Linking nonlinear neural dynamics to single-trial human behavior

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Abstract

Human neural dynamics are complex and high-dimensional. There seem to be limitless possibilities for developing novel data-driven analyses to examine patterns of activity that unfold over time, frequency, and space, and interactions within and among these dimensions. A better understanding of the neurophysiological mechanisms that support cognition, however, requires linking these complex neural dynamics to ongoing behavioral performance. Performance on cognitive tasks (measured, e.g., via response accuracy and reaction time) typically varies across trials, thus providing a means to determine which neural dynamical processes are related to which cognitive processes. In this chapter we will review and present several methods for linking nonlinear neural dynamics, based on oscillatory phase, phase-based synchronization, and phase-amplitude cross-frequency coupling. In general, the approach of linking nonlinear neural dynamics based on phase values with trial variations in task performance have two significant advantages for understanding neurocognitive processes: (1) They allow researchers to distinguish those neural dynamics specifically related to cognitive task performance from other neural dynamics that reflect more generic background neural dynamics, and (2) Oscillation phase has been linked to a variety of synaptic, cellular, and systems-level phenomena implicated in learning, information processing, and network formation, and therefore provide a neurophysiologically grounded framework within which to interpret results.

Neural dynamics are complex

Populations of neurons produce oscillations, which reflect rhythmic fluctuations in the summed dendritic and synaptic activity (Wang, 2010), and have been linked to a wide variety of biological and psychological phenomena over multiple spatial scales, ranging from long-term-potentiation to spike-time-dependent-plasticity to conscious visual object recognition. Further, oscillations occur over a wide range of frequencies, from ultra-slow (< 1 Hz) to ultra-fast (>600 Hz) (Steriade, 2006). Although slow oscillations are traditionally associated with deep sleep and anesthesia, <1 Hz oscillations have also been shown to modulate cognitive and perceptual processing (Lakatos et al., 2008; Monto et al., 2008; Van Someren et al., 2011). Different regions of the brain seem to have "preferred" or dominant frequency ranges, which may be linked to different neuron types, configurations, or functional characteristics (Rosanova et al., 2009; Kopell et al., 2010; Hipp et al., 2012; Siegel et al., 2012). Within the cortex, different layers produce oscillations at different frequencies (Roopun et al., 2006; Sun and Dan, 2009; Buffalo et al., 2011). Interactions among activities in different frequency bands within the same or across spatially distributed neural networks (i.e., cross-frequency coupling) have been linked to neurobiological and cognitive processes (Young and Eggermont, 2009; Canolty and Knight, 2010). Neural oscillation dynamics are modulated by a variety of neurochemicals, which have differing effects on neural dynamics that depend on region, frequency band, and behavioral state.

Action potentials of individual neurons can become synchronized with the phase of local oscillations (Wu et al., 2008; Buffalo et al., 2011; Lepage et al., 2011) in a task-dependent manner (Siegel et al., 2009; Liebe et al., 2012). The relative timing of action potentials with respect to oscillations has been implicated in information processing schemes such as phase coding (Lisman, 2005), as well as long-range inter-regional communication and coordination. Thus, synchronous oscillations across neural populations is thought to be a mechanism for facilitating the functional unification of spatially disparate neurons into a cohesive network.

Synchronous oscillations among brain regions is thought to be a means of coordinating information processing, leading to the formation of functionally coupled networks (Fries, 2005; Wang, 2010). This synchrony is often manifest as phase-locking, with the idea that in-phase oscillators can more efficiently transfer information. For example, synchronous neural inputs produce nonlinear increases in synaptic efficacy (Niebur et al., 2002), which is a foundation of Hebbian learning. Oscillatory phase synchronization facilitates such input timing. Further, field potential oscillations may play a causal role in modulating neural activity (Anastassiou et al., 2011).

In other words, neural dynamics are complex. Oscillations appear to be a ubiquitous and fundamental neural mechanism that supports myriad aspects of synaptic, cellular, and systems-level brain function. At present, oscillations are perhaps the most promising bridge across multiple spatial and temporal scales of neural activity, from fast synaptic dynamics that regulate gamma oscillations, to slower fluctuations that predict conscious perception. For the same reasons, oscillations are also arguably the most promising bridge across multiple disciplines within neuroscience, and across multiple species.

Data analysis techniques and possibilities are expanding rapidly

In the early nineteenth century Joseph Fourier proved that any time series can be represented as the sum of time-varying sinusoids of different frequencies. This demonstration is the basis for all modern time-frequency analyses. Researchers use spectral analyses of neurophysiological data for decades. However, until digital computing became ubiquitous, most frequency analyses were limited to examining band-specific amplitude changes. Prior to the digital era, frequency spectral analysis was carried out either by counting the number of zero-crossings—that is the number of times the EEG signal crossed the zero-line (Legewie and Probst, 1969)—or by specialized “electronic frequency analyzers” and comparing the results of the EEG pen-deflections with an input signal of known amplitude. These methods were labor-intensive, however: “so little data [could] be processed… that physiological correlation [was] impractical.” (Burch, 1959; see also Figure 1).

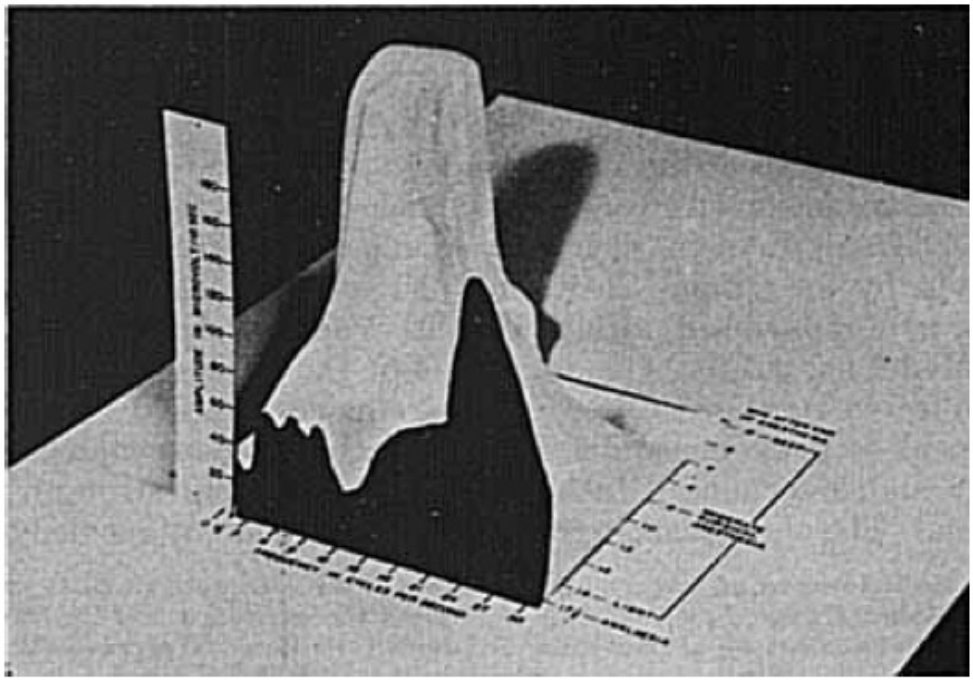

Figure 1*. Taken from Bellville and Artusio (1956) showing frequency on the x-axis, depth of anesthesia on the y-axis, and amplitude on the z-axis. This figure is actually a photograph of a physical model built by the authors to display their power spectral results.*

Of course, time-varying sinusoids carry information not just about frequency and amplitude, but also instantaneous phase information. As EEG research moved away from analog pen-and-paper recordings to digital storage, offline analysis of EEG became more commonplace. This move allowed researchers to make use of digital filtering techniques and move away from power spectral density analyses to time-frequency analyses. There are now many techniques used to extract time-frequency information from neurophysiological data, including: short-time or sliding-window Fourier transforms; wavelet and other template convolution techniques, including matching pursuit algorithms; and filtering and Hilbert transform. While formally different, these three methods are essentially equivalent with the only differences between them due to differences in implementation parameters (e.g., bandwidth, window length) (Bruns, 2004).

Currently, it is easy to extract the analytic signal (containing information about amplitude and phase over time, frequency, and electrode), and even small laptop computers can do analyses that were out of reach only a few decades ago. Perhaps in the near future scientists will analyze data on their phone. And with modern high-end computing (compute clusters, cloud computing, and other distributed computing solutions), even the most complex analyses on very large datasets can be done in hours or days.

The importance of linking neural dynamics to behavior dynamics

Here we argue that an important criterion for evaluating the functional significance of neural oscillations is the link between neural dynamics and behavioral/perceptual dynamics. We focus specifically on methods to link nonlinear neural dynamics to behavior, because linear methods are better established and more widely used in neuroscience.

It is difficult to estimate the dimensionality of neural dynamics. Time, frequency, and space (i.e., brain region, cortical column, neuron) are three important dimensions. Power (the squared amplitude of the oscillation) and phase (the timing of the oscillation, measured in phase angle of a sinusoid) are discrete dimensions that provide largely independent information regarding, respectively, neural activity strength and timing (note that power and phase are not entirely independent, because with decreasing power, phase becomes increasingly difficult to estimate; at the extreme case of zero power, phase at that frequency is undefined). There are interactions amongst various dimensions of information. For example, activity can be coupled across different frequency bands and spatially distributed neural populations (van der Meij et al., 2012). These kinds of complex interactions can in some cases be modulated by sensory information processing (Lakatos et al., 2008), suggesting a functional computational role for multidimensional nonlinear neural dynamics.

This massive complexity provides nearly limitless possibilities for the brain to encode, process, and transfer information. Given the enormous repertoire of cognitive/emotional/social processes of which our brains are capable, ranging from

occluded object identification to complex hypothesis generation, it is likely that the brain uses multiple and multidimensional information processing schemes that operate flexibly and in parallel.

On the one hand, this allows and inspires researchers to develop increasingly sophisticated mathematical techniques to characterize and model brain activity. On the other hand, at a practical level, the search space is so large that nearly any possible analysis approach is likely to fit some pattern of data. This is compounded by the fact that there is often a limited amount of data, and data (particularly when recorded as mesoscopic levels, as in human neuroscience) contain noise. Thus, there is a danger that novel analysis approaches will fit some pattern of data in a particular dataset but will not be reflective of or relevant to fundamental and natural neural computations.

We argue that a useful approach to identifying patterns of neural dynamics that are most relevant for function (that is, perceptual, behavioral, and cognitive processes) is to link neural dynamics to ongoing behavior of the subject or changes in the environment. By "behavior" we mean actions taken by the subject as part of the experimental design, such as key presses, saccades, or decisions to run down one or another maze arm. In this sense, behavior could also imply differences as a function of disease state or brain development. Changes in the environment need not require a behavioral response, however. Presentations of Gabor patches with different gradients or luminances, for example, can be used to link neural activity to visual decoding with no behavioral responses necessary.

We do not suggest that the discovery, characterization, and modeling of neural dynamics without specific links to behavior is misguided or not useful, nor do we suggest that such results are uninterpretable. Rather, if the goal of the research is to identify the patterns of activity that are most relevant for neural computations and brain function, fluctuations in those patterns should be linked to fluctuations in behavior or perception. Neural dynamics without any clear identifiable behavioral correlate may reflect emergent properties of neural architecture, or may support computation in more complex ways than our current approaches can uncover.

This argument may seem to invalidate *in vitro* studies, but this is not the case. *In vitro* studies provide valuable information regarding cellular and synaptic processes that can then be used to better understand the neurobiological mechanisms underlying brain-behavior links made in *in vivo* studies. Indeed, fundamental principles of synaptic and cellular mechanisms in many cases cannot be learned through meso- or macro-scopic level recordings.

Linear approaches of linking neural and behavior dynamics

Linear approaches to linking neural and behavioral dynamics rely mainly on correlations, such as inter-trial correlations between the amplitude of a neural response and inter-trial variation in behavior or stimulus features. Indeed, this is the idea of applying general linear models to hemodynamic and electrophysiological activity, which is perhaps the most commonly and widely accepted statistical approach used in cognitive neuroscience studies. In many situations, linear or monotonic brain-behavior relationships are appropriate. Indeed, experiments are often designed specifically to be tested using linear models.

The main limitation of linear approaches to brain-behavior links, obviously, is that they are limited to linear relationships. Given the enormous wealth of neuroscience investigations using linear statistical approaches, it is clear that much can be learned about the functions and computations of the brain using linear models.

But neural dynamics can also be nonlinear, and thus linear approaches might be inappropriate or lead to misleading conclusions in some situations. For example, if the rate of action potentials is unrelated to stimulus intensity, but the timing of action potentials with respect to simultaneous gamma phase is related to stimulus intensity, linear analyses would lead one to the incorrect conclusion that that neuron was unrelated to visual processing (Lepage et al., 2011).

In the next sections, we describe several methods for linking nonlinear neural dynamics to behavior. Most of these methods are centered on oscillation phase; as discussed earlier, phase is an important index of population-level neural timing, and is inherently nonlinear.

Nonlinear dynamics and behavior: Phase modulations

One of the main utilizations of phase information in cognitive experiments in which there are repeated trials of the same or similar stimuli is to compute inter-trial phase consistency (ITPC; also sometimes called phase-locking, phase-reset, or cross-trial coherence). ITPC measures the extent to which the distribution of phase angles at each time/frequency point over many trials deviates from a uniform distribution; the larger the deviation from uniform distribution, the more the phase angles (*i.e.*, oscillation timing) are likely to take on specific values at specific post-stimulus times. To compute ITPC, the phase angles at each trial (at one time-frequency point) are considered to be vectors in a unit circle, with an angle corresponding to the phase angles. After many trials, a distribution of phase angles is obtained, and the average vector is computed. The magnitude (length) of that vector is ITPC, and reflects the extent to which phase angles are non-uniformly distributed: If the polar distribution is roughly uniform, the average vector will have a small magnitude (approaching zero), and the interpretation is that the timing of activity at that time point at that frequency is unrelated to the stimulus. On the other hand, if the distribution is unipolar, the average vector will have a larger magnitude (with a maximum of 1), and the interpretation is that the timing of band-specific activity is highly related to the stimulus. In math:

$$\mathrm{ITPC} = \left| n^{-1} \sum_{t=1}^{n} e^{ik_t} \right|, \qquad (1)$$

where n is the number of trials, k is the phase angle at a time-frequency point, t is a trial index, i is the imaginary operator, and e is the natural log.

There are two disadvantages of this "standard" measure of ITPC. The first is that it assumes that oscillation phase is relevant when the oscillation has a similar phase value across trials

at each time-frequency point. This approach therefore mixes a number of potential causes of phase coherence, including stimulus-evoked responses, general orienting or attention responses, and task-specific dynamics, thus precluding a precise interpretation with respect to trial-varying cognitive/perceptual dynamics. The second disadvantage is that this approach precludes discovery of phase dynamics that are related to the task but are not consistent across trials, that is, the phase angle is not in the same narrow range across trials.

We argue for an adjustment to ITPC that affords a better link to task dynamics and thus a more cognitively precise interpretation. "Weighted ITPC" does not require phase values to be similar across trials; rather, this analysis is sensitive to experiment-specified task modulations of phase values even if those phases are randomly distributed across trials (Cohen and Cavanagh, 2011).

With weighted ITPC, rather than the magnitude of all vectors being 1.0, the magnitude of each vector is scaled according to the behavioral or experimental variable on that trial (e.g., reaction time or trial-specific stimulus property). (Note that some variables may need to be scaled, e.g., if they contain negative numbers, because vectors cannot have negative length.) From here, calculation of weighted ITPC proceeds as does ITPC: The length of the mean vector of the distribution is calculated.

However, statistical treatment of weighted ITPC differs from standard ITPC. Procedures for statistical analyses of ITPC have been established. If one assumes a von Mises distribution under the null hypothesis, a statistical *p*-value can be computed as $e^{-n*ITPC^2}$. Weighted ITPC, however, is not appropriate for this test because trial vector lengths are not 1.0 but rather scale with whatever behavioral or experimental manipulation is being examined (e.g., reaction time or stimulus property); thus, the average vector length can exceed 1.0.

Non-parametric permutation testing is an appropriate statistical strategy in this case. Permutation testing addresses the aforementioned issue and has the additional advantage

that it does not rely on assumptions regarding phase angle distributions. The null hypothesis in this test is that there is no consistent relationship between the behavior variable and phase angles. Note that this null hypothesis does not require a non-uniform distribution of phase angles; in other words, there can be simultaneously weak ITPC and strong weighted ITPC (see Figure 2). At each iteration in the permutation testing, the pairing of behavior/stimulus and phase angle is shuffled across trials, and weighted ITPC is computed. This shuffling can be done hundreds or thousands of times, thus creating a distribution of reaction time-phase modulations under the null hypothesis. Finally, the observed weighted ITPC (with the true behavior-phase angle pairing) can be compared to this null distribution by subtracting from the observed value the average of the shuffled values, and divided by the standard deviation of the shuffled values. This creates a standard Z score that can be interpreted in standard deviation units, and can be easily transformed into a p-value for statistical significance.

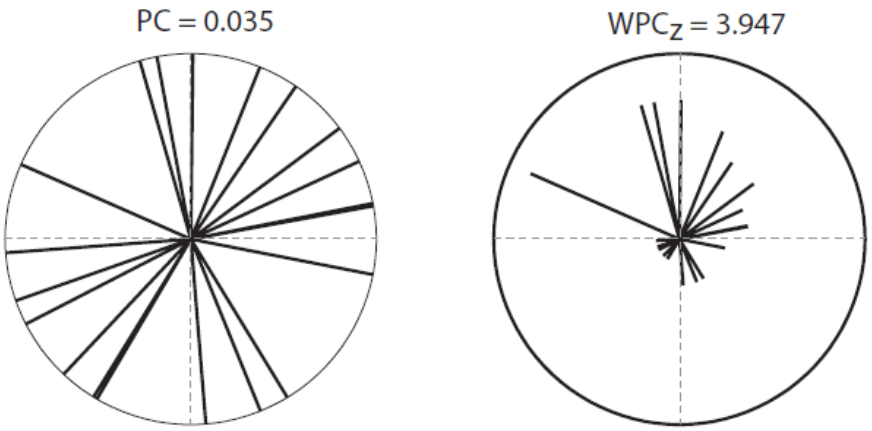

Figure 2*. Phase coherence (PC) and weighted phase coherence. Twenty random angles were generated, which results in very low coherence (0.035, on a scale from 0 to 1). The same vectors, when their length is modulated by an experiment variable such as reaction time or stimulus intensity, can reveal a link between behavior and nonlinear oscillation dynamics. A Z of 3.947 corresponds to p<0.001.*

Unfortunately, weighted ITPC is, in most situations, uninterpretable without the aforementioned permutation testing and Z-transformation. The reason is that the length of the mean vector is entirely dependent on the scale of the weighting function. Multiplying the same weighting data by a factor of say, 100, will increase the pre-Z-transformed vector length without changing the relationship between behavior and phase.

Another common use of phase information in cognitive electrophysiology is to compute inter-channel phase synchronization (ICPS). Here the goal is to assess the extent to which band-specific timing dynamics recorded from two different sensors are synchronous. ICPS is computed similarly as ITPC—the vector length of the average of unit vectors is taken as the strength of synchronization—except that the phase angles defining those vectors are differences between two phase angles (from two different sensors). Weighted ICPS can thus also be computed to assess the extent to which connectivity between two sites is modulated by behavior or stimulus properties.

These two analytic approaches—ITPC and weighted ITPC (or, ICPS and weighted ICPS) are complementary and provide different kinds of information regarding neurocognitive processing. ITPC provides insights into the overall stimulus- or response-related phase consistencies, and could be driven by a number of cognitive factors, some of which may have little relevance to the purpose of the experiment (e.g., general task orienting, working memory access, attention), whereas weighted ITPC is specific to the behavior or stimulus under investigation. For example, the simulated results presented in Figure 2 do not indicate that phase is irrelevant; rather, they show that phase is modulated by reaction time but is not "phase-reset" by the stimulus (see Cohen and Cavanagh, 2011, for examples with real data).

Cross-frequency coupling

Cross-frequency coupling (CFC) refers to a statistical relationship between two non-overlapping frequency bands. Given that two forms of information can be extracted from any frequency band—phase angle and amplitude—CFC can therefore take three forms:

amplitude/amplitude correlations (not further discussed here); *n*:*m* phase synchronization; and phase/amplitude coupling (PAC).

The mammalian neo- and archicortices generate oscillatory rhythms (Engel et al., 2001; Buzsaki and Draguhn, 2004) that interact to facilitate communication (Fries, 2005; Frohlich and McCormick, 2010). There is emerging evidence that single-frequency rhythms are often nested within other frequency bands (Schanze and Eckhorn, 1997; Roopun et al., 2008; Tort et al., 2008; Canolty and Knight, 2010), and that the "carrier" frequency to which faster oscillations are coupled depends to some extent on brain region and task (Voytek et al., 2010; Foster and Parvizi, 2012). It has been proposed that PAC reflects interactions between local microscale (Colgin et al., 2009; Quilichini et al., 2010) and systems-level macroscale neuronal ensembles (Lisman and Idiart, 1995; Fries, 2005; Canolty and Knight, 2010) that index cortical excitability and network interactions (Vanhatalo et al., 2004; Lakatos et al., 2008). From a behavioral viewpoint PAC has been shown to track learning and memory (Tort et al., 2009; Axmacher et al., 2010; Kendrick et al., 2011). PAC magnitude also fluctuates at an extremely low (<0.1 Hz) rate comparable to that seen in functional connectivity derived from BOLD fMRI data (Foster and Parvizi, 2012). Recent evidence (Voytek et al.-b, under review) has proposed a "PAC communication model" (Figure 3).

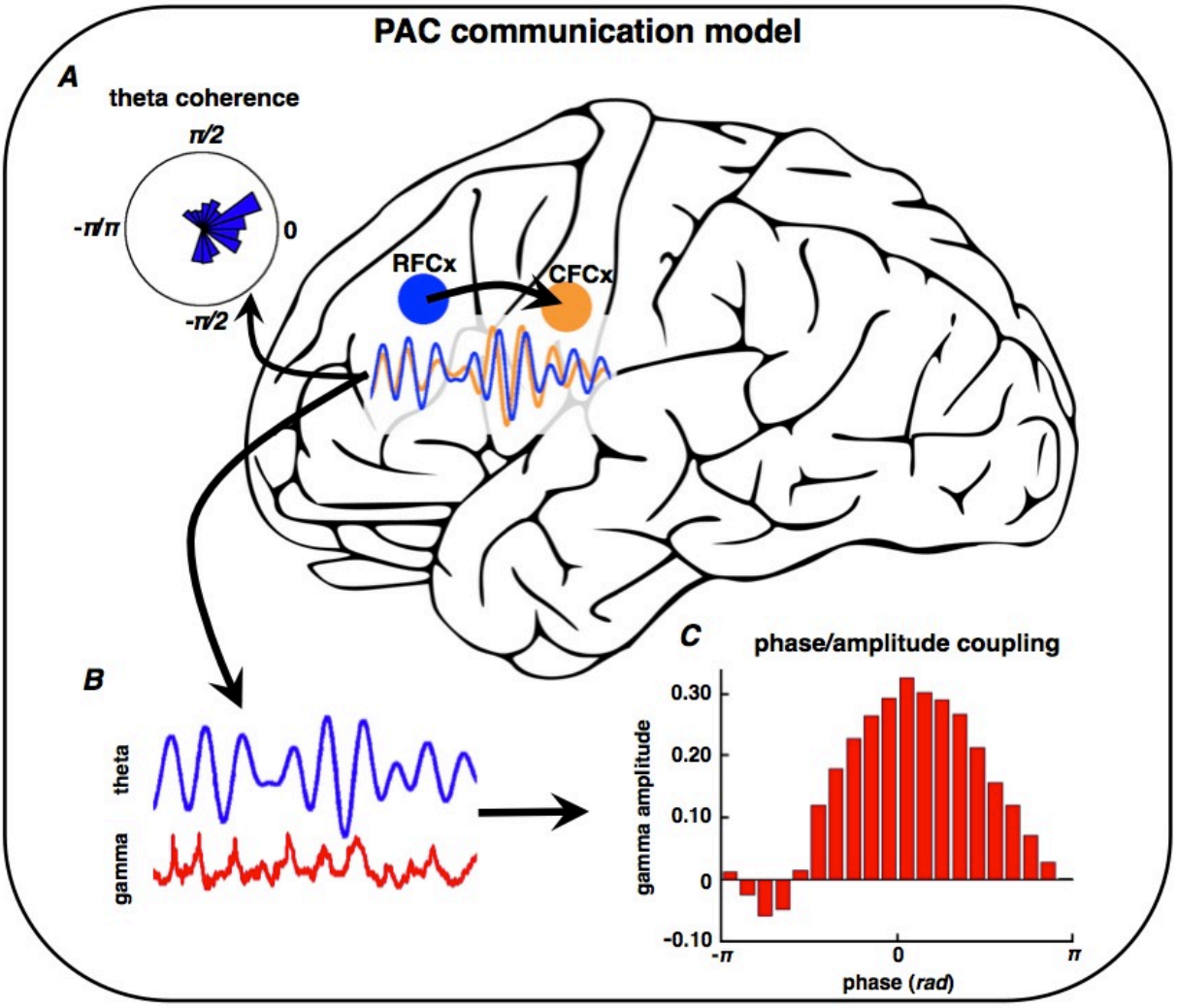

Figure 3*. Frontal PAC communication model from Voytek et al. (under review-b). (A) Two interacting brain regions, RFCx (blue) and CFCx (orange) are phase coherent—visible in the blue and orange time series—quantified by the degree of phase coherence between them (inset; in this case, near zero radians). (B) Phase coherence between regions is also associated with coupling of theta (4-8 Hz) phase (blue) to high gamma (80-150 Hz) amplitude (red) within a region. Such intraregional phase/amplitude coupling (PAC) can be seen in the co-modulation of theta phase and local neuronal activity. (C) This phase/amplitude coupling is statistically assessed as non-uniformity in the distribution of high gamma amplitude by theta phase.*

The statistical relationship between the phases of two distinct frequency bands φ_x and φ_y can be assessed as n:m phase synchronization when the ratio between the frequencies is

given by the integers n and m such that $n\varphi_x = m\varphi_y$. The mean vector between $n\varphi_x$ and $m\varphi_y$ is then computed (Penny et al., 2008):

$$P_{\varphi_x\varphi_y} = \left| \frac{1}{N} \sum_{n=1}^{N} \exp(i(n\varphi_x[t] - m\varphi_y[t])) \right|, \quad (2)$$

where a P_{xy} of unity represents perfect phase-locking between the two frequency bands and $P_{xy} = 0$ represents random relationship. This technique can be used to quantify the phase relationship between same or different frequencies within or across channels. Because P_{xy} is constrained to values between 0 and 1, for distribution-dependent (i.e., non-resampling) statistical assessments of significance it is best to apply a Fisher's z-transform to normalize the data, although resampling methods are preferable:

$$z_P = \frac{1}{2} \log\left(\frac{1+P}{1-P}\right), \quad (3)$$

There are several implementations for computing PAC, including the phase-locking algorithm in eq. 4, with a slight alteration. After extracting the phase information from a relatively lower frequency pass-band φ_x and the analytic amplitude from a higher frequency pass-band a_x, the analytic amplitude time series is then filtered again using the same pass-band used for φ_x, and a second Hilbert transform is applied to obtain an estimate of the phase modulation in the analytic amplitude (e.g., Mormann et al., 2005). The statistical relationship between these two phase time series is then calculate after eq. 2.

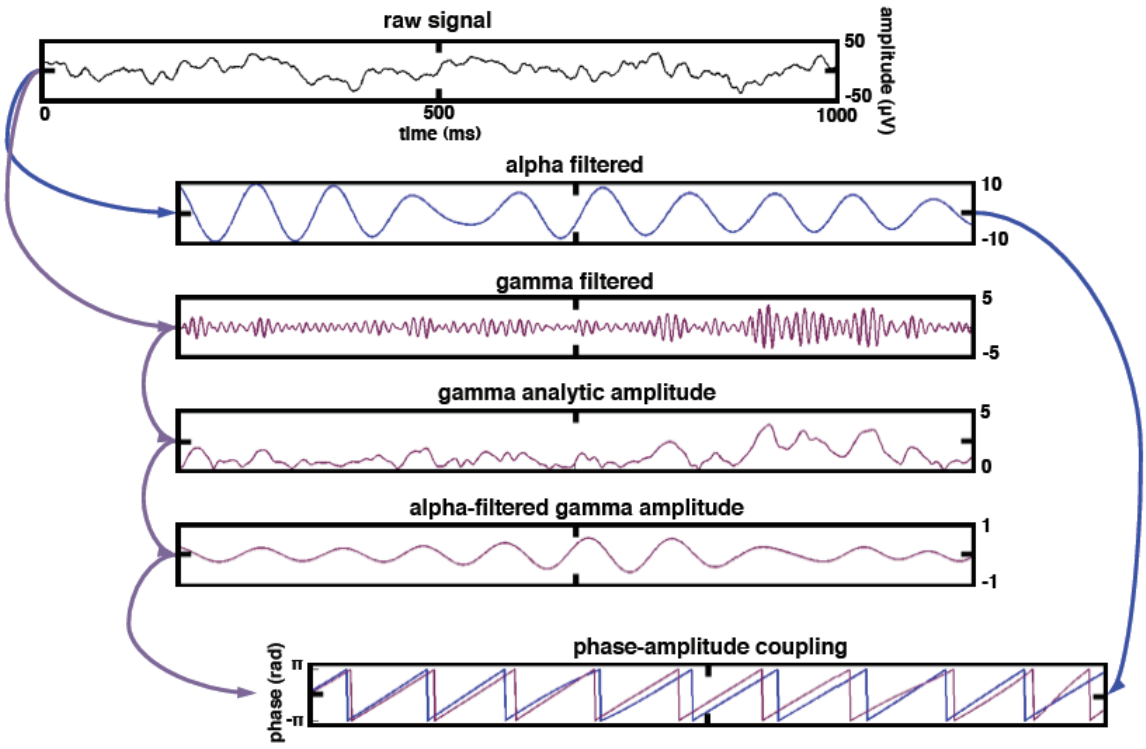

Figure 4*. Taken from Voytek et al. (2010) demonstrating the processing schematic for one technique for estimating phase-amplitude coupling. To estimate alpha phase (8-12 Hz) to broadband gamma (80-150 Hz) PAC, the raw signal was simultaneously bandpass filtered into both a low frequency alpha component as well as a high frequency broadband gamma component. The analytic amplitude of the band-passed high gamma is filtered a second time at the same frequency as alpha, giving the alpha modulation in high gamma amplitude. The phase of both the alpha-filtered signal and the alpha-filtered high gamma analytic amplitude is extracted and the phase locking between these two signals is computer. This phase locking represents the degree to which the high gamma amplitude is comodulated with the alpha phase.*

There are several other methods of computing PAC (Young and Eggermont, 2009; Canolty and Knight, 2010), for example based on a general linear model approach (Penny et al., 2008) or more exploratory techniques (Cohen, 2008). Nonetheless, the principles outlined here are the basis for most existing cross-frequency coupling techniques.

Linking cross-frequency coupling to behavior

The easiest and most straight-forward way to link CFC to behavior is to test for condition differences, or changes as a function of learning, either in the modulation strength or peak phase of CFC (Lakatos et al., 2008; Cohen et al., 2009b; Tort et al., 2009; Axmacher et al., 2010; Voytek et al., 2010; Kendrick et al., 2011), or differences between specific patient groups and matched controls (Lopez-Azcarate et al., 2010; Allen et al., 2011). It is particularly important to link CFC to behavior not only to distinguish cognition-relevant from "background" dynamics, as discussed earlier, but also because CFC can, in some cases, be spuriously detected in the presence of some artifacts (e.g., edge artifacts; Kramer et al., 2008). With proper experiment design and sufficient trials, even if such artifacts are present in the data, they would not be expected to differ as a function of task condition or performance.

PAC has been shown to track learning and memory in humans (Axmacher et al., 2010), rats (Tort et al., 2009), and sheep (Kendrick et al., 2011), as well as in theoretical simulations (Lisman and Idiart, 1995). For example, Tort et al. found that theta/gamma PAC in the rat hippocampus increased during learning and correlated strongly with behavioral performance, and PAC correlated with learning more strongly than amplitude changes alone. This result suggests that PAC may be a better neural correlate of some behavioral outcomes than band-specific amplitude alone. Similarly, Voytek et al. observed that frontal lobe theta/gamma PAC in humans increased as a function of task abstraction, and that PAC was stronger in the task-relevant theta phase-coherent frontal network compared to outside of that network.

PAC has also been linked to reward processing in human ventral striatum (Cohen et al., 2009a, 2009b). With scalp EEG, PAC has been linked to error monitoring and adaptation (Cohen and van Gaal, 2012). Specifically, frontal theta-alpha coupling reflected just-made errors, whereas parietal/occipital alpha-gamma coupling predicted accuracy of the upcoming trial. These and other (Voytek et al., 2010) findings demonstrate that different brain regions use PAC in different frequency bands to process different kinds of goal-relevant information.

Currently, the majority of PAC calculation algorithms compute a value averaged across a semi-arbitrary time window (Canolty et al., 2006; Cohen et al., 2009a; Tort et al., 2010; Voytek et al., 2010). The minimum length of this time window is bounded by the frequency of the coupling phase, as at least one full cycle is needed to calculate the distribution of values of the coupling amplitude. This means, for example, if one is investigating PAC between theta phase (4-8 Hz) and high gamma amplitude (80-150 Hz), the best temporal resolution one could achieve at 4 Hz would be 250 ms. However, the PAC metric is sensitive to noise, and recent simulations made use of >200 cycles to get a reliable PAC estimate (Tort et al., 2010). Thus, 50,000 ms or more may be required for reliable estimates of PAC (one full cycle of a 4 Hz oscillation—the minimum bound of the phase coupling bandpass—for at least 200 cycles). This requires researchers to use block designs (Voytek et al., 2010), use long trial windows at the cost of temporal resolution (Tort et al., 2009), or to concatenate time series across trials, which could introduce spurious PAC due to edge artifacts (Kramer et al., 2008).

These limitations present a problem for analyzing subcomponents of a task such as encoding, delay, and retrieval periods during working memory. However, recent work (Voytek et al. B, under review) has shown that the above methods can be used to calculate PAC relationships at an instantaneous time point across many behavioral trials in an event-related manner (ERPAC). As shown in the figure below, traditional PAC measures may miss PAC effects that are observed when analyzed using our ERPAC technique. This is likely due to the underlying differences between what the two methods address: traditional PAC asks, “what is the statistical relationship between phase and amplitude across time?” at the expense of temporal resolution. In contrast, ERPAC asks, “what is the statistical relationship between phase and amplitude across trials, at each time point?”

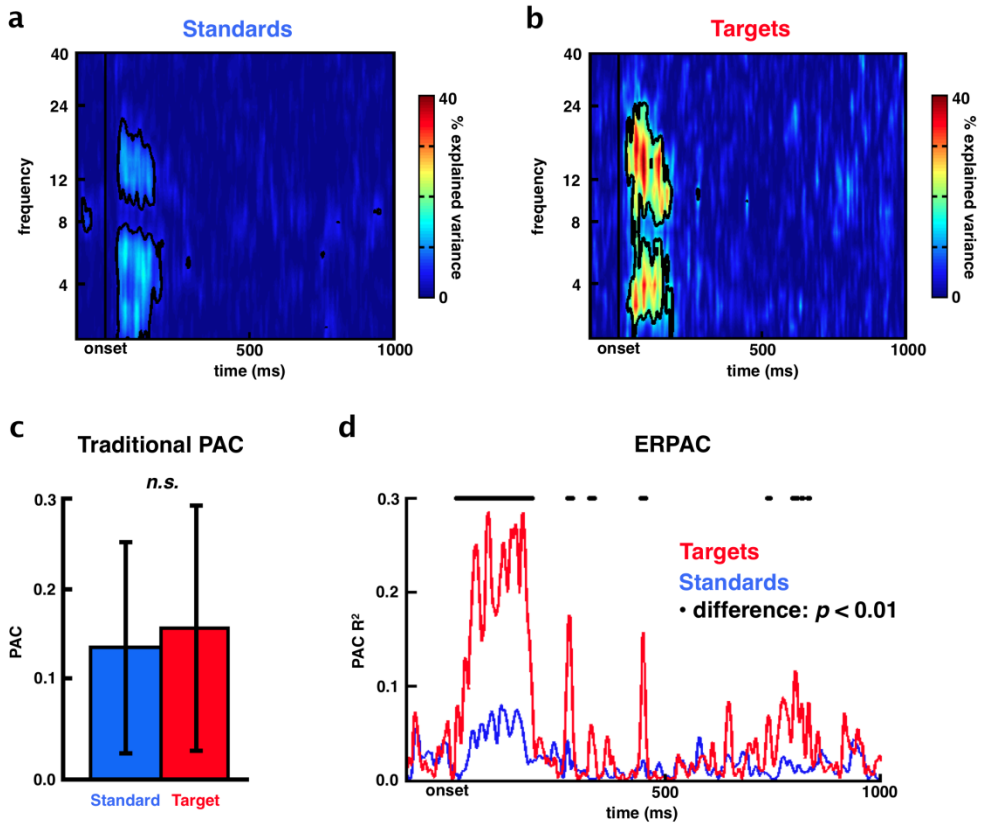

Figure 5*. Taken from Voytek et al. (under review-a). Trial-by-trial variance in low frequency phase explains a significant amount of the trial-by-trial variance in γ amplitude in visual cortex in response to (a) attended non-target standard and (b) attended target stimuli (data are from intracranial EEG form the human visual cortex). (c) Traditional PAC for a priori alpha/gamma coupling across the first 250 ms post-stimulus onset shows no significant difference between non-targets (blue) and targets (red). Note the lack of temporal resolution because PAC is calculated across time and averaged across trials. In contrast, ERPAC (d) is calculated across trials on a time point-by-time point basis. This shows that PAC in response to targets (red) is significantly higher compared to non-targets (blue) during the same 250 ms post-stimulus time window where traditional PAC showed no differences (black dots above ERPAC traces denote time points with a significant PAC difference between stimuli at p < 0.01).*

These results suggest that PAC in early visual cortex is modulated by behavioral state. Taken in conjunction with the PAC communication model outlined in Figure 3, one can interpret these results in the context of top-down communication between the prefrontal

cortex and visual cortex. In this framework, the prefrontal cortex is representing the task rules (attend to target, ignore non-targets) through phase-specific modulations of visual cortical activity. When an attended target is seen, visual cortical neuronal activity to targets is increased relative to non-target stimuli due to phase-specific modulations. This framework is intriguing because it provides a testable, neurophysiological model for top-down cognitive control.

Testing for causal involvement of nonlinear dynamics in cognition and behavior

Needless to say, assessing whether nonlinear dynamics are causally involved in the mechanisms of neural information processing is important for understanding fundamental brain processes. A lack of compelling evidence for causal involvement would suggest that nonlinear dynamics are merely useful indices of neural mechanisms, rather than reflecting core mechanisms.

There are several methods for testing the causal involvement of nonlinear dynamics in humans or behaving animals. One approach is transcranial magnetic stimulation (TMS), which refers to applying brief (<1 ms) and spatially focused magnetic pulses that transiently disrupt neural activity. TMS is known to reset ongoing brain oscillations at the dominant frequency of each brain region (Van Der Werf and Paus, 2006; Thut et al., 2011; Romei et al., 2012). In combination with EEG, TMS can be used to stimulate task-relevant brain regions at specific neural configurations, such as specific oscillation phase values or specific patterns of cross-frequency interactions (Dugue et al., 2011).

Another method for testing the causal involvement of nonlinear dynamics is transcranial alternating current stimulation (TACS). TACS is similar to TMS but uses electrical stimulation instead of magnetic stimulation, and has poorer spatial precision. One advantage of TACS is that specific temporal patterns of electrical activity can be introduced into the brain. For example, TACS can stimulate at specific frequencies (typically between 1-100 Hz), or it can stimulate at broad-band (a useful control condition). For example, stimulating at subject-specific alpha band (~8-12 Hz, but the peak frequency varies across

individuals) enhances subsequent resting-state alpha power at the stimulated frequency (Zaehle et al., 2010). TACS in combination with behavioral testing can be used to test whether processing of a stimulus is modulated according to the phase of the stimulated oscillation.

Conclusions

The overall goal of cognitive electrophysiology is to understand how neural electrical dynamics support or give rise to cognition and behavior. Here we argue that linking neural dynamics—in particular, nonlinear neural dynamics—to changes in ongoing behavior or environment properties is an important criteria for determining whether those neural dynamics are specifically involved in information processing, or whether they reflect a background state of the brain. There are several methods for linking neural dynamics to behavior dynamics using linear functions, but there are fewer methods for establishing and statistically analyzing nonlinear brain-behavior relationships. Here we reviewed several different methods for forming such nonlinear links. We hope this field will progress further in the coming years.

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