Analysis of stimulus-related activity in rat auditory cortex using complex spectral coefficients

Bryan M. Krause†, B.S. and Matthew I. Banks, Ph.D.*

Department of Anesthesiology, University of Wisconsin, Madison, WI53706

*Associate Professor of Anesthesiology
†Research Assistant, Neuroscience Training Program

Address correspondence to:
Matthew I. Banks, Ph.D.
Associate Professor
Department of Anesthesiology
University of Wisconsin
1300 University Avenue, Room 4605
Madison, WI 53706
tel. (608)261-1143
fax (608)263-2592
E-mail: mibanks@wisc.edu

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Running title: Analysis of stimulus-related activity in auditory cortex
The neural mechanisms of sensory responses recorded from the scalp or cortical surface remain controversial. Evoked versus induced response components (i.e. changes in mean versus variance) are associated with bottom-up versus top-down processing, but trial-by-trial response variability can confound this interpretation. Phase reset of ongoing oscillations has also been postulated to contribute to sensory responses. Here, we present evidence that responses under passive listening conditions are dominated by variable evoked response components. We measured the mean, variance and phase of complex time-frequency coefficients of epidurally-recorded responses to acoustic stimuli in rats. During the stimulus, changes in mean, variance and phase tended to co-occur. After the stimulus, there was a small, low frequency offset response in the mean, and modest, prolonged desynchronization in the alpha band. Simulations showed that trial-by-trial variability in the mean can account for most of the variance and phase changes observed during the stimulus. This variability was state-dependent, with smallest variability during periods of greatest arousal. Our data suggest that cortical responses to auditory stimuli reflect variable inputs to the cortical network. These analyses suggest that caution should be exercised when interpreting variance and phase changes in terms of top-down cortical processing.

Neural responses recorded from sensory cortex as stimulus-related surface potentials (SRSPs, e.g. from the scalp or dura) are frequently used to investigate drug effects on perception and cognition and circuit manifestations of neuropathologies (Kane et al 2000; Banoub et al 2003; Roach and Mathalon 2008). A critical issue when interpreting SRSPs is the source of the response itself. SRSPs may consist of a rearrangement of ongoing activity and/or an entirely new, additive component. Because ongoing activity in cortex is large compared to perturbations associated with sensory stimuli, under experimental and diagnostic conditions the stimulus typically is repeated and SRSPs averaged over many trials to capture the 'evoked' response, which reflects additive components precisely time-locked to stimulus onset. However, a
substantial amount of information is discarded when considering only the evoked response, as
cortical responses are quite variable and this trial-by-trial variability may contain information
about the circuit components responding to the stimulus and about their recent activity. Some of
the latter information is captured in the ‘induced’ response, which reflects poorly phase-locked
additive components and rearrangements of ongoing activity that contribute to the variance but

The distinction between evoked and induced responses is of interest because of the
postulated mechanisms generating these components. Evoked activity is thought to arise from
feed-forward propagation of sensory information through the cortical network, and is typically
associated with the response of a static network to input from the periphery. Under this model,
the evoked response results from a linear combination of an invariant additive component with
variable background activity. By contrast, the induced response is thought to arise from stimulus-
related modulation of network parameters (e.g. connection strength, membrane properties)
and/or activation of cortico-cortical or cortico-thalamo-cortical feedback loops (Pfurtscheller and
Lopes da Silva 1999; David et al 2006). By far the most common method for extracting the
'induced' component is to obtain the residual after subtracting the averaged evoked component
from the single trial responses and estimate its power (Kalcher and Pfurtscheller 1995; Klimesch
et al 1998). To the extent that this theoretical dichotomy holds, it is useful for assigning neural
mechanisms to different response components. In reality, however, evoked and induced
responses can become entangled in several ways, complicating their interpretation in terms of
bottom-up versus top-down and static versus dynamic network properties. Nonlinear interactions
between stimulus and ongoing activity can result in non-stationary background activity, and the
evoked response itself can vary from trial to trial. Thus, the residual is a combination of both
components due to processes commonly ascribed to induced components, e.g. reorganization of
ongoing activity and indirect triggering of oscillatory responses, as well as contributions due to
trial-by-trial variability in amplitude and timing of the evoked response (Truccolo et al 2002;

A third contributor to SRSPs is a phase reset of ongoing oscillatory activity. Phase synchrony has been proposed as a useful mechanism for facilitating integration between local neural assemblies (Varela et al 2001). A phase reset produces an average time-domain response in the absence of an additive component. However, commonly used measures of phase reset such as inter-trial coherence (ITC) (Tallon-Baudry et al 1996; Makeig et al 2002; Lakatos et al 2007) are particularly susceptible to confounds due to additive components (Yeung et al 2004; Martinez-Montes et al 2008; Krieg et al 2011), and other methods are susceptible to this confound as well (e.g. Jansen et al 2003; for a more complete discussion, see Krieg et al 2011). Thus, as for evoked versus induced components, phase reset and additive components can become entangled, complicating their interpretation, and the contribution of phase reset to auditory SRSPs remains controversial (Sayers et al 1974; Jervis et al 1983; Makeig et al 2002; Makinen et al 2005; Hanslmayr et al 2007; Sauseng et al 2007; Krieg et al 2011). Here, we present and discuss methods to separate these components that would be useful for simplifying their interpretation.

In particular, we show that trial-by-trial variability in an additive component can be manifested as changes in variance and phase, and thus open to misinterpretation. The primary means by which we show this is via simulations based on our recorded data. The purpose of analyzing simulated responses was twofold: first, these analyses provide a proof of principle that apparent induced and phase reset responses can be produced solely by trial-by-trial variability in the amplitude or latency of evoked components. Second, a crucial benefit of having a generative or forward model of trial-by-trial variability is that we can address key questions about the relationship between the variability of evoked responses and background activity. We estimate the amplitude and latency variability of evoked responses by fitting the simulation model to empirical data features, then show that this variability is state dependent and correlates with
electrophysiological measures of cortical arousal. This would not be possible without a
generative model with which we could estimate the amplitude and latency variations.

Ongoing activity and SRSPs are broadband, and distinct frequency components have been
associated with specific behavioral states, cortical loci and circuit mechanisms (Buzsaki 2006).
Thus, substantial information about underlying cortical processes may be gained via spectral
decomposition, most typically via time-frequency analysis (Jordan et al 1997), which yields
spectrograms that portray the evolution of frequency-specific activity over time relative to
stimulus onset. The utility of analyzing complex spectral coefficients for disentangling evoked,
induced and phase reset response components has been highlighted recently (Martinez-Montes et
al 2008; Krieg et al 2011). In this analysis, the set of coefficients at each time-frequency point
recorded over many trials and plotted in the complex plane was shown to exhibit specific
stimulus-related behaviors depending on the components contributing to the response. We have
adapted this analysis to assist in disentangling changes in mean, variance and phase of spectral
coefficients, and we discuss several ways in which this analysis can still be confounded due to
trial-by-trial variability in the additive component.
Materials and Methods

All experimental protocols conformed to American Physiological Society/National Institutes of Health guidelines and were approved by the University of Wisconsin Research Animal Resources Committee.

Electrode preparation

Epidural electrode arrays were used for all electrophysiological recordings. The arrays consisted of 16 formvar-insulated stainless steel microwires (100 µm diameter; stainless steel 304; California Fine Wire, Grover Beach, CA) separated by 660 µm and arranged in three rows separated by 1000 µm and embedded in a 4.0 mm diameter, 2 mm thick epoxy disc. Wires were cut flush with the surface of the epoxy disc and the disc ground with a curved burr bit to form a concavity that complemented the surface of the brain. The microwires were attached to an electrode interface board (EIB-16, Neuralynx Inc., Bozeman, MT) which provided contact with a small profile connector (0.025 dual row 18 pin connector, Omnetics Connector Corporation, Minneapolis, MN) for the amplifier head stage. The impedance of the electrodes at 1 kHz was typically 50 – 200 kΩ.

Electrode implantation

Sixteen female rats 8 – 12 weeks old were surgically implanted with electrode arrays over the left (n = 10) or right (n = 6) auditory cortex. Results from recordings from the right versus left hemispheres were indistinguishable and were pooled for analysis. The surgical procedures were as follows. Anesthesia was induced using isoflurane. Following induction, animals were medicated with midazolam (3 mg/kg, IP, to reduce the anesthetic requirement during surgery), the non-steroidal anti-inflammatory agent ketoprofen (5 mg/kg, SQ, for postoperative swelling and pain), the opiate analgesic buprenorphine (0.05 mg/kg, SQ, for postoperative pain), the local
anesthetic bupivacaine (1 mg/kg, SQ, applied to the injection site and into the left or right
temporalis muscle, depending on the implant site, for perioperative pain). Animals were then
placed in a stereotaxic head holder (Model 1900, David Kopf Instruments, Tujunga, CA).
Anesthesia was maintained with isoflurane at 1.2 – 1.6% mixed with 50% O₂ and 50% room air
applied through a small rodent anesthesia mask, with the exact dosage adjusted to maintain an
adequate surgical level as determined by immobility and lack of response to toe pinch. Animals
were hydrated via subcutaneous injections of ~2 ml 0.9% saline, and ophthalmic ointment was
applied to prevent dehydration of the cornea. The animal’s body temperature was monitored
using a rectal probe thermometer, and was maintained at ~37°C throughout the surgery by
wrapping the animal in a warm water blanket.

The fur over the dorsal skull was removed with a clipper and the skin disinfected with
iodine solution and alcohol. An incision was made in the scalp overlying the dorsal surface of the
skull along the midline, the skin retracted to expose the skull, and subcutaneous tissue and
periosteum retracted laterally. Membranous tissue was removed from the skull using a scraper.
Self-tapping stainless steel bone screws (1.17 mm diameter; Fine Science Tools, Foster City,
CA) were placed in the skull in the ipsilateral frontal, contralateral parietal and ipsilateral
occipital bones to assist in anchoring the electrode and interface board. A silver wire was
attached to the screw in the parietal bone and served as a reference electrode. The ipsilateral
temporalis muscle was dissected away from the skull and retracted laterally and ventrally using a
three-pronged retractor to expose the skull ridge. Care was taken to minimize damage to the
temporalis muscle to facilitate recovery after the surgery. A hole 4 mm in diameter was made in
the temporal bone centered over the auditory cortex using a trephine (#18004-50, Fine Science
Tools, Foster City, CA) while leaving the dura intact. Published stereotaxic coordinates of
auditory cortex in the rat were used to determine the center of the craniotomy (Doron et al, 2002).

The multielectrode recording array was lowered onto the dura and covered in dental acrylic, and the electrode interface board cemented onto the top of the skull using dental acrylic to form a head cap. Buprenorphine (0.05 mg/kg, SQ, every 12 hours) and ketoprofen (5 mg/kg, SQ, every 24 hours) were administered for three days postoperatively for pain.

**Electrophysiological recordings**

Animals were allowed to recover one week before their first recording session. Animals were placed in a home-made acrylic enclosure (length x width x height = 24 x 18 x 12 cm) inside a sound attenuation chamber (Industrial Acoustics Company, Inc., Bronx, NY). A small speaker (TDT-ES1, Tucker Davis Technologies, Alachua, FL) was mounted on the top (‘ceiling’) of the enclosure, oriented towards the animal. The speaker was calibrated using a microphone (#4016, ACO Pacific, Inc., Belmont, CA) placed approximately 4 cm from the speaker, and stimuli presented at approximately 75 dB SPL assuming the animal’s head was this distance from the speaker. Speaker output varied by ±3 dB SPL over the range 10 – 20 kHz. A sixteen channel preamplifier on a flexible tether (HS16, Neuralynx Inc., Bozeman, MT) entered the enclosure and was attached to the animal’s head. The animal was able to move freely in the enclosure. Since the animal was unrestrained, actual stimulus levels on each trial varied slightly.

Free-field stimuli were applied using software (RPVDX, Tucker-Davis Technologies, Alachua, FL) triggered by the electrophysiological recording software (pClamp v8.2, Molecular Devices, Sunnyvale, CA). Stimuli consisted of 250 ms FM sweeps (10 – 20 kHz), presented every 8 seconds for a period of one hour. We note that this intertrial interval is long relative to most studies in which shorter, nonrandom inter-trial intervals result in more predictable stimulus times and possibly minimize endogenous sources of response variability. We observed considerable variability of responses during the initial portion of the recording session as the animals became acclimated to the environment, and the data presented here represent the final
100 trials from each recording session. Sporadic remote video observations during this period indicated that the animals typically were awake but immobile during this time period, but we did not verify the animal’s behavioral state on a trial-by-trial basis. Data were pooled across multiple recording sessions (n = 2 – 7 recording sessions for each animal, one session per day). Responses were bandpass-filtered at 0.1-3000 Hz, amplified 2500X (Lynx 8, Neuralynx, Tucson, AZ) and digitized at 6.25 kHz (Digidata 1322A, Molecular Devices, Sunnyvale, CA). Each trial consisted of a single stimulus presentation presented at time $t = 0$. For each trial, data were collected for 3200 ms, beginning 658 ms before the stimulus.

**Analysis of electrophysiological data**

Recorded auditory responses were averaged, and the channel with the shortest latency and largest amplitude response (i.e. largest root-mean-square power computed during the time window $0 < t < 300$ ms) was assumed to be over primary auditory cortex and was chosen for analysis. We will refer to the single trial responses as $y_{i,k}, i = 1..L, k = 1..N_{\text{Samples}}$, where $L$ is the number of trials and $N_{\text{Samples}}$ is the number of sampled data points in a trial. Two criteria were used to reject trials contaminated by electrical or mechanical artifacts. The first criterion eliminated trials during which the headstage amplifier saturated following mechanical impact, e.g. with the walls of the recording chamber: $\mu_i > \mu_{\text{Crit}}$, where $\mu_i = \sum_{k=1}^{N_{\text{Samples}}} y_{i,k} / N_{\text{Samples}}$ and $\mu_{\text{Crit}}$ was set to 1 mV. The second criterion eliminated trials that had large spurious electrical and mechanical artifacts: $\sigma_i > \sigma_{\text{Crit}}$, where $\sigma_i = \sqrt{\sum_{k=1}^{N_{\text{Samples}}} (y_{i,k} - \mu_i)^2 / (N_{\sigma} - 1)}$, computed over the portion of the trial excluding the window $0 < t < 1000$ ms (so as not to exclude trials due to unusually large responses), $N_{\sigma}$ is the number of sample points in the computation, and $\sigma_{\text{Crit}}$ was set to 0.25 mV. In all experiments, $\leq 5\%$ of the trials were rejected under these criteria.
**Time-frequency analysis**

We used time-frequency analysis to gain a detailed view of how specific frequency components contributed to the stimulus-related response, and how the stimulus-related changes in these components related to ongoing activity. Time-frequency analysis of neural activity recorded over auditory cortex was performed using short-term Fourier transforms (STFT) for five frequencies from 3 to 16 Hz and continuous complex Morlet wavelet transforms (5 cycles) for frequencies from 16 to 300 Hz. STFTs were implemented by first down-sampling the data by a factor of 4 (sample interval = 0.64 msec), then tapering the data with a Hamming window and computing sliding Fourier transforms with window width of 512 points and window overlap of 496 points. This choice of window width was a compromise between time and frequency resolution, and determined the minimum analysis frequency of 3 Hz. For the analysis of Figure 11 in which we explored the state-dependence of variability in the additive component of the response, we also calculated the coefficients at ~1.5 Hz by doubling the size of this window to 1024 points. Pre-stimulus delta power for this analysis was then calculated by averaging the power at $f = 1.5 \text{ Hz}$ and $f = 3 \text{ Hz}$. Wavelet transforms were implemented as in (Jordan et al 1997), with 35 frequencies spaced exponentially to ensure 90% overlap in the pass band of adjacent Morlet filters. Transforms were computed for each trial for the initial 16384 data samples (2621 ms). The frequency boundary (16 Hz) at which we transitioned from STFT to wavelet analysis was chosen based on the time resolution of the method, which was 164 msec for the STFT analysis and $\leq 164 \text{ msec}$ (and improving with increasing frequency) for the wavelet analysis.

Statistical analysis of wavelet and STFT data was performed using a recently described method that performs tests on the complex coefficients computed on each trial for each
Briefly, the time-frequency analysis yields a complex valued coefficient $z_i(t,f)$ on the $i^{\text{th}}$ trial at each time point and for each frequency. At any time point, these coefficients can be visualized as points or vectors in the complex plane, specified by their magnitude and phase. In the pre-stimulus period, ongoing activity is characterized by coefficients whose magnitudes and phases are randomly distributed and over many trials will form a cloud centered at the origin with zero mean and a uniform distribution of phases. The radius of the cloud, which is related to its variance, represents the amplitude of ongoing activity for that frequency component at that time point. A sensory stimulus may alter this ongoing activity, and thus this cloud of coefficients, in three ways. First, evoked activity describes new ('added') activity at a particular frequency that is time-locked to the stimulus onset. Evoked activity is represented in the complex plane as a shift of the complex coefficients in the direction of a vector representing the additive component's amplitude and phase (i.e. its angle with the horizontal axis). Second, an increase or decrease in the magnitude of the frequency component that is not time-locked to the stimulus (i.e. a change in variance) corresponds to induced synchronization or desynchronization of activity. Induced activity will change the variance of the cloud, but will not shift its center away from origin. Note that the terms 'synchronization' and 'desynchronization' suggest a simple reorganization of extant neuronal activity, but could also involve an increase or decrease in activity levels (i.e. more or fewer neurons participating) as long as those changes are not time-locked to the stimulus. Finally, if the stimulus does not evoke additional activity but instead reorganizes the ongoing activity in the cortical network, i.e. triggers a phase reset, the coefficients will have nonrandom phase, but the magnitude of the distance from the origin to each point will be unchanged from the pre-stimulus
condition. The stimulus may trigger evoked, induced and/or phase reset responses simultaneously. Among the several ways we will measure the average properties of these complex coefficients, there are two that are distinct but easily confused. The complex mean ('mean') is the mean of all the points in the cloud, taking into account their directions from the origin. Stimulus-related changes in the mean are usually associated with additive response components, but the mean can also be changed by phase reset. Synchronization and desynchronization (i.e. increases and decreases in the variance of complex coefficients) refer to amplitude changes that are phase-invariant and have no effect on the mean. By contrast, the power of the coefficients is their magnitude squared, regardless of their phase, and is represented by the average of single-trial power spectrograms. The power is equal to the variance plus the square of the magnitude of the mean. Thus, both additive and synchronizing/desynchronizing effects will appear as changes in the power spectrum, as in both cases the magnitude of the complex coefficients will change, whereas phase resets will not affect power (as any increases in the magnitude of the mean are offset by decreases in the variance). The analysis utilized here is intended to better distinguish between the three mechanisms that could mediate changes in the mean and the power spectrum. It should be noted that while the three mechanisms proposed are independent, their measures (as discussed in the following paragraphs) are not. In the Results section, "Disentangling effects on mean, variance and phase", we estimate the contribution of this interdependence to the observed measures.

The three measures of interest, i.e. mean, variance and phaseSTM, are defined (Martinez-Montes et al 2008) as

\[
\text{mean}(t, f) = \frac{1}{L} \sum_{i=1}^{L} z_i(t, f)
\]

\[
\text{variance}(t, f) = \frac{1}{L-1} \sum_{i=1}^{L} |z_i(t, f) - \overline{z}(t, f)|^2
\]
where $L$ is the number of trials, and $\bar{z}$ is the mean of the coefficients across trials. The mean and variance measures are standard forms; when plotting data, it was often more convenient to plot the square root of the variance (i.e. standard deviation), to which we will refer as $\text{var}^{1/2}$. The phaseSTM measure merits some additional comments. This measure, the second trigonometric moment or STM (Krieg et al 2011), tries to capture any phase concentrations that may occur as the result of a stimulus and attempts to correct for the possibility that phase concentration is due to an additive shift in the complex coefficients by first subtracting the mean and then measuring the uniformity of phase values such that a bimodal distribution results in high values of the measure and a uniform distribution results in low values.

To determine the effects of the stimulus on the mean, variance and phaseSTM measures, we followed the procedure of Martinez-Montes et al (Martinez-Montes et al 2008) and computed 't-like' statistics that compare the value of these measures at any particular point in the time-frequency plane with the pre-stimulus distribution in a comparison window ($t = -550$ to -125 milliseconds) as follows:

$$T\text{-mean}(t, f) = \sqrt{N-1} \left( \frac{\text{mean}(t, f) - \mu_{\text{mean}}(f)|_{\text{comparison}}}{\sigma_{\text{mean}}(f)|_{\text{comparison}}} \right)$$

where $\mu_{\text{mean}}(f)$ and $\sigma_{\text{mean}}(f)$ are the mean and standard deviation of $\text{mean}(t,f)$ computed across trials over the time window spanning the comparison region and $N$ is the number of points in the comparison region. The t-variance and t-phaseSTM statistics are computed in an analogous manner. These statistics are called ‘t-like’ because they do not follow the t-distribution, even
though they are computed similarly. Because the distribution of these statistics is not known a priori, we tested the significance of these effects by comparing the computed t-statistics with a null distribution computed using data from the pre-stimulus period. The major problem with testing the significance of effects on coefficients in the time-frequency plane is correcting for multiple comparisons - there are many hundreds or thousands depending on the time and frequency resolution. We used a procedure similar to Martinez-Montes et al (Martinez-Montes et al 2008) and computed the local false discovery rate (fdr; Efron 2004), i.e. the ratio of the expected distribution (the null distribution normalized to the number of observations) to the data distribution, with a threshold criterion of $q < 0.1$, i.e. bins in the data distribution in which there are $>10$ times as many points as there are in the expected distribution were assumed to be significant. The value of 0.1 is the upper limit on the false positive rate yielded by the analysis over all bins. In practice, this rate is much lower, and is obtained by dividing the tail area of the expected distribution by the tail area of the data distribution, with the tail defined as all bins $\leq$ smallest significant bin on the right side $\leq$ largest significant bin on the left side. Here, these rates varied from 0.0034 to 0.030, with a median of 0.011. Note that wavelet and STFT coefficients were analyzed separately, as their time resolution was different. (For an alternative approach to statistical analysis of time-frequency data, see Kilner et al 2005).

To obtain the null distribution, we computed the t-like statistics on the pre-stimulus data, smoothed this distribution using a Gaussian filter with $\sigma = 2$ bins, and computed the expected distribution by scaling this estimate of the null to match the area of the similarly smoothed data distribution (i.e. the t-like statistics obtained from the post-stimulus data; the portion of the data used for scaling were the bins corresponding to the central 98% of the null distribution). We note that our implementation of the local fdr analysis diverges from that of Efron and Martinez-
Montes et al in our choice of the null distribution. In the original description of this technique, the null distribution was obtained by fitting the middle part of the data distribution, (i.e. the distribution not including the tails) under the assumption that the 'uninteresting' data points are normally distributed and that the 'interesting' data points are only located in the tails. This method is highly dependent on the assumed distribution (e.g., an assumption of normality) and the range of data used to fit the chosen distribution. Fitting to a narrow range of data is likely to result in poor estimates of the null distribution, particularly if the null diverges from the assumed distribution, and fits to a large range of data may inadvertently incorporate 'interesting' data points into the null. By contrast, we know *a priori* that the pre-stimulus baseline period of our data consists entirely of 'uninteresting' points, and thus provides an excellent estimate for the null distribution under the relatively benign assumption that the statistical properties of the null distribution do not change over the ~2 second recording window. Our method also does not require assumptions about the shape of the null distribution, which is unknown for the t-like statistics. We note, however, that this choice is nonstandard and has not been rigorously tested. We also note that different, independent methods for determining statistically significant response components across our dataset (see below) gave very similar results (Figure 6), indicating that the method is sound at least in this context.

To pool data across animals, we compared two methods. In the first, we calculated for each animal the significance at each time-frequency point of changes in the *mean*, *variance* and *phase*STM according to the local _fdr_ method described above, then calculated the fraction of animals exhibiting significant changes at each time frequency point (for *variance* and *phase*STM, we accounted for the sign of the change by coding in each animal at each time frequency point a significant decrease as -1 and a significant increase as +1, adding up these values across animals and then dividing by the number of animals). In the second method, we computed the _mean_,
variance and phaseSTM measures across trials as described above, then tested for significant changes from baseline using the Mann-Whitney U test. Before significance testing, mean and variance measures were normalized at each frequency to $\sqrt{\text{var}}$ of the ongoing activity at that frequency. We used two correction methods for multiple comparisons: the local fdr method described above, and the unweighted Bonferroni correction (i.e. the significance level is adjusted by dividing by the number of simultaneous tests, here the number of points in the time-frequency plane). The two methods yielded very similar results, differing qualitatively only for the phaseSTM measure. Because the Bonferroni method strictly minimizes type I errors (i.e. false positives) at the expense of statistical power, it is considered to be an extremely conservative correction (Shaffer 1995). By contrast, false discovery rate methods are designed to maximize statistical power while setting less stringent control on type I errors (Efron 2004). Thus, it is likely that these two methods provide an upper and lower bound on the occurrence of significant stimulus-related changes in the measures of interest.

All electrophysiological data were analyzed using software written in Matlab v7.11 (Mathworks, Inc., Natick, MA).

**Simulations**

We used simulations to determine the extent to which trial-by-trial variability in the amplitude and latency of an additive component could account for the observed changes in variance. Simulations were specific to each experiment, using ongoing activity and the evoked response from that experiment. For each experiment, we first estimated the spectrum of the ongoing activity just prior to the stimulus by averaging the wavelet transform and STFT data over the time period -0.5<t<-0.1 sec, where the stimulus onset occurred at $t = 0$. Next, for each trial, we simulated ongoing activity by adding sinusoidal components (frequency resolution = 1Hz, $1<f<f_{\text{Nyquist}}$) with phases uniformly distributed over $(0, 2\pi)$ and amplitudes normally distributed over $(\mu = 1, \sigma^2 = 0.5)$ across frequencies and trials. The spectrum of this simulated ongoing activity was matched to the recorded ongoing activity by multiplying each frequency
component by the corresponding magnitude in the ongoing spectrum. For the additive
component, we took the average time-domain response from that experiment from $-0.1 < t < 0.5$
sec and windowed it by a tapered cosine (Tukey) window with $\alpha = 0.05$. This additive
component was then scaled by a normally distributed amplitude factor ($\mu_{\text{amp}} = 1, 0 < \sigma_{\text{amp}} < 2.4$)
added at variable latency ($\mu_{\text{lat}} = 0, 0 < \sigma_{\text{lat}} < 3.0$ ms) to the ongoing activity on each trial. As
expected, the simulated mean measure matched well the recorded mean measure. The variance
measure was a function of $\sigma_{\text{amp}}$ and $\sigma_{\text{lat}}$. We compared the simulation results with the recorded
data by finding the values for $\sigma_{\text{amp}}$ and $\sigma_{\text{lat}}$ that minimized the mean squared error between the
normalized $\text{var}^{1/2}$ for the simulated and recorded data. To simplify this calculation, we evaluated
the $\text{var}^{1/2}$ measure at one time point for each frequency, corresponding to the maximum of the
mean measure during the peri-stimulus time window. Because the frequency components were
logarithmically spaced, the error function was weighted by $1/t^{0.5}$.

Phase resets will appear as increases in the mean measure and will also affect the variance
measure. We used simulations to evaluate the magnitude of this effect, essentially asking
whether the changes in mean and variance could be due to a phase reset whose magnitude
equaled the observed phase concentration (Fig. 10). We simulated ongoing activity as complex
coefficients having real and imaginary parts that are jointly normally distributed with common
variance. To simulate a pure phase reset, the magnitudes of these coefficients were maintained
but their phases concentrated to adhere to a von Mises distribution with variable standard
development. We then computed the complex mean and variance of the phase-concentrated
simulated data, and created lookup tables to relate these mean and variance values to the
$\text{phase}_{\text{STM}}$ measure (Fig. 10A). Finally, we took the median $\text{phase}_{\text{STM}}$ across animals and, using
the lookup tables, computed the expected changes in the normalized mean and $\text{var}^{1/2}$ measures
that would occur if they were entirely due to a phase reset producing these $\text{phase}_{\text{STM}}$ values (Fig.
10B).
Results

Ongoing and stimulus-related activity in the time and time-frequency domain

Time-domain responses to acoustic stimuli averaged across trials were similar to epidurally-recorded auditory responses reported previously in rats (Fig. 1A) (e.g. Ruusuvirta et al. 1998; Lazar and Metherate 2003; Nakamura et al. 2011), with a short latency component that peaked between 10 and 20 ms after stimulus onset, followed by a series of peaks and troughs lasting for several hundred milliseconds. As previously described for cortical sensory responses, we observed a large amount of trial-by-trial variability; in many cases, single trial responses were only as large as or were even dwarfed by ongoing activity (Fig. 1A). As we describe below, this variability has implications for interpreting responses in terms of evoked and induced components. We used time-frequency analysis to investigate ongoing and stimulus-related activity in more detail.

Time-frequency spectra of single trial responses (Fig. 1B) also exhibited considerable trial-by-trial variability. Mean spectrograms averaged across trials (Fig. 1C) illustrate that power in the pre-stimulus period falls off rapidly with frequency, as expected, and suggest that sensory stimuli evoke a strong, broad-band, transient response that terminates with stimulus offset (Fig. 1C). To help visualize these features, we averaged these spectrograms across specific time windows before and after stimulus onset to yield the average spectral content of ongoing and stimulus-related cortical signals (Fig. 2). Mean pre-stimulus spectra were similar in shape across animals, but spanned an order of magnitude in overall power. Spectra from individual animals and spectra averaged across animals showed that ongoing activity rarely exhibited distinct peaks that would correspond to strong oscillations; instead, the power of ongoing activity fell off as \( \sim 1/f^2 \) (Fig 2Ai, dashed line).

Power spectra averaged across trials and across several time windows during and following the stimulus (20 msec-wide windows centered at \( t = 25, 125, 250 \) and 500 ms, where stimulus
onset is at $t = 0$ ms and offset is at $t = 250$ ms) are illustrated in Figure 2Aii-v; the power spectrum of ongoing activity averaged across animals is replotted in each panel for comparison (dotted line). The relative increase in power due to the stimulus was computed by taking the ratio of the mean spectrum in each time window to the mean ongoing spectrum (Fig. 2B). Relative to ongoing activity, auditory stimuli triggered a rapid increase in power that grew in magnitude with frequency, and was particularly pronounced at ~20 and ~200 Hz (Fig. 2Aii; Fig. 2B, thick solid line). Midway through and at the end of the stimulus, there was a relative increase in low frequency components, while the high frequency components had largely returned to baseline (Fig. 2Aiii,iv; Fig. 2B, dashed and dotted lines). A small relative decrease in power was observed following stimulus offset at ~10 Hz (Fig 2B, dot-dashed line). In general, however, analysis of relative increases in these power spectra cannot resolve the contribution of evoked versus induced response components. Below, we will dissect these contributions using a more sensitive analysis method of complex spectral coefficients.

**Complex coefficients in the time-frequency domain**

As illustrated in Figure 1, there was marked trial-by-trial variability in ongoing activity and the responses to acoustic stimuli. This variability can be visualized by plotting the magnitude and phase of each frequency component on successive trials in the complex plane. In Figure 3, we show the values of complex coefficients of four frequency components (rows, from top to bottom: $f = 100, 30, 10$ and 3 Hz) measured at a single time point ($t = -0.25$ sec; left column) during the pre-stimulus period and at specific times following stimulus onset ($2^{nd}, 3^{rd}$ and $4^{th}$ columns: $t = 0.025, 0.2$ and $0.75$ sec) for all 664 trials from this animal (pooled across 7 recording sessions). In these plots, each point is the coefficient from one trial and one instant in
time plotted in the complex plane. The magnitude of the frequency component is the distance of this point from the origin; the angle this vector forms with the positive real axis is the phase of the frequency component at that instant in time. The mean of the coefficients across trials is indicated by the line emanating from the origin. During the pre-stimulus period (left column), the coefficients have approximately zero mean (i.e. the clouds are centered at the origin). Changes in the mean of the coefficients correspond to an additive component at constant phase at that frequency, i.e. an evoked response. The variance of the coefficients across trials is indicated by the radius of the circle, which is centered at the mean. Changes in the variance correspond to an increase or decrease in the magnitude of that frequency component at random phase, i.e. so-called induced response components. Transient changes in the mean and variance of the coefficients are evident following the stimulus, as indicated by shifts in the centers of the circles (i.e. changes in the mean) and changes in the radii of the circles (i.e. changes in variance). For example, at 10 Hz, there is a large shift in the mean following stimulus onset, with a small associated change in the variance (Fig. 3, 3rd row, 2nd column), while after stimulus offset a small decrease in variance (i.e. desynchronization) is apparent (Fig. 3, 3rd row, 4th column). Stimulus-triggered phase concentrations would appear as deviations from circularity of the data cloud at particular angles relative to the positive real axis. One example is the first post-stimulus time point for the 10 Hz component (Fig. 3, 3rd row, 2nd column). It is evident from these plots that (1) both the mean and variance of the data cloud can be affected by the stimulus, but (2) that they also can be affected independently and (3) that strong phase concentrations, i.e. non-circularity of the data clouds, occur only occasionally and transiently. These three points are illustrated more clearly in Figure 4, which plots the magnitude of the mean, \( \text{var}^{1/2} \) and \( \text{phase}_{\text{STM}} \) measures averaged across trials for these four frequency components as a function of time.
relative to stimulus onset. In this example, changes in mean and variance are tightly linked during the stimulus (0<t<0.25 sec), though for the 3 Hz component the later changes in mean occur without concomitant changes in variance (Fig. 4D). Note also that changes in the $\phi_{STM}$ measure tended to occur near peak changes in the mean.

**Statistical analysis of complex coefficients**

To quantify changes in the distribution of complex coefficients and determine the time course of these changes relative to baseline, we compared the mean, variance and $\phi_{STM}$ values with those recorded in the pre-stimulus period by calculating 't-like' statistics as described in Methods. Because we do not know the distributions of these statistics *a priori*, we tested the significance of these changes by comparing the calculated distributions with a null distribution of t-values computed during the pre-stimulus period (Fig. 5A) using the local fdr measure (Efron 2004; Martinez-Montes et al 2008). Histograms of t-mean (Fig. 5A, left), t-variance (Fig. 5A, center) and t-\phi_{STM} (Fig. 5A, right) values from the null region are smoothed to create null distributions (dashed lines). We used these empirically derived null distributions to determine significance. The corresponding raw (bars) and smoothed (solid lines) histograms of t-values for the post-stimulus data at one specific frequency (9 Hz) are shown in Figure 5B, in which we also plot the expected distributions (dashed lines; see Methods). The underlying assumption of the local fdr technique is that the interesting (i.e. significant) data points are those with t-values that are in the tails of the data distribution, i.e. t-values that are rarely observed in the null distribution. These 'interesting' points are illustrated in Figure 5B (black bars) and their t-values are indicated via color-code in the time-frequency contour plots of Figure 5C. In this experiment, the auditory stimulus triggered a broad-band increase in the mean that for low frequencies lasted
well beyond the stimulus offset (Fig. 5C, left). A broadband increase in variance (synchronization) during the stimulus was also observed, which at lower frequencies was followed by an extended period of desynchronization (Fig. 5C, center). Significant changes in phaseSTM were observed at lower frequencies during the stimulus (Fig. 5C, right). Note that the increases in variance and phaseSTM during the stimulus tended to co-occur with increases in the mean. Below, we show evidence that these correlated (i.e. co-occurring and of the same sign) changes in mean, variance and phaseSTM during the stimulus are likely the result of trial-by-trial variability in the additive (i.e. evoked) component, rather than reflecting independent modulation of ongoing activity or true phase resets, as they are often interpreted.

**Summary across animals**

The method illustrated in Figure 5 for determining significance of stimulus-related effects on mean, variance and phaseSTM is effective for a single experiment, but leaves open the issue of summarizing data across experiments and subjects. Epidural signals can vary widely across subjects in terms of raw power (Fig. 2), potentially complicating statistical comparisons. We compared two approaches to summarizing data across subjects, illustrated in Figure 6. In the first approach, we computed 'significance maps' averaged across animals (Figure 6A; see Methods), representing the fraction of animals showing significant stimulus-related effects at each point in the time-frequency plane. [Note that for the variance map, negative values indicate the fraction of animals showing a decrease in variance.] Key features of the stimulus-related activity are (1) a broadband increase in the mean and an offset response that persists for up to 500 msec at the lowest frequencies analyzed (Fig. 6A, left column), (2) a broadband synchronization that is always shorter than the duration of the stimulus (Fig. 6A, center column), (3) a late
desynchronization for frequencies <30 Hz that lasts for several hundred milliseconds after
stimulus offset (Fig. 6A, center column), and (4) a phase concentration that is significant in a
minority of animals and that is broadband and brief at high frequencies but progressively longer
at frequencies<30 Hz (Fig. 6, right column). Note that using this analysis technique (and unlike
our observations using the power spectra of Figure 2), we are able to detect substantial effects on
spectral coefficients after stimulus offset.

Presentation of data as in Figure 6A demonstrates the location of significant changes in the
time-frequency plane but is not sufficient for describing the magnitude of these effects, and it is
not easy to compare the relative effects across frequencies or between measures using these
plots. Therefore, in Figure 6B we summarize the measures themselves across animals by plotting
the grand median for all points in the time-frequency plane, and in Figure 6C-E we present these
measures after thresholding for significance across animals as tested using a Mann-Whitney U
test at each time-frequency point and corrected for multiple comparisons using local \( fdr \) (Fig. 6C,
E) or the much more conservative Bonferroni correction (Fig. 6D). Values at each frequency are
normalized to the mean of \( \text{var}^{1/2} \) at that frequency during the pre-stimulus period for each
experiment, and then the grand median at each time-frequency point was computed across
animals. For the \textit{mean} measure (Fig. 6B-E, left), a value of 1 indicates an additive component
equal in power to the pre-stimulus ongoing activity. Peaks in the \textit{mean} measure occurred at \( \approx 155 \)
Hz (latency \( \approx 10 \) msec), 50.1 Hz (\( \approx 25 \) msec), 19.2 Hz (\( \approx 35 \) msec) and 9.19 Hz (\( \approx 65 \) msec). The
persistent post-stimulus \textit{mean} component detected in this analysis was less prominent that in the
analysis of Figure 6A, and appeared only at <30 Hz and had a duration <150 msec. In the center
column of Figure 6B-E, we plot the \( \text{var}^{1/2} \) measure normalized as for the \textit{mean} measure, and thus
a value of 1 represents no change compared to the pre-stimulus ongoing activity. Changes in the
variance during the stimulus were highly correlated with changes in the mean (best seen in the expanded view of Fig. 6E; for example compare the high frequency peak >100Hz, as well as the secondary peaks in the gamma and beta range). As in Figure 6A, after stimulus offset there is a late and long-lasting desynchronization in the alpha frequency band (~10 Hz; Fig. 6C&D, center) that is not associated with any changes in the mean. The phaseSTM measure (Fig. 6B-E, right) can take on values ranging from zero to one (and thus needs no normalization), where one represents perfect phase alignment and zero represents uniform phase distribution. On average, we observed values of the phaseSTM measure that were at most ~0.15 (Fig. 6B, right) but were consistent enough across animals to be statistically significant using the local fdr correction (Fig. 6C, E, right) but not the Bonferroni correction. As with the variance measure, these changes in the phaseSTM measure were highly correlated with changes in the mean component. Below, we examine the origin and interpretation of the observed peri-stimulus changes in the variance and phaseSTM measures.

**Disentangling effects on mean, variance and phase**

**Origin of stimulus-related changes in variance.** When interpreting the data of Figure 6, it is important to explore the potential confounds that may be introduced by the entanglement of the mean, variance and phaseSTM measures. For example, two aspects of our data raise the possibility that the observed changes in variance may be due to variability in the timing or amplitude of the additive component, rather than a modulation of ongoing activity expected of an 'induced' response. These aspects relate to the nature of variance changes that would be expected if these changes were due to timing and amplitude variability in the additive component, and are illustrated in Figure 7A. The result of such variability would be a distortion of the data clouds of spectral coefficients at each time-frequency point across trials in two different ways. Variability
in the amplitude of an additive component will result in increased variance, i.e. a bulge in the cloud, in the direction of the mean component vector. This effect is easily understood if one considers the extreme case in which on half the trials the additive component is zero and on half its amplitude is constant and nonzero (Figure 7A, top row). In this case, the data cloud would split into two sub-clouds, and the variance across the whole cloud would be increased.

Importantly, this variance would be correlated with the amplitude of the additive component (Figure 7A, top row). (Note also that such variability would also lead to a phase concentration, and thus a change in the $\text{phase}_{\text{STM}}$ measure. This issue will be discussed in more detail below.)

Variability in timing of an additive component would result in increased variance in the orthogonal dimension. Again, this effect is easily illustrated by considering the extreme case in which on half the trials one latency (i.e. phase) is observed and on the other half a second phase is observed, splitting the data into two subclouds at right angles to the direction of the additive component (Figure 7A, bottom row). Less extreme cases of amplitude and latency variability will lead to smaller effects on variance (not shown), and it should be noted that simultaneous variability in latency and amplitude will have additive effects on the variance, but will mitigate apparent phase concentrations (due to a less distorted data cloud). We will return to this point below.

Previous work (David et al 2006) has shown, based on theoretical considerations, that amplitude and latency variability will have different effects on the mean and variance measures. Introducing trial-by-trial variability in the amplitude of the additive component without changing its average value will result in correlated increases in the variance measure without decreases in stimulus-related changes in the mean measure. By contrast, varying the latency of the additive component on each trial will change its average value, thus decreasing the changes in the mean
measure. However, this effect will be frequency dependent, with larger effects at higher frequencies (Figure 7A, bottom row): if the latency variability is frequency-independent (e.g. $\sigma = 3$ msec), then frequencies with periods comparable to this latency variability will be smeared out and their mean reduced and variance increased, while frequencies with periods much greater will be relatively unaffected. In this case, high frequency components of the mean measure will be transferred to the corresponding frequencies in the variance measure. Our data suggest that both sources of variability contributed to stimulus related changes in variance.

When considering the observed changes in mean and variance illustrated in Figure 6B, we note that these changes were quite similar in their duration and frequency range, as would be expected if the stimulus-related variance changes were secondary to trial-by-trial variability in the amplitude of an additive component. Figure 7B summarizes the co-occurrence of mean and variance changes as measured by the two-dimensional (i.e. time and frequency) cross correlation of changes in mean and variance over the peri-stimulus time window. For both STFT ($f < 16$ Hz) and wavelet coefficients (i.e. $f > 16$ Hz), we observed a significant correlation in all animals (median correlation coefficients = 0.68 & 0.59, respectively).

Although stimulus-related changes in mean and variance tended to co-occur, leading to the correlation illustrated in Figure 7B, the magnitude of changes in variance relative to simultaneous changes in mean was greater for high versus low frequency components, as would be expected if the underlying mechanism was variability in the latency of additive components (David et al 2006). We quantified this effect by measuring $\text{var}^{1/2}$ at one time point for each frequency, corresponding to the time of the peak of the change in the mean measure. The median normalized $\text{var}^{1/2}$ across our dataset is much larger for frequencies above about 100 Hz (Figure
7C), an observation that is consistent with trial-by-trial variability in latency of the additive component contributing to the observed stimulus-related changes in variance (David et al 2006).

To determine whether these two types of variability could account for the observed peri-stimulus changes in variance, we simulated the occurrence of only an additive component, which varied from trial to trial in amplitude and latency, and looked for the effects on the variance and phaseSTM measures. Simulations based on data from one experiment are illustrated in Figure 8.

The top row (Fig. 8A) shows the mean spectrogram (left column), normalized mean and \( \text{var}^{1/2} \) measures (middle columns) and phaseSTM measure (right column). The raw recorded data from this experiment (Fig. 8A) are typical, i.e. the changes in variance and mean are highly correlated during the stimulus (2-D correlation coefficient for the window \( 0<t<0.25 \) sec is 0.73 for \( 3<f<16 \) Hz and 0.52 for \( 16<f<300 \) Hz), but the change in variance at high frequencies is much larger, relative to the mean, compared to lower frequencies. As expected, when we simulate the ongoing activity with an invariant additive component (Fig. 8B), the mean spectrogram and normalized mean measure (left two columns) exhibit an excellent fit to the recorded data, and with no variability included in the model there are no observed changes in variance and phaseSTM (right two columns). We varied \( \sigma_{\text{amp}} \) and \( \sigma_{\text{lat}} \) systematically over a wide range of values and found the best fit of the model to the data by finding the parameter values that minimized the difference between the observed and simulated changes in normalized \( \text{var}^{1/2} \) measure (see Methods). With \( \sigma_{\text{lat}} = 0 \), the best fit of the model occurred for \( \sigma_{\text{amp}} = 1.0 \) (i.e. equal to the mean amplitude; Fig. 8C). This amplitude variability successfully captured key features of the recorded variance changes, i.e. the simulated changes in variance measure were highly correlated with the changes in mean, especially for \( f<100 \) Hz. At higher frequencies, the magnitude of changes in the recorded variance measure was far greater than could be accounted for by amplitude variability.
alone. In addition, the amplitude variability caused an apparent phase concentration, as expected due to the elongation of the data cloud along the direction of the additive vector, and this phase concentration was somewhat larger than observed in the recorded data. When we varied both $\sigma_{\text{amp}}$ (0.8) and $\sigma_{\text{lat}}$ (1.8 ms), we could capture some of the ‘extra’ variance at high frequencies (Fig. 8D), though the observed variance still exceeded that of the model, and because the latency variability caused an elongation in the data cloud in the orthogonal direction, the apparent phase concentration was reduced.

We determined the optimal model parameters by minimizing the difference between the recorded data and the model output over the normalized $\text{var}^{1/2}$ as a function of frequency. The resulting functions for the experiment of Fig. 8A-D are shown in Fig. 8E. We repeated this analysis for each animal and found that the median across animals of the optimal variability was 0.9 ($1^{\text{st}}, 3^{\text{rd}}$ quartiles = 0.7, 1.8) for $\sigma_{\text{amp}}$ and 1.8 msec ($1^{\text{st}}, 3^{\text{rd}}$ quartiles = 0.7, 2.0 msec) for $\sigma_{\text{lat}}$. Using these best fits, we computed the median of the normalized $\text{var}^{1/2}$ as a function of frequency across animals (Figure 8F). In both the single animal example in Figure 8E and the summary across animals in Figure 8F, we note that the model produced excellent fits for $f < 100$ Hz with $\sigma_{\text{lat}} = 0$, and improved fits for $f > 100$ Hz when $\sigma_{\text{lat}}$ was also varied. The divergence of the fits for $f > 100$ Hz reflects a limitation of the model, which is based solely on the observed additive component. Introducing amplitude variability is straightforward; such variability will not affect the mean of the additive component. However, introducing latency variability is more complicated, as varying the latency of the additive component will alter its mean in a frequency-dependent manner (i.e. the additive component becomes smeared, and the smearing is worse for frequency components on the order of the inverse of the latency variability). Therefore, with this modeling approach, we are likely to underestimate the contribution of an additive component.
with variable latency to the observed variance at those high frequencies. In spite of this limitation, the modeling results strongly suggest that broadband changes in variance that co-occur with changes in the mean, as well as high frequency changes in variance that can occur even in the absence of changes in the mean, are all likely to reflect variability in amplitude and latency, respectively, of an additive component, rather than induced responses secondary to reorganization of ongoing activity or top-down modulation of network connectivity parameters.

To summarize these simulations across animals, we computed the median stimulus-related changes in normalized \( \text{var}^{1/2} \) and \( \text{phase}_{\text{STM}} \), as in Figure 6B, from the best fits of the model for each experiment. This analysis is illustrated in Figure 9, where we have also plotted the recorded data for comparison (Fig. 9A&B; first column). Over the dataset, the model with only amplitude variability was able to capture much of the changes in variance that were correlated with changes in the mean (Fig. 9A, second column), but in this case the changes in phaseSTM were far stronger than those in the recorded data (Fig. 9B, second column). A modest improvement in model fit for variance and a substantial improvement in phaseSTM was observed with both amplitude and latency variability (Fig. 9A&B, third column). Although the phaseSTM values still exceeded those in the recorded data, subtracting the model fit from the data revealed that those differences were modest (Fig. 9B, fourth column). By subtracting the variance measure obtained from simulations from the recorded data (Fig. 9A, fourth column), we observe that nearly all the early variance changes <30 Hz, and most of these early changes up to 100 Hz, could be accounted for by the model with both amplitude and latency variability.

**Effect of phase reset on stimulus-related changes in mean.** As stated above, additive components can appear as phase concentrations, and the \( \text{phase}_{\text{STM}} \) measure employed here was specifically designed to address this confound (at least in the case of invariant amplitude).
However, the complementary problem is not addressed: phase resets can still appear as changes in the *mean* (this problem is why phase resets can contribute to the time domain mean response and have thus been postulated to underlie evoked responses Sayers et al 1974; Makeig et al 2002). The conflation of phase reset and amplitude variability has also been observed in the context of relating amplitude variations and dynamic correlations in human MEG data (Friston et al 1997). This effect is easily illustrated when considering the coefficients in the complex plane. Beginning with a cloud of coefficients scattered about the origin (i.e. with zero mean), as in Figure 3 (*left column*), changing the phases of those points so that they are all restricted to one quadrant will produce a data cloud with nonzero *mean* and altered *variance* (see Martinez-Montes et al 2008 for illustrative figures). Thus, it is possible in the data of Figure 6 that some portion of the stimulus-related change in *mean* (Fig. 6, *left column*) may actually be due to a stimulus-related phase concentration (Fig. 6, *right column*). Ideally, one would estimate the contribution of phase reset to the *mean* effect using the $\phi_{\text{STM}}$ measure, i.e. by calculating how much of a change in the *mean* is expected from the observed phase concentration. However, because of the way the $\phi_{\text{STM}}$ measure is defined, its values cannot be analytically translated into relative effects on the *mean*. Instead, we used simulations to estimate the changes in normalized *mean* and $\text{var}^{1/2}$ expected if they were entirely due to phase resets whose magnitude is given by changes in the $\phi_{\text{STM}}$ measure (see Methods; Fig. 10A&B). From these simulations, it is clear that phase resets can have non-trivial effects on the *mean* and *variance* of coefficients (Fig. 10B). However, when we compare these phase effects with the observed changes in *mean* and *variance* (Fig. 10C), we note two major discrepancies. First, the magnitude of predicted changes in the *mean* are far smaller than those observed (Fig. 10B&C, *left column*), and second, the simulated phase reset is associated with a *decrease* in *variance*, not the large
increase that we observe (Fig. 10B&C, center column). Thus, although we cannot rule out the possibility that the observed $\text{phase}_{\text{STM}}$ values represent true phase resets and contribute to the changes in mean and variance observed, these effects cannot account for all of the observed changes in the mean, and would require a large compensatory increase in variance. As we illustrated above, a far more parsimonious explanation for the observed changes in mean, variance and $\text{phase}_{\text{STM}}$ derives from variability in the additive component.

State-dependence of response variability

Previous reports have shown that cortical response variability is state-dependent (Kisley and Gerstein 1999; Curto et al 2009; Pasley et al 2009; White et al 2012), and in humans discriminability of acoustic stimuli depends upon the level of ongoing activity in auditory cortex (Sadaghiani et al 2009). Delta power is an indicator of level of arousal (Santamaria and Chiappa 1987; Jung et al 1997), and sensory responses have been shown to depend on delta power and delta phase previously (Lakatos et al 2005; Curto et al 2009; Luo et al 2010). We investigated whether the variability of the additive component depended on the state of the cortical network by comparing this variability for each animal with the ratio of gamma to delta power in the pre-stimulus period. Low values of this ratio are associated with lower levels of arousal (Curto et al 2009). Amplitude and latency variability for each animal was measured using the parameters $\sigma_{\text{amp}}$ and $\sigma_{\text{lat}}$, respectively, of the best model fit to the data. We found that $\text{SD}_{\text{amp}}$ declined exponentially with gamma/delta ratio over the sixteen recorded animals, and a linear fit to $\sigma_{\text{amp}}$ versus the log of this ratio yielded a significant negative correlation (Fig. 11A; slope = -0.78; $r^2 = 0.38; p = 0.01$). No significant correlation was evident for $\sigma_{\text{lat}}$ (not shown; $m = 0.50; r^2 = 0.17; p = 0.11$).
The data of Figure 11A indicate that animals exhibiting higher levels of cortical arousal had less variable additive components in their stimulus-related responses. Because the data were collected over a period of ~0.5 – 1.5 hours spread across multiple days, it is likely that cortical state varied over the recording period and even on a trial-by-trial basis. To obtain a single trial measure of response variability, we calculated the Euclidean distance between single trial responses and the mean response (over the first 125 msec of the response), and compared that distance measure to the gamma to delta power ratio on that trial. Large values of the distance measure indicate responses that are very different from the typical response, and thus more variable. An example from one animal is shown in Figure 11B, which exhibited a small but significant negative correlation between distance and gamma/delta ratio, indicating (as in Fig. 11A) that variability tended to be smallest on trials in which the animal was most aroused.

Similar results were obtained in 14 of 16 animals (Fig. 11C).

Unlike the data of Figure 11A, the Euclidean distance measure of Figures 11B&C cannot distinguish between variability in the response due to ongoing activity summing with an invariant additive component and variability in the additive component itself. Thus it is possible that some of the effect observed in Figure 11B is due to variability introduced directly by ongoing delta oscillations on trials in which gamma/delta ratio was low. By contrast, it is also possible that the delta component of the evoked response is correlated with the ongoing delta power and that this evoked delta component contributes to the state-dependent variability. We repeated the analysis of Figures 11B&C on data that had been high pass filtered above 4Hz, and thus lacked significant delta power (the gamma/delta ratio was still computed on the unfiltered data). Although we cannot differentiate between these two possible contributions of the delta component using this method, this filtering would eliminate both of the effects discussed above.
High pass filtering reduced the dependence of the distance measure on gamma/delta ratio (Fig. 11D), but 8 of 16 animals still exhibited significant negative correlations. Since this filtering is potentially removing components of the response that are relevant to the variability in the additive component, the true dependence likely lies somewhere in between the analysis of Figure 11C (which may include effects of ongoing delta power) and the analysis of Figure 11D (which may lack state-dependent effects on the variability of the delta component of the response).
Discussion

Summary and Conclusions

By analyzing the mean, variance and phase of complex spectral coefficients of cortical neural activity in rats, we demonstrate that auditory stimuli lead to broadband changes in all three measures that are onset-dominated and tend to co-occur. In the peri-stimulus response window, the high correlation in these measures in the time-frequency plane is consistent with a simple model in which an evoked response component is elicited on each trial with variable amplitude and latency. Simulations of trial-by-trial variability using this model account for most of the observed changes in variance and $\phi_{STM}$ without engaging any nonlinear, ‘top-down’ changes in ongoing activity typically associated with induced responses or true phase resets. The only unequivocal induced response component we detected in our dataset was a long-latency, long-lasting desynchronization in the alpha band that was modest but consistent across animals. Using simulations and single trial measures of variability in our recorded data, we show that this variability was most pronounced when ongoing cortical activity indicated the lowest levels of cortical arousal. These observations are consistent with auditory cortical responses in these passive listening conditions being dominated by a variable, state-dependent, ‘bottom-up’ information stream, with only modest, long-lasting changes in cortical network activity.

Variability in amplitude and latency of additive components

The contribution of amplitude and latency variability to apparent induced responses has been noted previously (David et al 2006). The classical model of evoked response generation consists of an additive component with fixed latency and amplitude that linearly combines with variable ongoing activity to produce single trial responses. According to this model, averaging
can reliably recover the invariant additive component, and subtraction of this mean evoked response from single trials will reveal interactions between the evoked response and ongoing activity that comprise the induced response. However, it is now well-established that this model can result in a poor estimate of the evoked response, whose amplitude and latency can vary considerably from trial to trial (Mocks et al 1987; Lange et al 1997; Truccolo et al 2002; D'Avanzo et al 2011). Nevertheless, the most common method for computing the induced response component continues to be subtraction of the time-domain evoked response from single trial responses (e.g. Crone et al 2001; Trautner et al 2006; Steinschneider et al 2008). Our data shows that caution must be used when interpreting induced responses, particularly when they co-occur with evoked responses, and that trial-by-trial variability in latency and amplitude can account for a significant portion of observed increases in variance of spectral coefficients.

Contribution of phase reset to stimulus-related activity

The contribution to evoked responses of phase reset versus additive components continues to be hotly debated, and previous studies in humans investigating the origin of the evoked response and the contribution of phase reset have reached contradictory conclusions (Sayers et al 1974; Jervis et al 1983; Makeig et al 2002; Makinen et al 2005; Hanslmayr et al 2007; Sauseng et al 2007; Krieg et al 2011). Detailed analyses and simulations have shown that it is often difficult to conclude unequivocally that observed phase concentrations are due to phase resets per se rather than an additive component (Sauseng et al 2007; Krieg et al 2011). The $\text{phase}_{\text{STM}}$ measure employed here, in which the mean is subtracted before calculating the phase concentration (Martinez-Montes et al 2008), was developed specifically to address this confound, and performs well in the case of an invariant additive component (Krieg et al 2011). However, our simulations show that variability in the amplitude of the additive component will also lead to a phase concentration, as this variability elongates the cloud of spectral coefficients in the complex plane along the axis of the mean component, and thus would be detected as a
phase concentration even after subtracting the averaged *mean* component. Indeed, such an effect can be pronounced (e.g. Fig. 9B, *second column*). Adding to the model variability in the latency of the additive component reduces this effect, especially at high frequencies (Fig. 9B, *third column*), by widening the data cloud in the orthogonal direction and thereby reducing the apparent phase concentration. Importantly, these simulations illustrate that a phase concentration exceeding that observed in our recorded data (Fig. 9) can be produced solely through variability in the amplitude and latency of an additive component. Because there is strong evidence that such variability is occurring in the animals recorded here in response to acoustic stimuli, it is not necessary to invoke a true phase reset of ongoing activity to account for the observed phase concentration.

A few studies that pay careful attention to these confounds have presented some evidence for the contribution of phase reset to cortical sensory responses (Krieg et al 2011), but in auditory cortex such responses appear to be limited to integration with stimuli from other modalities (Lakatos et al 2007; Luo et al 2010). This is consistent with our results that phase reset contributes little to auditory cortical responses under passive listening conditions in the frequency range examined (3 – 300 Hz). However, in our recordings, we also observed very little structure in the frequency content of ongoing activity (Fig. 2), and it is possible that phase reset of ongoing components may contribute more to the evoked response when there is more structure to the ongoing activity (Sauseng et al 2007), or during dynamic naturalistic stimuli (Ng et al 2013). Finally, it should be noted that although phase concentration due to an additive component is not the same as a phase reset of ongoing of activity, and implies primarily bottom-up influences rather than modulation of ongoing activity, the end result of both mechanisms is an alignment or phase synchronization that could equivalently facilitate integration within the cortical network.
We note here that the opposite confound can also occur, i.e., a phase reset can also cause apparent changes in the mean and variance (Fig. 10), as has been reported previously (Sauseng et al. 2007; Krieg et al. 2011), and an intuitive understanding of this effect can also be gained by considering the cloud of spectral coefficients in the complex plane. However, we have used simulations of phase reset to show that resulting changes in the mean and variance are smaller than (in the case of the mean) or are in the opposite direction of (in the case of the variance) the changes observed in our recordings, and thus a phase reset is unlikely to contribute to the changes in mean and variance reported here.

Spectral content of ongoing activity

In our recordings, we observed little evidence for peaks in power spectra derived from ongoing activity (Fig. 2). In one previous study on auditory cortex in monkeys, peaks in the delta, theta and gamma bands were suggestive of consistent oscillations in these frequency ranges, and stimulus-triggered phase resets of these oscillations are reported to contribute to the response (Lakatos et al. 2005). Other studies did not find such peaks in ongoing activity (Brosch et al. 2002), indicating that such structure could be state-dependent. It is unclear, however, what bearing such peaks have on the relationship between ongoing activity and stimulus-related responses. For example, a dominant peak in the power spectrum may not be necessary for phase reset at that frequency to occur (Sauseng et al. 2007). The presence of induced response components may similarly be unconnected to such peaks. For example, we observed evidence for stimulus-related alpha band desynchronization (Fig. 6) even in the absence of a prominent alpha peak in the spectrum of ongoing activity (Fig. 2), and induced oscillatory activity in the gamma band has been observed in the absence of detectable gamma peaks in the ongoing spectrum (Brosch et al. 2002). Thus the presence or absence of ‘peaks’ in the ongoing spectrum may not be indicative of the network’s capacity for stimulus-induced reorganization of
oscillatory activity, perhaps because of the local nature of these rhythms or modulation of specific dynamic components of the network in a stimulus-specific manner.

Alpha band desynchronization

We observed desynchronization centered in the alpha band around 10 Hz (Fig. 6A-D, center column). Cortical alpha band desynchronization is well known in human studies of visual, somatosensory and auditory sensory processing to reflect arousal and attentional mechanisms (for recent reviews, see Palva and Palva 2007; Weisz et al 2011; Foxe and Snyder 2011). The desynchronization we observed in the alpha band is similar to what has been observed in human auditory cortex (Lehtela et al 1997; Crone et al 2001; Palva and Palva 2007), though other studies report increases in alpha power in response to acoustic stimulation (Krause et al 1996; Karrasch et al 1998) (Steinschneider et al 2008). Interestingly, there have been few reports of alpha desynchronization in auditory cortex of animals, though this response has been observed in other sensory cortices (Wiest and Nicolelis 2003; Sobolewski et al 2011). It is possible that the modest reduction in variance that we observed here is common and may have remained undetected in some studies. In human subjects, alpha desynchronization coincides with increased excitation in the cortical circuit during information processing (Klimesch et al 2007; Weisz et al 2011), i.e. alpha power is positively correlated with local inhibitory tone, and is postulated to reflect ‘behavioral idling’ that is suppressed during enhanced information flow through the thalamo-cortical network (Sobolewski et al 2011). Thus, according to this model, the long-lasting desynchronization reflects a long-lasting rebound excitation (Recanzone et al 2000; Qin et al 2007), in parallel with a similar rebound or persistent excitation indicated by the post-stimulus change in mean. If the desynchronization does indeed reflect changes in inhibitory
network activity, the observation that these changes are not time-locked to the stimulus may
mean that changes in inhibitory tone are governed by intracortical connections, e.g. top-down
inputs (Klimesch et al 2007).

**Gamma response components**

In sensory cortex, changes in gamma band (30 – 120 Hz) power and in gamma frequency
synchronization across cortical regions have been linked to feature binding, object
representation, perception and memory of meaningful stimuli in humans (Tallon-Baudry et al
1996; Pulvermuller et al 1996). In auditory cortex, gamma band activity evoked by acoustic
stimuli typically has a short latency, evoked (i.e. phase-locked) component (Galambos et al
1981; Pantev et al 1991), as well as both short latency and prolonged induced components that
are poorly phase-locked and can outlast the stimulus duration by hundreds of milliseconds
(MacDonald and Barth 1995; Tallon-Baudry and Bertrand 1999; Crone et al 2001; Brosch et al
2002; Steinschneider et al 2008; Jeschke et al 2008; Lenz et al 2008). In our recordings, we
observed stimulus related activity throughout the gamma range, but our data and simulations
indicate that these responses were dominated by evoked response components. This result is in
contrast to results obtained during discrimination tasks in humans and rodents (Crone et al 2001;
Lenz et al 2008; Jeschke et al 2008), in which ‘induced’ gamma band responses were observed
and whose power could correlate with memory and sensory processes. The differences between
these results and those reported here could be ascribed to the passive listening conditions under
which we recorded our data, though high gamma induced responses have also been reported for
passive listening conditions in monkeys (Steinschneider et al 2008). It should be noted that in
these studies no attempt was made to distinguish between changes in variance associated with
amplitude and latency variability in an additive component, versus changes in variance due to reorganization of ongoing activity or top-down modulation of cortical network connectivity. Indeed, although the latency of the induced high gamma activity in the latter study (~50 msec) was longer than in our recordings, it was striking that these effects were concentrated in the highest frequency components, consistent with these ‘induced’ components being due to latency variability in the evoked component.

State-dependence of variability and functional implications

It is widely recognized that cortical responses exhibit substantial trial-by-trial variability (Whitsel et al 1977; Shadlen and Newsome 1998; de Kock et al 2007; Luczak et al 2013). However, the origin of this variability is still under debate, with some reports arguing that cortical responses can be modeled as a constant additive component combined with variable ongoing activity (Dawson 1954; Arieli et al 1996; Shah et al 2004; Risner et al 2009), while others demonstrate that models including variable response components provide superior fits to the data (Truccolo et al 2002). The difference between these models depends on the relative importance of local variable ongoing activity in the cortical network itself, as opposed to variability in ascending input to the network. Our data are consistent with these latter models, and provide strong evidence that under passive listening conditions, stimulus related responses in auditory cortex of rats are dominated by an evoked component with variable amplitude and latency, consistent with variability in the ascending input to auditory cortex. This trial-by-trial variability is not surprising given the probabilistic nature of neuronal responses throughout the ascending sensory pathway. Although responses of cortical cells tend to be more variable than
their thalamic inputs, the latter still exhibit substantial trial-by-trial variability (de Kock et al 2007) and in the ascending auditory pathway information content, reflecting in part variability in responses, is comparable between thalamus and cortex (Chechik et al 2006). Understanding the source of this variability and how it changes with behavioral state will yield insight into the state-dependence of sensory processing and the neural basis of sensory awareness.

We present evidence that the variability of stimulus-related activity depends on the state of the cortical network (Fig. 11). Using two different measures, we find that the amplitude variability of the additive component is smallest when the ratio of gamma to delta power is high. Because the latter is commonly used as a metric of arousal, this result suggests that arousal is associated with reduced response variability. We note that since variability was highest when the animals were most quiescent, it is unlikely to derive from trial-by-trial variability in positioning of the animals’ heads relative to the speakers. The inter-trial interval employed here is far longer than is typical for electrophysiological studies of the auditory system, in which intervals of 1 second or less are not uncommon. These long intervals likely reduce the predictability of the stimulus time and thus may reveal more strongly endogenous sources of response variability. Previous reports have demonstrated such state-dependence of response variability. For example, the variability of cortical responses is reduced over the course of perceptual learning (Adab and Vogels 2011), and exhibits dose-dependence under general anesthesia (Kisley and Gerstein 1999). Attention also reduces variability and is associated with improved behavioral performance (Ledberg et al 2012). However, in some reports spontaneous cortical activity is reduced on average during slow wave sleep (Steriade et al 1978; Nir et al 2012), when delta power is high, and this would likely reduce response variability, contrary to our findings that variability is maximal when delta power is low. Analyses such as those presented here that can identify this
variability and how it changes with learning or awareness will prove useful tools for understanding the underlying mechanisms of these state changes.
Figure Captions

Figure 1. Ongoing and stimulus-related activity. Time domain (A) and time-frequency domain (B-C) representations of epidural field potentials recorded from auditory cortex of a rat. A. Three randomly selected trials (top traces) and the average of 664 trials (bottom trace). Scale bars for single trials: 100 ms, 0.1 mV. Scale bars for average: 100 ms, 0.05 mV. B. Corresponding power spectrograms for the three single trials in A. C. Average of 664 single trial spectrograms. Color scale in C represents \( \log_{10} \) power and applies to B as well. Horizontal lines in B & C mark transition from STFT (low frequencies) to wavelet (high frequencies) transforms. Time scale in C applies to A and B as well.

Figure 2. Analysis of mean spectra. A. Mean spectra averaged over the pre-stimulus period (i; ‘Baseline’) and during four time windows relative to stimulus onset (ii-v; stimulus duration = 250 msec), then averaged across all trials for individual animals (grey lines), and finally averaged across animals (grand average; solid black lines). Dashed line in i is the line \( y = k/f^2 \), where \( k \) is an arbitrary constant and \( f \) is frequency. Dotted lines in ii-v are the grand average spectrum from the pre-stimulus period (i) replotted for comparison. B. The relative effect of the stimulus as a function of frequency during the time windows indicated in A is illustrated by plotting the ratios of the grand average spectra from ii-v to the ongoing spectrum in i.

Figure 3. Spectral coefficients in the complex plane. Complex coefficients of the time-frequency transforms from the experiment in Figure 1 for the four indicated frequencies (rows) at the four indicated time points (columns). Each point represents the coefficient for a single trial at a single time and frequency. The left column represents baseline (i.e. pre-stimulus) activity. The
center two columns represent peri-stimulus activity, and the right column represents post-stimulus activity. In each scatter plot, the mean of the coefficients across trials is indicated by a vector (black line), while the var^{1/2} is indicated by the radius of the circle, whose origin is translated to the mean. The dashed circles in the right three columns are the var^{1/2} from the ongoing activity replotted for comparison. In all panels, the real and imaginary axis limits are identical. The same axis limits apply throughout the row. The axis limits for each row are as follows: 3 Hz, ±0.055; 10 Hz, ±0.038; 30 Hz, ±0.0092; 100 Hz, ±0.0028.

**Figure 4. Mean, variance and phaseSTM measures.** Same experiment as Figure 3. Shown are the mean (solid black lines), var^{1/2} (dashed black lines) and phaseSTM (grey lines) as a function of time relative to stimulus onset at t=0 for the four indicated frequencies. The mean and var^{1/2} measures have been normalized to the average of the var^{1/2} during the pre-stimulus period. Note that the auditory stimulus causes a broadband increase in the mean of spectral coefficients whose time course differs for different frequencies. Note for the 3 Hz and 10 Hz components, the time resolution is ~150 msec, which is the window width of the STFT used for analysis of low frequency components, but for the 30 Hz and 100 Hz components the time resolution is an inverse function of frequency, as it is governed by the width of the wavelets used to analyze high frequency components. Thick lines identify epochs significantly different from baseline according to the local fdr method (see subsequent figure).

**Figure 5. Complex t-statistics and local fdr analysis. A., B.** The process of determining which t-values are "interesting" (i.e. significant) for one frequency component from this experiment (9 Hz) is shown. The mean (left), variance (middle), and phaseSTM (right) at each point in the time-
frequency plane were analyzed by computing complex t-statistics, calculated by comparing data in the test region to the comparison region prior to the stimulus (see Methods). Null distributions for each measure ($A$) were created by calculating t-values within the pre-stimulus comparison region and smoothing the resulting histograms ($A$, dashed lines). Scaling the null distribution to account for the number of data points in the post-stimulus region gives the expected distribution ($B$, dashed lines). The expected distribution is compared to the smoothed histogram of values from the test region ($B$, solid lines). By the local $fdr$ method, bins where at least 10 times more observations were observed than expected were deemed “interesting” ($B$, black bars), while the rest are “uninteresting” ($B$, gray bars).

C. Time-frequency contour plots of t-values showing the results of the analysis applied to every time-frequency point. The plot is thresholded such that non-significant points are set to zero (blue in left and right columns, green in center column). Time and frequency scales in left panel apply to center and right panels as well. Note that unlike for the t-mean statistic, the t-variance and t-phaseSTM statistics can be either positive (hot colors) or negative (cold colors). Colorbar ranges for $f>16$ and $f<16$ Hz, respectively, are: t-mean: 0 - 10, 0 - 2.5; t-variance: -500 - 500, -100 - 100; t-phaseSTM: 0 - 400, 0 - 100.

**Figure 6. Summary across animals of stimulus-related effects on mean, variance, and phaseSTM.** A. For each animal, points in the time-frequency plane showing a significant increase in the mean, variance or phaseSTM measure were assigned a 1, and points showing a significant decrease were assigned a -1 (variance and phaseSTM only). These significance maps were then averaged across animals, giving a summary map that shows the fraction of animals exhibiting significant changes at each time-frequency point. B. Grand median of mean (left column), $var^{1/2}$ (center column) and phaseSTM (right column). Mean and $var^{1/2}$ measures were normalized for
each animal to the $\text{var}^{1/2}$ averaged over the pre-stimulus period. \textbf{C.} The same as \textit{B}, but thresholded for significance across animals as assessed using Mann-Whitney and corrected for multiple comparisons by local \textit{fdr}. \textbf{D.} The same as \textit{C}, but corrected for multiple comparisons using Bonferroni correction. \textbf{E.} Same data from \textit{C} plotted on an expanded time scale. Note the high correlation, during the peri-stimulus period, of the \textit{mean} and \text{var}^{1/2} measures.

\textbf{Figure 7.} Evidence that \textit{variance} changes are secondary to trial-by-trial variability in the \textit{mean}. \textbf{A.} Illustration of effects of amplitude and latency variability on the \textit{variance} of complex coefficients. Complex coefficients were simulated with real and imaginary components normally distributed with \textit{mean} = 0 and \textit{variance} = 1 (\textit{top row, left panel}). In all panels, \text{var}^{1/2} is indicated by the radius of the \textit{circle}, and the \textit{mean} is indicated by the \textit{black line} connecting the origin to the center of the circle. The \text{var}^{1/2} of the original data cloud (\textit{top left panel}) is indicated by the \textit{dashed circle}. \textit{Top row} shows effect of amplitude variability on the \text{var}^{1/2} measure, and that it is a monotonically increasing function of the magnitude of the additive component. For these data, half the points are unchanged, and half have a constant additive component with magnitude indicated in the panel title. \textit{Bottom row} shows the effect of latency variability on the \text{var}^{1/2} measure, and that it is a monotonically increasing function of the ratio of latency to 1/f. For these data, all points were summed with an additive component with constant amplitude, but for the two halves of the points the additive component had two different phase values, and the difference between the two phase values was set by the ratio of latency (3 ms) to 1/f multiplied by $\pi/4$. \textbf{B.} Two-dimensional (time-frequency) correlation coefficients between normalized \textit{mean} and \text{var}^{1/2} computed over the peri-stimulus time window for STFT coefficients (i.e. 3<f<16 Hz: \textit{left}) and wavelet coefficients (i.e. 16<f<300 Hz; \textit{right}). Data from individual animals appear as
open circles. Box plots denote median (horizontal line) and first and third quartiles (box). Note the high correlation in most animals, as would be expected for variability in the amplitude of the additive component. C. Median (thick line) and first and third quartiles (thin lines) across animals of the normalized $\text{var}^{1/2}$, computed at each frequency at the time point corresponding to the peak in the normalized mean (see Methods). Note that the $\text{var}^{1/2}$ increases with frequency, as would be expected for variability in the latency of the additive component.

**Figure 8. Variance changes in simulations incorporating trial-by-trial variability in amplitude and latency.** A – D. Time-frequency spectra (left column), normalized mean (second column), normalized $\text{var}^{1/2}$ (third column) and $\text{phase}_{\text{STM}}$ (right column) measures for data from a single animal (A) and simulations with zero trial-by-trial variability (B), variability only in the amplitude (C; $\sigma_{\text{amp}} = 1.0$) and variability in both amplitude and latency (D; $\sigma_{\text{amp}} = 0.8$, $\sigma_{\text{lat}} = 1.8$ msec). Note the absence of variance and $\text{phase}_{\text{STM}}$ changes in the absence of amplitude and latency variability (B), the presence of variance changes similar to the recorded data with such variability (C, D) and the improved fit of the $\text{phase}_{\text{STM}}$ measure to the recorded data with both amplitude and latency variability (D) compared to amplitude variability alone (C). E. Normalized $\text{var}^{1/2}$ (evaluated at each frequency at the peak of the normalized change in mean) from the experiment and simulations in A-D for the recorded data (blue line), simulated data with no trial-by-trial variability (green line), with only amplitude variability ($\sigma_{\text{amp}} = 1.0$; red line) and with both amplitude and latency variability ($\sigma_{\text{amp}} = 0.8$, $\sigma_{\text{lat}} = 1.8$ msec; black line). F. Same as E, but for the median data across animals. Simulations were the best fits to the data from each animal.
Figure 9. Summary of variance and $\text{phase}_{\text{STM}}$ changes observed with simulations. Plotted are the median recorded data (left column), and median best simulation results with only amplitude variability (second column), amplitude and latency variability (third column), and the difference between the recorded data and best simulation with both types of variability (right column) for the normalized $\text{var}^{1/2}$ ($A$) and $\text{phase}_{\text{STM}}$ ($B$) measures. Note that for $f<100$ Hz, the simulations are able to recreate most of the observed changes in variance, and that the $\text{phase}_{\text{STM}}$ measure is more similar to the recorded data when both types of variability are included in the model.

Figure 10. $\text{phase}_{\text{STM}}$ measure simulations and predicted changes in mean and variance assuming the changes were entirely due to phase reset. Data were simulated by assuming that ongoing activity was described by complex coefficients having real and imaginary parts that are jointly normally distributed with common variance. The magnitudes of these coefficients were maintained but their phases concentrated to adhere to a von Mises distribution with the indicated standard deviation. A. Right panel shows the $\text{phase}_{\text{STM}}$ measure (STM) as function of phase dispersal. The expected changes in normalized mean and $\text{var}^{1/2}$ given a phase concentration yielding the indicated $\text{phase}_{\text{STM}}$ value are shown in the left and center panels, respectively. B. Corresponding mean and $\text{var}^{1/2}$ plots assuming that these were due entirely to a phase reset as measured by the $\text{phase}_{\text{STM}}$ in the right panel. C. The median raw data across animals, replotted from Figure 6.

Figure 11. Cortical state-dependence of amplitude variability. A. Amplitude variability ($\sigma_{\text{amp}}$) from best fit of model to observed $\text{var}^{1/2}$ for each animal as a function of the log of the ratio of gamma to delta power in the pre-stimulus period averaged over all trials for that animal. Solid
line is linear regression fit to data (slope = -0.78, r^2 = 0.38, p = 0.01). Note that amplitude variability was greatest in animals with small gamma/delta ratios. B. Single trial analysis for all trials recorded in one animal. For each trial, we calculated the Euclidean distance between that single trial response and the mean response for this animal. These single trial distance measures are plotted as a function of log gamma/delta ratio. Straight line is linear regression fit to the data (slope = -0.27, r^2 = 0.14, p = 1.1x10^{-16}). Grey circles are the same data after shuffling trial number 100 times. C, D. Slopes (black circles) and 95% confidence intervals (black lines) obtained from linear regression fits as in B for all 16 animals without additional high pass filtering (C) and after filtering >4Hz (D). Note that before filtering 14 of 16 animals exhibit significant regression slopes, and that after filtering significant slopes are seen in 8 of 16 animals.


Foxe JJ and Snyder AC. The Role of Alpha-Band Brain Oscillations as a Sensory Suppression Mechanism during Selective Attention. *Front Psychol* 2: 154, 2011.


