indexes areas that are similar across subjects. Further, human lesion studies have shown that damage to Brodmann areas 41-42 or Brodmann area 17 leads to a loss of auditory or visual function (Peretz et al., 1994; Moore et al., 2001), respectively. However, it remains unknown whether the temporal patterns of the neural ac-

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tivity associated with auditory processing are similar across humans, and how this activity may be related to the underlying anatomy. We addressed these two questions using cortical surface recordings in seven human subjects.

2. Materials and Methods

2.1. Subjects and Data Collection

We recorded electrical activity from the surface of the brain (electrocorticography (ECoG)) of seven epileptic subjects (2 men, 5 women) 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 eloquent cortex and the source of the epileptic seizure prior to surgical resection. The implanted electrode grids consisted of platinum-iridium electrodes that were 4 mm in diameter (2.3 mm exposed) and spaced with an inter-electrode distance of 0.6 or 1 cm. The total numbers of implanted electrodes were 98, 96, 83, 109, 58, 120, and 58 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 et al., 2004). ECoG signals were recorded while the subjects were listening to the song, which was 3:10 min long, digitized at 44.1 kHz in waveform 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 clearly contain ECoG signals or had epileptic activity, which left 93, 86, 82, 104, 56, 108, and 57 electrodes for the different subjects. The ECoG signals from these electrodes were submitted to the analyses described below.

2.2. Extraction of ECoG and Sound Features

To determine whether the brain's instantaneous neural activity at a particular location is similar across individuals, we first extracted the time course of two ECoG processes (i.e., amplitudes in the alpha (8-12 Hz) and high gamma (70-170 Hz) frequency bands). Activity in the alpha band is thought to represent thalamo-cortical interactions (Steriade et al., 1990; da Silva, 1991; Zhang et al., 2004), whereas activity in the high gamma band is believed to index the activity of local population of neurons (Miller et al., 2009; Miller, 2010). To extract the time course of alpha and high gamma activity, we filtered ECoG signals from each electrode at each specific frequency band using an IIR band-pass filter, and removed spatial 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, low-pass filtered the result at 5 Hz using an IIR filter, down-sampled the result to 10 Hz, and removed the linear trends from the resulting time series. 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 0.5 Hz and down-sampling the result to 10 Hz. 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 whether the time courses of ECoG alpha and gamma amplitudes were similar across subjects.

2.3. Intersubject Correlation Analysis (ISC)

We first 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).

We then related ECoG activity across subjects. Because the location of the electrodes usually varies across subjects, 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 way, brain activity from one individual was exclusively compared to brain activity from other subjects.) For each such pair of electrodes, we computed the average Talairach coordinate, which resulted in a total of 6852 locations (314±117 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 band, we computed the pairwise Spearman correlation coefficient (intersubject correlation (ISC) r) and its significance (i.e., p-value). We repeated the same procedure for all locations and all 21 combinations of subjects. Next, we determined all locations whose p-values were significantly different than chance at the 0.001 level (i.e., $p < 0.001$ after Bonferroni correction for 6852 locations), and projected the negative logarithm of the corresponding p-values ($-log_{10}(p)$) on to the 3D brain cortical template provided by the Montreal Neurological Institute (MNI).

In addition, we calculated Granger causality (Granger, 1969) to test the hypothesis whether alpha activity statistically causes high gamma activity or vice versa. In this analysis, we used a model order of 10, which was suggested by the Bayesian information criterion (BIC) (Schwarz, 1978). Finally, we determined the lag between activity in these two time courses by identifying the time of the peak of the cross-correlation function.

3. Results

3.1. Relevant Cortical Locations

The black dots and colored areas in Fig. 2a give the locations and corresponding $-log_{10}(p)$ values accumulated across all subjects, and highlight areas wherein neural activity at these two frequency bands was similar across individuals during the task (i.e., listening to music, left panels) as opposed to the control condition of rest (i.e., relaxing on a bed with eyes open, right panels). There were a total of 277 significant locations across all subjects, the two frequency bands, and the task and control conditions. Specifically, for the ECoG recordings during the task condition, 29 locations had significant alpha-ISC values (mean correlation ± standard deviation across the 29 locations: $r = 0.14 \pm 0.01$, max $r = 0.18$) and were primarily located in areas close to primary auditory cortex (Fig. 2a, top-left). Moreover, 246 locations had significant gamma-ISC values ($r = 0.19 \pm 0.05$, max $r = 0.33$) and were not only located in areas close to primary auditory cortex but also over auditory association and premotor areas (Fig. 2a, bottom-left). In contrast, for the ECoG recordings during rest, only 2 (Fig. 2a, top-right) 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 band, this was not the case for beta (12-30 Hz, 0 locations), low gamma (40-65 Hz, 1 location), and very high gamma (250-350 Hz, 0 locations) frequency bands.

3.2. Temporal Relationship

We then investigated the temporal relationship between alpha and high gamma activity, as well as 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 = -0.47), 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= 0.28), in line with our previous findings (Potes et al., 2012), as well as significant negative correlation between alpha activity and sound intensity (r = -0.21). (p<0.0001, Spearman's correlation, n=1800). The scatter plots shown in Fig. 3b further illustrate these relationships. Importantly, Granger analysis assessing information flow 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.

3.3. Spatial Relationship

To answer the second question of this study, we investigated the spatial relationship of these two ECoG processes (i.e., alpha and high gamma activity) with the underlying auditory anatomy. To do this, we related those cortical areas with significant alpha- and gamma-ISC values to the cortical and subcortical areas that are known to be involved in auditory processing. Specifically, previous neurophysiological 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. Theoretical considerations suggested that thalamo-cortical projections (Fig. 4a) contribute to oscillations at low frequencies (6-12 Hz) (Llinás et al., 1999), and recent experimental evidence in animals is beginning to confirm the important role of thalamic modulation of cortical activity (Saalmann et al., 2012). Our results identified significant alpha-ISC values close to primary auditory cortex, and thereby links anatomical structures related to auditory processing to oscillatory electrophysiological activity and its hypothesized origin (Fig. 4b, c). Together with the findings that high gamma and alpha activity are negatively correlated, and that high gamma activity predicts alpha activity, our results are consistent with the hypothesis that activity in the alpha band reflects interactions between the thalamus and the cortex (Zatorre et al., 2007; Hackett, 2008; Saalmann et al., 2012), and that these interactions are driven by activity of local populations of neurons in the cortex.

4. Discussion

This study shows for the first time that the time-course of neural activity recorded during listening to music is conserved across individuals in cortical areas that are implicated in auditory processing — not only in areas that process low-level aspects of auditory stimuli (i.e., areas close to primary auditory cortex) but also in areas that process higher-level aspects of auditory stimuli (i.e., auditory associate and premotor areas).

The results shown here also provide exciting new hints about fundamental mechanisms of auditory processing. Previous studies have provided increasing evidence that oscillations in the alpha band modulate cortical excitability (Saalmann et al., 2012). Other studies suggested that activity in the high gamma band reflects the firing rate of the cortical neuronal population beneath each electrode (Miller et al., 2009; Miller, 2010). Based on these existing hypotheses about the mechanism of these distinct neurophysiological processes, one may expect to find task-related activity in the alpha band only close to auditory cortex, and task-related activity in the high gamma band in all cortical areas related to auditory processing. Our results provide the first direct electrophysiological confirmation of this expectation. Specifically, the locations of significant alpha-ISC values highlight early auditory cortical cortex (Fig. 4c), whereas the locations of significant gamma-ISC values highlight cortical areas that have been proposed to be activated in established cortical auditory models (Kaas and Hackett, 1999; Zatorre and Belin, 2001; Griffiths and Warren, 2002; Zatorre et al., 2002, 2007; Hackett, 2008).

Taken together, our results suggest that thalamo-cortical projections transmit auditory information from the thalamus to early auditory cortex, from where cortico-cortical projections relay the results to other (predominantly peri-sylvian) areas that process more complex auditory features (Zhang et al., 2004; Kumar et al., 2007; Zatorre et al., 2007) (see illustrative yellow arrows in Fig. 4c). Our results also suggest that stimulus-dependent activity in early auditory areas results in delayed feedback to the thalamus. In this view, the thalamus regulates the flow of auditory information into the cortex based on this feedback, such that increases in auditory stimulus intensity result in suppression of alpha activity, which in turn causes an enhancement of cortical excitability.

These results have several important implications. First, our approach provides a novel method to delineate task-related brain activity, which is currently evaluated mostly by comparing brain activity during a task to brain activity during rest within the same subject. 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, the finding that higher stimulus intensity leads to an increase in cortical excitability, and thus to a presumed increase in the consequences of the stimulus, may suggest a general mechanism to prioritize different competing sensory streams, and could thus be useful in explaining different types of stimulus-driven or internally-generated (covert or overt) forms of attention. Finally, the concept that our brains speak a common "language" when they are coupled to the external world suggests that we not only share similarities in our bodies, but also in our minds. (Hasson, 2010).

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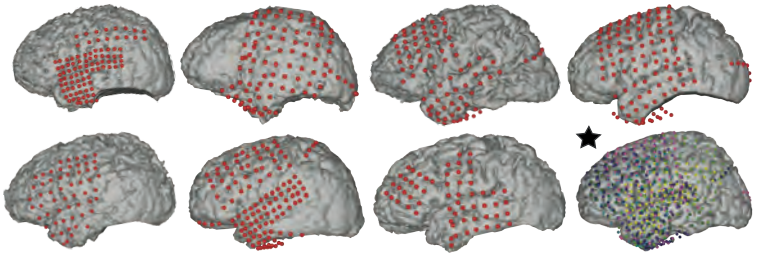

Figure 1: Subject-specific brain models and locations of implanted electrodes. The brain model template marked with a star shows the approximate location of implanted electrodes from all subjects.

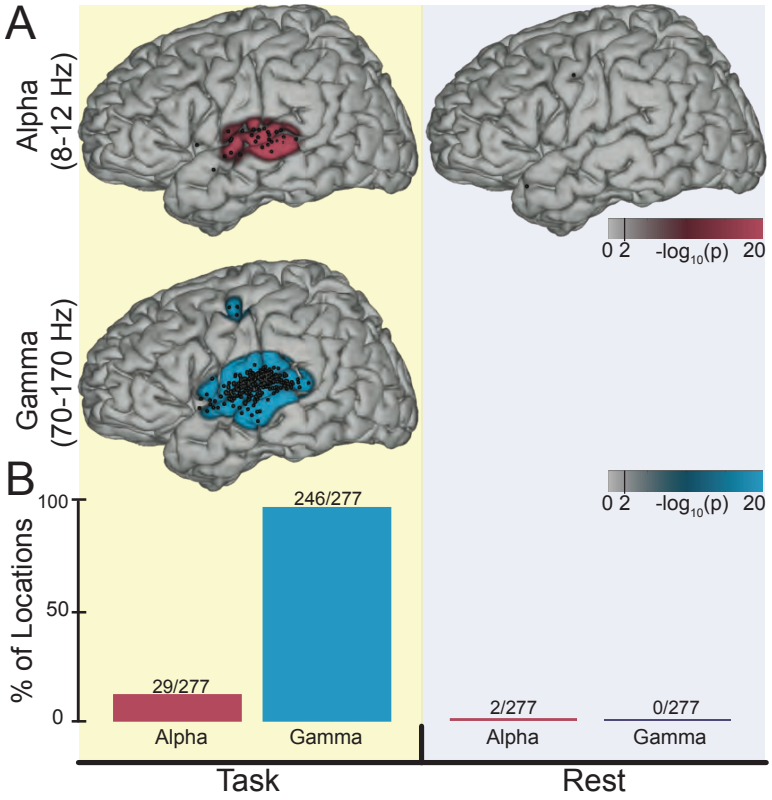

Figure 2: Intersubject correlation analysis. (A) Topographical distribution of accumulated negative log of the significance of the ISC values during the task (left panels) and rest (right panels) conditions for ECoG activity in the alpha (top row) and high gamma (bottom row) bands. Values larger than 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).

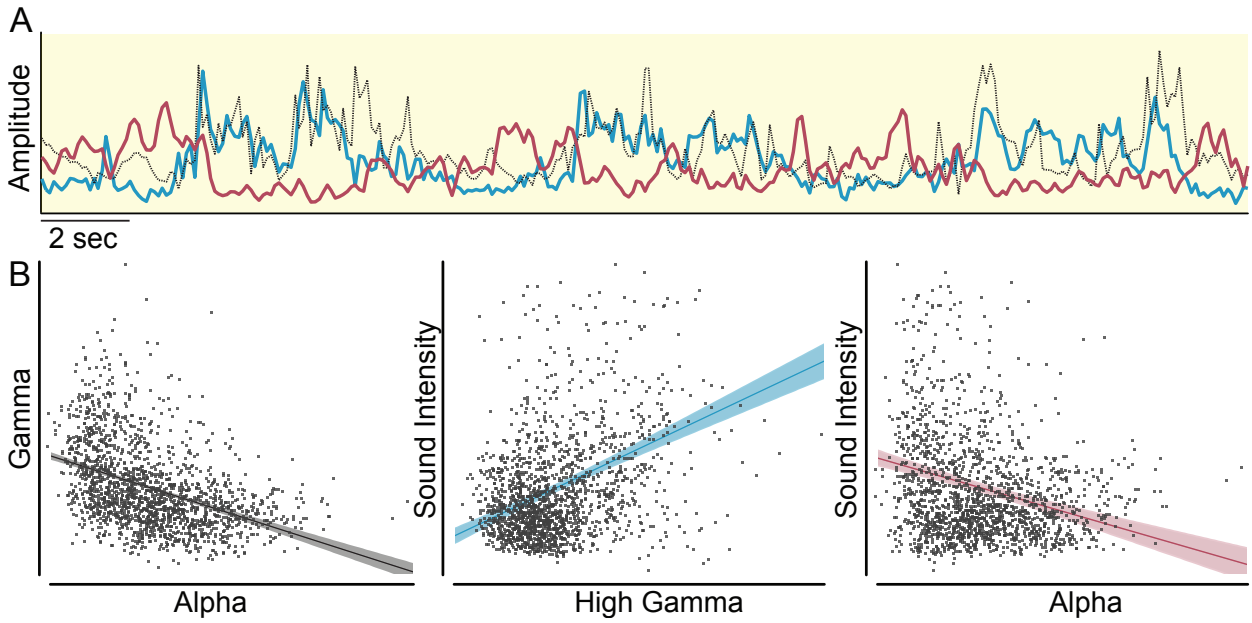

Figure 3: Temporal relationship between alpha, high gamma, and sound intensity. (A) Representative part of the time course of the sound intensity (black trace) and the average time course of ECoG gamma (blue trace) and alpha (red trace) activity. (B) Scatter plots illustrate the relationship between these three variables for all data points, as well as regression lines and their 95% confidence bands.

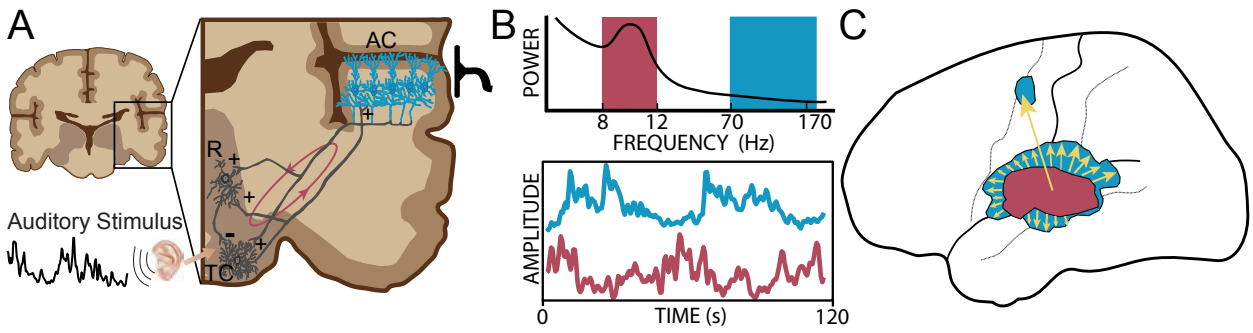

Figure 4: Relationship between anatomy of auditory processing, current understanding of ECoG physiology, and our results. (A) Auditory pathways between the medial geniculate nucleus of the thalamus and primary auditory cortex. Thalamic neurons (i.e., thalamo-cortical (TC) and reticular (R) neurons) are 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 (70-170 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. 1. 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).