



Rhythmic pulsing: linking ongoing brain activity with evoked responses

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The conventional assumption in human cognitive electrophysiology using EEG and MEG is that the presentation of a particular event such as visual or auditory stimuli evokes a “turning on” of additional brain activity that adds to the ongoing background activity. Averaging multiple event-locked trials is thought to result in the cancellation of the seemingly random phased ongoing activity while leaving the evoked response. However, recent work strongly challenges this conventional view and demonstrates that the ongoing activity is not averaged out due to specific non-sinusoidal properties. As a consequence, systematic modulations in ongoing activity can produce slow cortical evoked responses reflecting cognitive processing. In this review we introduce the concept of “rhythmic pulsing” to account for this specific non-sinusoidal property. We will explain how rhythmic pulsing can create slow evoked responses from a physiological perspective. We will also discuss how the notion of rhythmic pulsing provides a unifying framework linking ongoing oscillations, evoked responses and the brain’s capacity to process incoming information.

Keywords: alpha oscillations, evoked responses, inhibition, amplitude asymmetry

EEG and MEG are used in neuroimaging studies to provide a real-time measure of respectively electric and magnetic fields produced by neuronal activity in the brain. The majority of EEG/MEG research attempting to link human cognition to neuronal activity examines the neuronal events (i.e., evoked response) after the occurrence of an event. The ongoing activity (already present prior to the stimulus) is often considered irrelevant and is assumed to be “averaged out” across trials (Figure 1C). Recent work has challenged the dogma that ongoing activity can simply be averaged out across trials. The key aspect of these studies is the revelation that the ongoing activity in the frequency of 10 Hz (i.e., alpha band) contains a non-sinusoidal property referred to as “amplitude asymmetry” or “baseline shift” (Figure 1B) (Nikulin et al., 2007; Mazaheri and Jensen, 2008; van Dijk et al., 2010b).

The amplitude asymmetry of ongoing oscillations entails that the peaks are modulated stronger than troughs (or *vice versa*) (Figure 1B) irrespective of the DC offset/zero-line of the signal. Amplitude asymmetric oscillations have profound consequences for event-related averaging. For example if the amplitude of ongoing oscillations is suppressed such that only the peaks are reduced in magnitude but not the troughs, averaging across trials would result in the emergence of an evoked response with a shape that is similar to the time course of amplitude suppression of the oscillation (Figure 1D). Had the magnitudes of the peaks and troughs been symmetrically decreased, no evoked responses would have been generated. The critical prerequisite for this mechanism is the differential modulation of the peaks and troughs which we propose is caused by unidirectional primary currents in pyramidal cells producing the oscillations (to be discussed further).

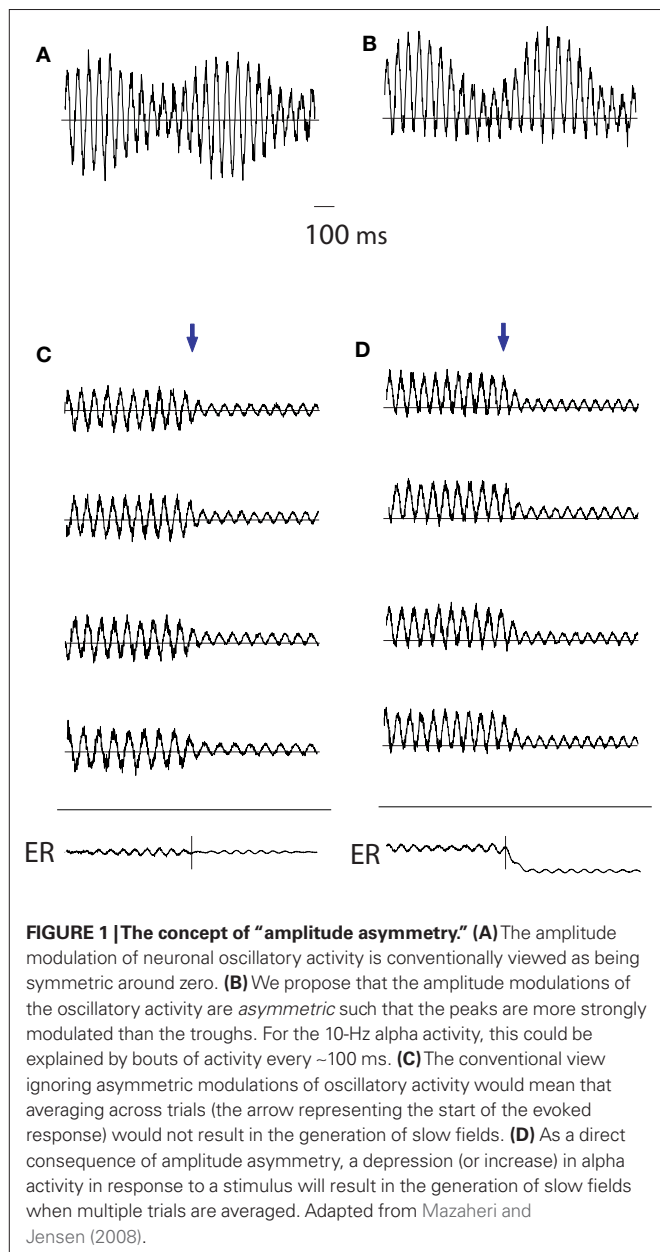
Because of the presence of amplitude asymmetry, slow evoked responses can be generated from simple changes in the amplitude of ongoing alpha activity without any turning “on” of additional brain activity.

In this review we will discuss the concept of amplitude asymmetry and its implications to the brain’s post-stimulus responses. Furthermore, we propose that ongoing alpha activity along with amplitude asymmetric properties can be conceived as rhythmic pulsing which produces bouts of inhibition every 100 ms. Processing of a stimulus can only occur between two alpha pulses; this is consistent with the view that visual processing relies on discrete processing (VanRullen and Koch, 2003). Importantly we conjecture that this rhythmic inhibition only occurs when the “pulses” of alpha activity are at a sufficiently high amplitude. We will attempt to demonstrate that the rhythmic pulsing framework fits nicely with other theoretical models of alpha activity and could potentially offer a unified account of the brain’s ongoing activity, discrete stimulus processing and evoked responses.

ONGOING OSCILLATIONS AND EVOKED RESPONSES

The evoked response reflects the brain’s transient time-locked response to a stimulus or event. Evoked responses are calculated by averaging several trials (typically 30 to a 100) time-locked to a given stimulus or event. Subsequently the pre-stimulus activity (typically in a 100- to 200-ms interval) is subtracted from the trial average. The relationship between ongoing activity and evoked responses has been a matter of debate for several decades. There are currently three different theories which attempt to account for how evoked responses are generated: *additivity*, *phase-resetting* and the recently proposed *amplitude asymmetry* mechanism (also termed *baseline-shift*).

The additive and phase-resetting models focus on the early evoked components. These early ERPs/ERFs (sometimes referred to as “exogenous components”) are transient components that occur within the first few hundred milliseconds of stimulus presentation, and are widely believed to index the arrival of information to the cortex (Coles and Rugg, 1995). The amplitude asymmetry theory focuses on the late occurring components (often referred to as “endogenous”) which emerge at least 100 ms after stimulus onset and are often sustained for hundred milliseconds or longer. There are numerous examples of the slow late components being modulated by various cognitive tasks and as such they can be viewed as a link between electrophysiology and cognition (Walter et al., 1964; Kutas and Hillyard, 1980; Sanquist et al., 1980; Hagoort and Brown, 2000; Soltani and Knight, 2000; Kilner et al., 2004; Vogel et al., 2005; Takashima et al., 2006; Rugg and Curran, 2007).



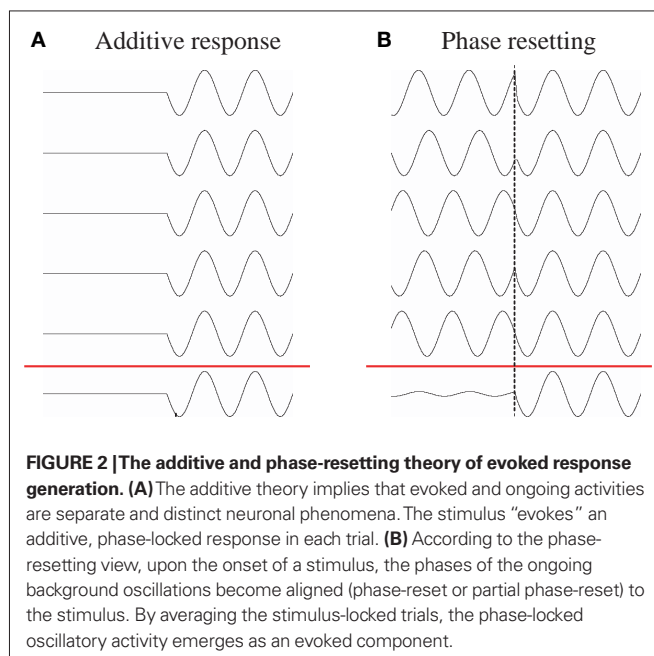
ADDITIVE THEORY VERSUS PHASE-RESETTING THEORY OF EVOKED RESPONSES

The additive theory implies that evoked and ongoing activities are separate and distinct neuronal phenomena. According to this view the stimulus “evokes” a phase-locked response adding to the activity in each trial (**Figure 2A**). In contrast, according to the phase-resetting theory, the phases of the ongoing background oscillations become aligned (phase-reset or partial phase-reset) to the stimulus (**Figure 2B**). By averaging the stimulus-locked trials, the phase-locked oscillatory activity emerges as the evoked component in the average. Since alpha oscillations (8–12 Hz) are the predominant ongoing activity in the EEG/MEG, it is believed that the phase-resetting of these oscillations is particularly relevant for producing the evoked activity (Makeig et al., 2002; Klimesch et al., 2004; Gruber et al., 2005).

Part of the issue in disambiguating the additive and phase-resetting theory is that the addition of a response can look much the same as a phase-reset of the oscillatory background activity. There are a number of informative and critical discussions about the merits of the phase-resetting versus additive modeling of evoked response generations (Fell et al., 2004; Shah et al., 2004; Makinen et al., 2005; Mazaheri and Jensen, 2006; Klimesch et al., 2007b, 2009; Min et al., 2007; Becker et al., 2008; Risner et al., 2009; Ritter and Becker, 2009). It is still a matter of debate how general the phase-resetting mechanism is for the generation of evoked responses.

AMPLITUDE ASYMMETRY AS A MECHANISM FOR THE GENERATION OF EVOKED RESPONSES

The amplitude fluctuations of oscillatory activity are conventionally viewed as being symmetric around zero (**Figure 1A**). Amplitude asymmetry refers to the observation that modulations of ongoing activity affect the peaks and the troughs of the alpha activity to different extents. This would mean that only the peak values



increase or decrease, while the trough values stay the same (*or vice versa*) (Figure 1B). Amplitude asymmetry can be found in a lot of systems around us. One way to conceptualize amplitude fluctuation asymmetry is to think of a bouncing ball: how high it jumps varies, but it cannot go lower than the floor. Another example is the light intensity in your office over days: the light at noon will vary a lot more over days compared to the light at mid-night.

One important consequence of this amplitude asymmetry of ongoing oscillations is that event-related modulations of oscillatory activity would not be “averaged out” over trials, but instead lead to the formation of slow evoked responses (Figure 1D). This is explained by a systematic depression of the peaks in response to the stimuli while the troughs remain the same. Since the phases of the individual trials are different, this will produce a slow deflection in the evoked response after trial averaging.

EVIDENCE FOR THE AMPLITUDE ASYMMETRY OF OSCILLATIONS

The amplitude asymmetry of the ongoing EEG was appreciated by Stam et al. using a measure that demonstrated that the predictability of the EEG signal in time was reduced when the signal was inverted from “peak to trough” (Stam et al., 1999b). However, the link between evoked responses and the “non-zero mean” property in oscillations was first discussed by Nikulin et al. (2007). The authors found a correlation between low frequency drifts (referred to as baseline shifts) and the ~10 Hz somatosensory rhythm. The authors speculated that the resulting baseline shifts could play a role in the formation of somatosensory evoked responses.

A direct link between the amplitude asymmetry property of oscillations and evoked responses was empirically demonstrated by Mazaheri and Jensen (2008). In this study, a measure called the Amplitude Fluctuation Asymmetry Index (AFA_{index}) was first developed to quantify the asymmetry of amplitude fluctuations. The AFA_{index} compares the variance of the peaks with the variance of the troughs by considering the normalized difference between the two measures. Later we will elaborate on the details of this measure. Using this AFA_{index} Mazaheri and Jensen (2008) were able to show that in ongoing posterior alpha activity the peaks and the troughs were indeed modulated differently. More importantly, it was shown that the direction (i.e., stronger modulation of peaks than troughs or *vice versa*) and magnitude of the AFA_{index} during a rest condition correlated with respectively the amplitude and polarity of slow ERFs in response to simple visual stimuli. Thus this study provided strong support for the notion that systematic modulations of oscillatory activity with amplitude asymmetry can produce slow evoked responses.

Recently, van Dijk et al. (2010b) were able to extend this link by demonstrating that an evoked response modulated by a cognitive task could be explained by systematic modulations in oscillatory activity. In particular the study focused on the contralateral delayed activity (CDA) component, which is a slow evoked response typically observed in working memory tasks in which hemifield specific attention is manipulated (Vogel and Machizawa, 2004; Vogel et al., 2005; Fukuda et al., 2010). The key finding was that the emergence of the CDA could be explained by modulations in alpha activity (Figure 3). Previous studies have suggested alpha activity to be

Relation between the CDA, alpha power and amplitude asymmetry

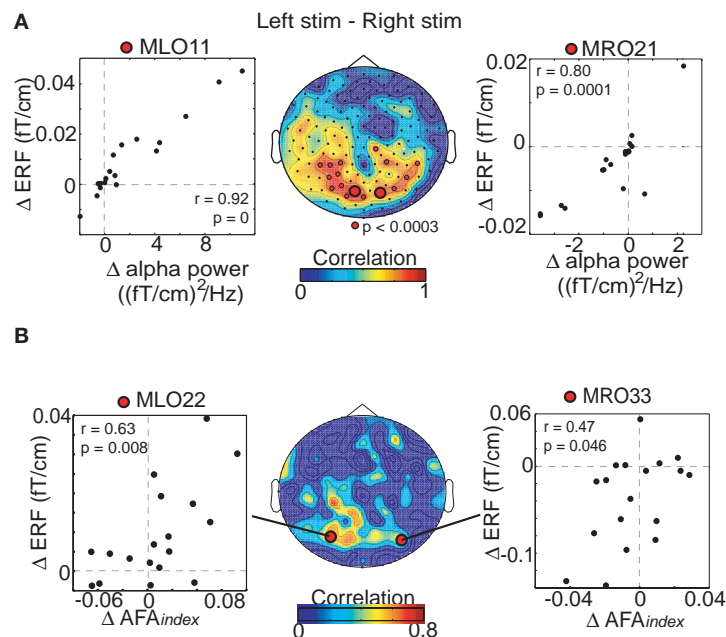


FIGURE 3 | Relation between the evoked component produced in a working memory task and modulations in hemispheric alpha power lateralization. (A) Correlation over subjects of differences in ERFs and alpha power modulations [left minus right target stimuli (stim)] for a left sensor and a right sensor (Left and Right, respectively). The correlations

were highly significant. The topography (Middle) of the correlation coefficients. **(B)** Correlations over subjects between the differences (left minus right stimuli) in sustained ERFs and the differences in absolute alpha amplitude asymmetry (AFA_{index}) during retention. Adapted from van Dijk et al. (2010b).

involved in the functional inhibition of task-irrelevant regions (Klimesch, 1999; Klimesch et al., 1999, 2007a; Jensen et al., 2002; Jokisch and Jensen, 2007; Tuladhar et al., 2007; Jensen and Mazaheri, in press). Thus van Dijk et al. (2010b) proposed that the CDA is not attributable to an additive process reflecting memory maintenance *per se* but rather to changes in ongoing oscillatory alpha activity reflecting inhibition of task-irrelevant regions, while routing information to task-relevant regions. This view is further supported by recent findings of Sauseng et al. (2009) in which a similar design was used to demonstrate that modulation of hemispheric alpha lateralization predicted memory capacity based on efficient suppression of irrelevant information in short-term memory.

Although the amplitude asymmetry model suggests that certain endogenous responses are produced by modulations in oscillatory power, this does not question the merits of previous ERP/ERF studies. If a specific slow ERP/ERF is revealed to be produced by modulations in oscillatory activity, this does not mean that the conventional ERP/ERF analysis is inappropriate as a tool in cognitive neuroscience. Rather, if the mechanism of a particular evoked response can be linked to a modulation of ongoing activity, it could provide a stronger account for the neuronal substrate generating the slow evoked responses. Also, it can help interpreting the functional role of the evoked responses given that one can build on the insight gained from the role of oscillatory activity (see, e.g., van Dijk et al., 2010b).

PREREQUISITE FOR LINKING THE MODULATION OF ONGOING OSCILLATIONS TO EVOKED COMPONENTS

How is it possible to determine if the mechanism behind a specific evoked response is due to modulation of ongoing activity with amplitude asymmetry? We introduce four prerequisites for linking modulations of oscillatory activity to evoked component generation.

1. The ongoing MEG/EEG oscillations must be modulated in amplitude by the stimuli or event
2. This amplitude modulation of the ongoing activity must correlate with the time course of the evoked response (over trials or subjects)
3. The ongoing oscillations must have an amplitude asymmetry
4. The magnitude and/or polarity of the amplitude asymmetry must relate to the amplitude and/or polarity of the evoked responses (over trials or subjects)

Event-related changes in oscillatory alpha activity have been demonstrated in many cognitive paradigms (Klimesch et al., 1997; Salenius et al., 1997; Klimesch, 1999; Jensen et al., 2002; Makeig et al., 2004; Mazaheri and Picton, 2005; Bastiaansen and Hagoort, 2006; Sauseng et al., 2006; Jokisch and Jensen, 2007). Perhaps the most challenging step in linking oscillatory changes to evoked responses is the quantification of the amplitude asymmetry of the ongoing signal. For this step, two different measures have so far been proposed: the AFA_{index} (Mazaheri and Jensen, 2008) and baseline shift index (BSI) (Nikulin et al., 2007).

ANALYTICAL METHODS FOR MEASURING AMPLITUDE ASYMMETRY

The AFA_{index} quantifies the ratio of the variance of the peaks and troughs where S_{peaks} and S_{troughs} refer to the peak and trough values identified in the ongoing oscillatory signal:

$$\text{AFA}_{\text{index}} = \frac{\text{Var}(S_{\text{peaks}}) - \text{Var}(S_{\text{troughs}})}{\text{Var}(S_{\text{peaks}}) + \text{Var}(S_{\text{troughs}})} \quad (1)$$

When using the AFA_{index}, the signal is first bandpass-filtered in the frequency band of interest (Figure 4A). Next the time points for the peaks and troughs of the bandpassed data can be identified. These time points are then used to obtain the signal values of peaks and troughs in the raw data. The variance of these values is then used to calculate the AFA_{index}.

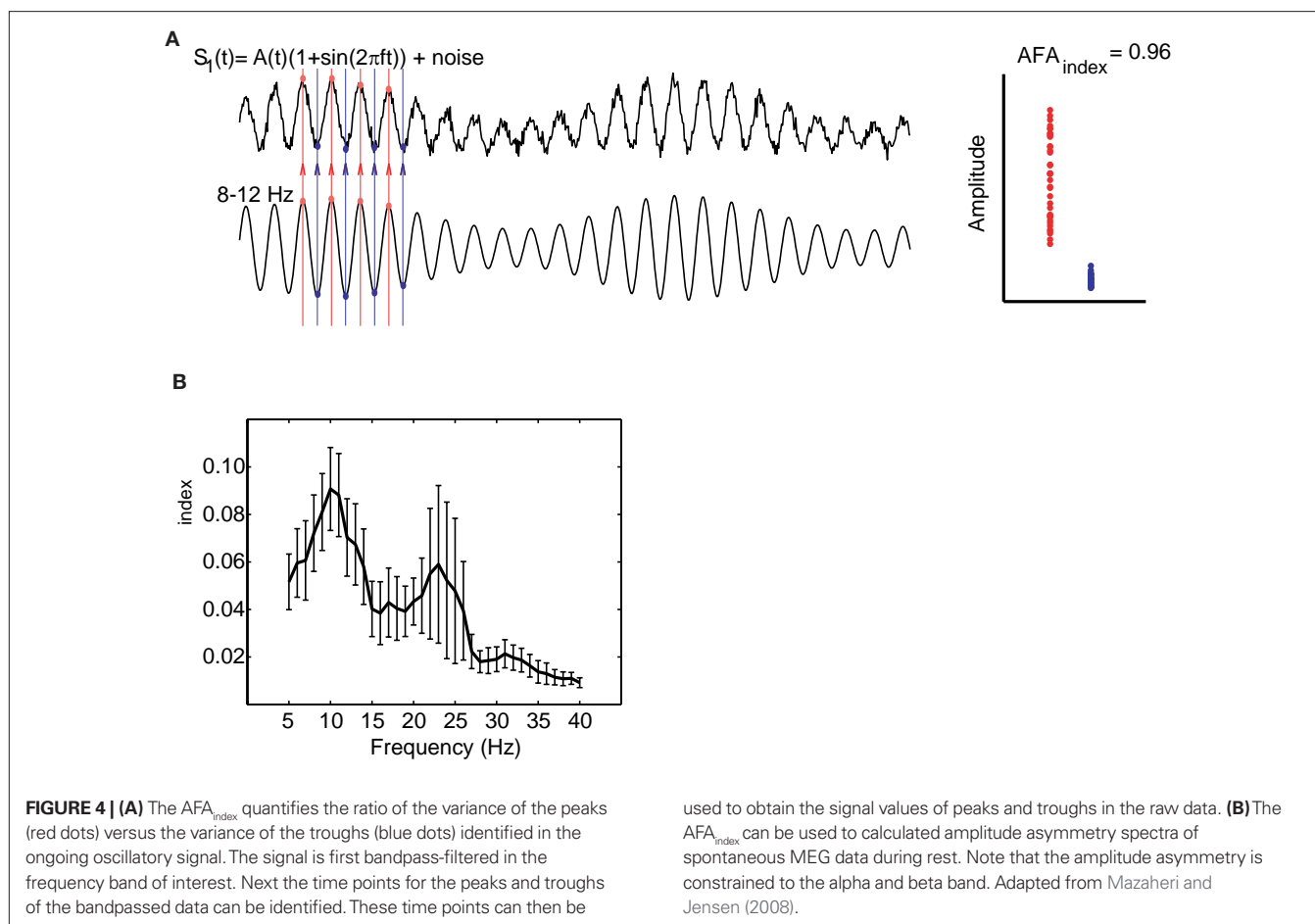
Accordingly, positive AFA_{index} values indicate a stronger modulation of the peaks and negative values indicate a stronger modulation of the troughs, while values close to zero indicate symmetrical modulation.

By considering the difference between the variance of the peaks and troughs to the ratio of amplitudes, this measure is relatively immune to DC-like offsets that sometimes appear in MEG and EEG measurements. In order to ensure that this measure was not a consequence of a slow DC offset interacting with the alpha rhythm we (Mazaheri and Jensen, 2008) investigated various principles of actions using constructed surrogate signals. These simulations demonstrated that the AFA_{index} successfully can detect true asymmetric amplitude fluctuation while being immune to slow multiplicative or additive modulations. The simulations can be seen in Figure 5.

When applying the AFA_{index} one issue to consider is the time window in which the variance across peaks and troughs are measured. This time window would be dependent on the frequency of interest. A very short time window is not optimal, since then there simply would not be enough peaks/troughs to reliably assess the variance. To quantify the amplitude asymmetry of alpha and beta oscillations Mazaheri and Jensen (2008) used a time window of 5 s to calculate the asymmetry index, whereas van Dijk et al. (2010b) was able to successfully do this using a period of 1 s. However, future empirical work needs to be done to precisely characterize the optimal temporal parameters relevant for detection of amplitude asymmetry.

It should be mentioned that the AFA_{index} can potentially be sensitive to harmonics present in the signal (Nikulin et al., 2010). For instance, 20 Hz harmonics can in some cases produce a non-zero AFA_{index} in the 10 Hz band. However, a non-zero AFA_{index} due to harmonics cannot produce slow evoked responses (Jensen et al., 2010; Nikulin et al., 2010) and as such would not have a relationship to the amplitude and polarity of evoked responses. One way to reduce the effect of harmonics on the AFA_{index} is to lowpass filter the raw data at the frequency below the harmonic but above the frequency of interest (in the case of the alpha band it would be ~15 Hz). Importantly the AFA_{index} can be correlated with both magnitude and/or the polarity of evoked responses (Figures 3 and 6). This has been successfully done for both visual evoked responses and working memory related evoked responses (Mazaheri and Jensen, 2008; van Dijk et al., 2010b). Thus, given that the AFA_{index} was strongly correlated with the evoked responses, these findings cannot be explained by harmonics of the alpha oscillation.

The BSI is an alternative measure to the AFA_{index} and quantifies the correlation between oscillatory activity in a given frequency band and low frequency fluctuations (Figure 7). First, the ongoing activity is filtered in two ways: using bandpass filters (e.g., 8–12 Hz) and a lowpass filter at 3 Hz. The BSI reflects the regression between the bandpassed and lowpass filtered signal's amplitude values



(Nikulin et al., 2007). The measure does depend on extensive pre-processing and it would be highly interesting to investigate if it has a quantitative relationship with evoked responses.

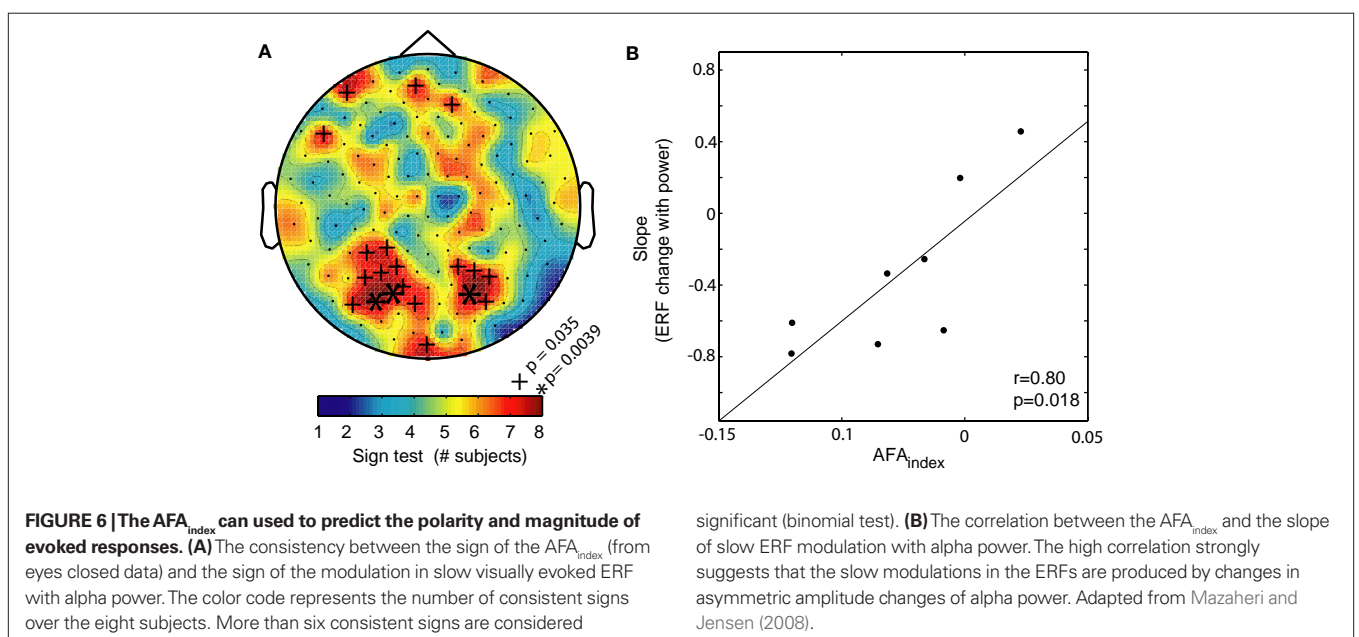
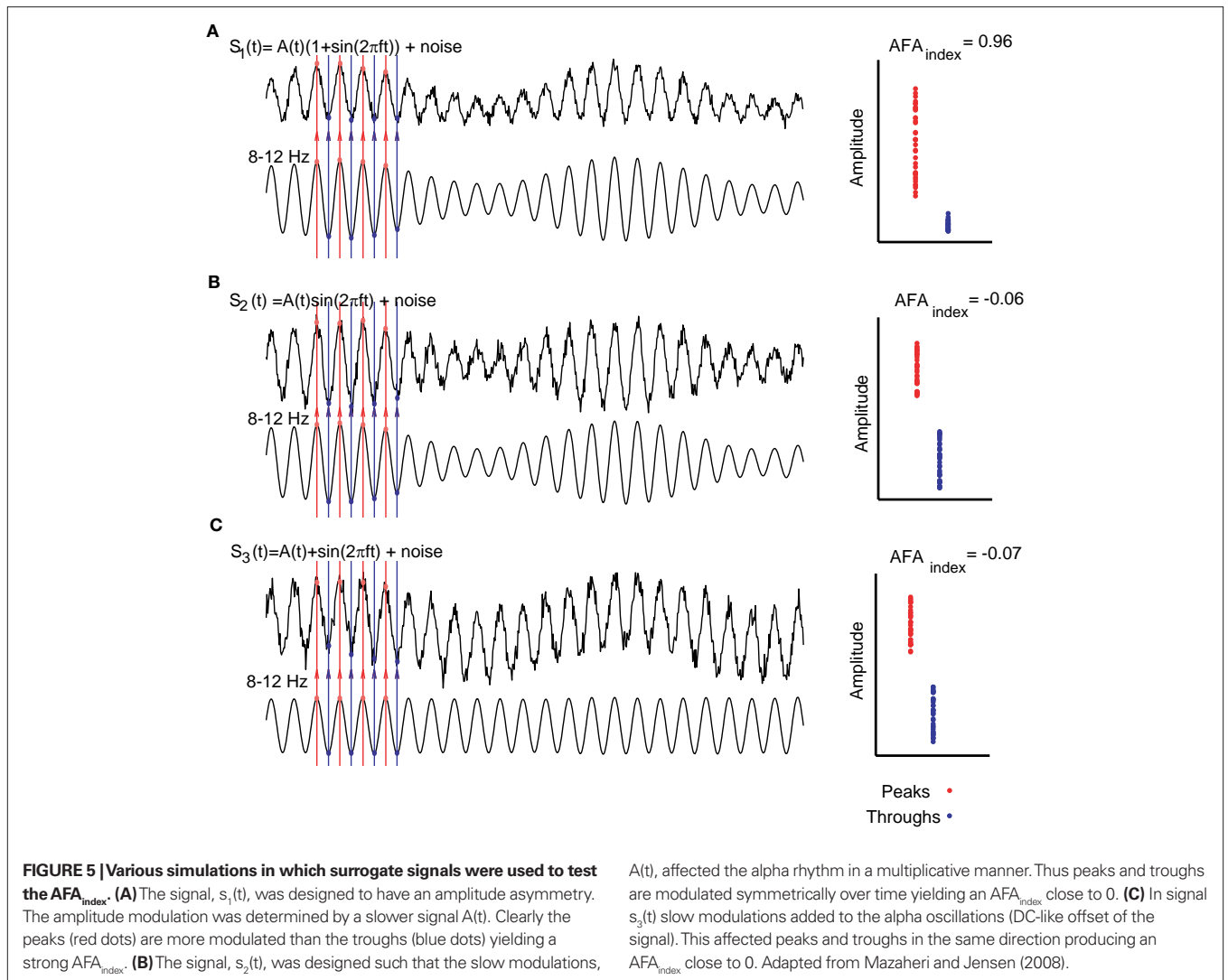
In conclusion amplitude asymmetry has been demonstrated to be an intrinsic property of ongoing oscillatory activity in the alpha band using different analytic techniques. Moreover a strong link between the amplitude asymmetry of alpha activity and evoked responses has also been established. We propose that amplitude asymmetric oscillations can be viewed as rhythmic pulsing through which information processing is facilitated or inhibited. In the next section we will discuss the hypothesized underlying physiology of amplitude asymmetric alpha activity and its function in rhythmic pulsing.

THE UNDERLYING PHYSIOLOGY OF RHYTHMIC PULSING

Which physiological mechanisms can account for amplitude asymmetry? EEG and MEG signals are primarily thought to be produced by dendritic currents in pyramidal cells (Hamalainen et al., 1993). These intracellular currents are typically generated by electrical events at the apical dendrite or the soma. Such events include excitatory synaptic input at distal dendrites and after-hyperpolarization currents (Wu and Okada, 1999; Murakami and Okada, 2006). In order to generate oscillatory activity with symmetric amplitude fluctuations (Figure 1A) there must be intracellular currents propagating forward and backward down the dendrites with the same magnitude (respectively producing the troughs and peaks).

However, even though back-propagating dendrite currents are known to exist, it would be unlikely that they exactly match the synaptic forward propagating currents. We conjecture that the currents producing the alpha activity are asymmetric, i.e., primarily explained by forward propagating dendritic currents most likely due to excitatory synaptic inputs and after-hyperpolarization currents. It is this asymmetry between the magnitude of forward and backwards current flow that gives the ongoing alpha activity its amplitude asymmetry property (Figures 1B and 8B). It should be mentioned that these primary intracellular dendritic currents produce instantaneous return currents (also known as volume currents). While MEG primarily detects the magnetic fields produced by the intracellular dendritic currents, EEG detects the differences in scalp potentials arising from the return currents. An illustration of this proposed neurobiological mechanism of asymmetry and its implications for MEG and EEG measurements can be seen in Figure 8.

We postulate that the amplitude asymmetric alpha activity can be viewed as rhythmic pulses producing bouts of inhibition repeated every 100 ms. How might this inhibition come about? GABAergic feedbacks from interneurons have been strongly implicated in the physiological mechanism generating the alpha rhythm (Lopes da Silva et al., 1976; Crunelli and Leresche, 1991; Jones et al., 2000). Thus it is possible that rhythmic neuronal activity generating the alpha oscillations is a consequence of a GABAergic inhibitory feedback paced by neocortical or thalamic rhythm generators (Hughes and Crunelli, 2005; Lorincz et al., 2008, 2009). This



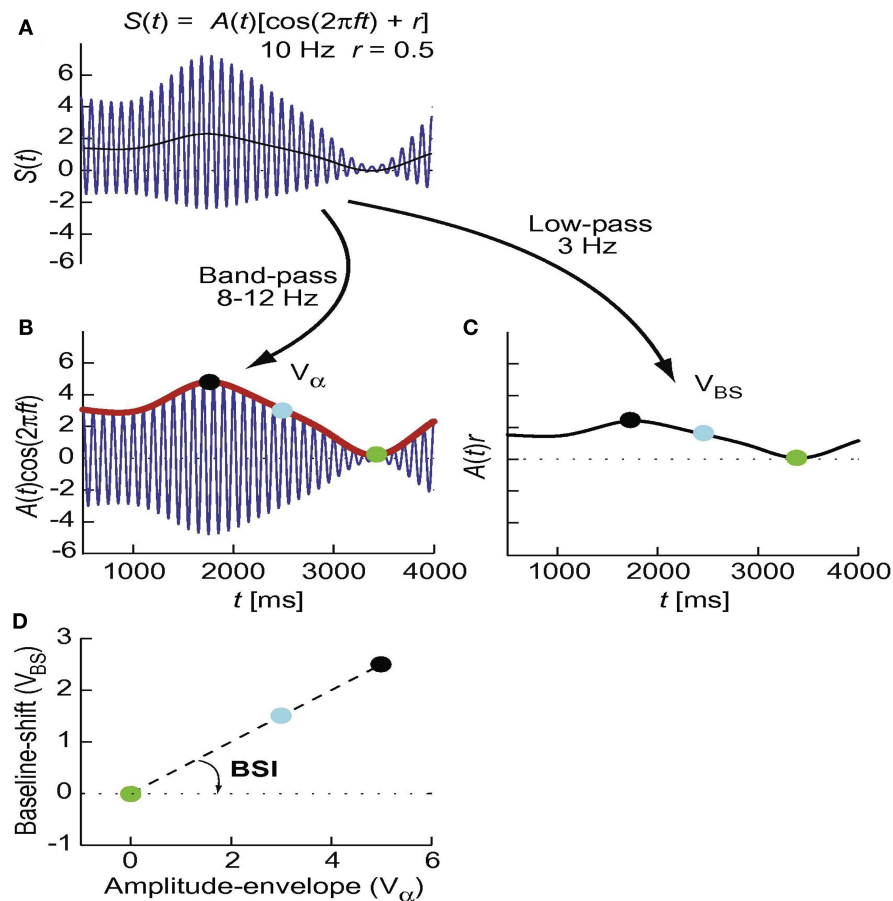


FIGURE 7 | Schematic presentation of the derivation of the baseline shift index (BSI). First, the signal in (A) is filtered in two ways to separate the amplitude envelope of the oscillations and the baseline shift $A(t)r$ [thin black line in (A)]. The amplitude envelope (V_α) is obtained using bandpass filters (e.g., 8–12 Hz) and the Hilbert transform [(B), red thick line]. The baseline shifts (V_{BS}) are part of the signal at considerably lower frequencies than the oscillatory “carrier” signal and, therefore, are obtained by lowpass filtering,

e.g., at 3 Hz (C). The amplitude-envelope values are sorted into bins (e.g., 20 bins) and values from the baseline shift signal are sorted into the corresponding bins (note the temporal correspondence of dots with the same color). (D) Within-bin averaged values for the amplitude envelope and baseline shifts are plotted against each other and the slope of the regression line is calculated. This slope is the baseline shift index or BSI. Adapted from Nikulin et al. (2007).

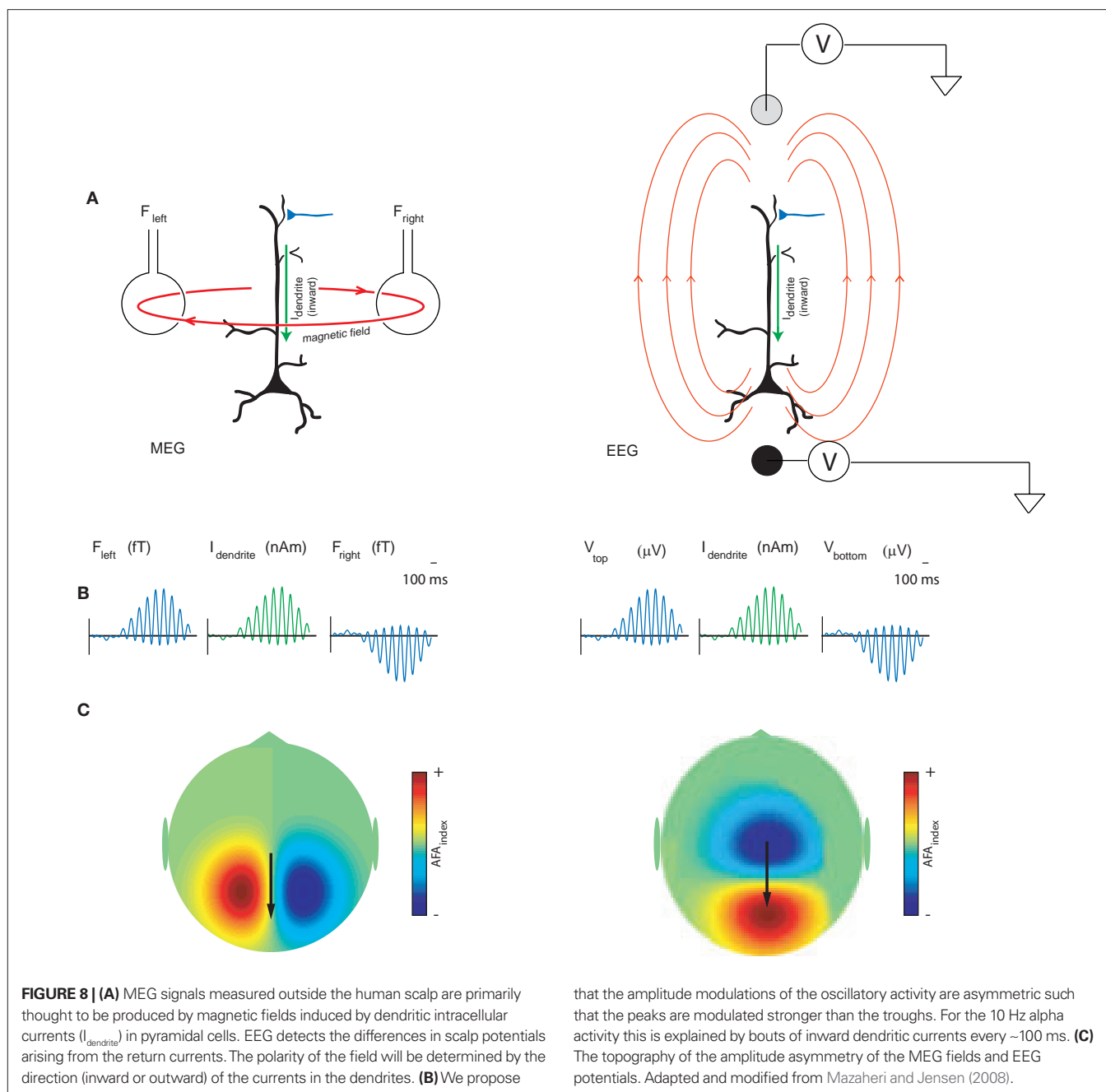
GABAergic feedback could serve to directly silence processing in pyramidal neurons or reduce the efficacy of excitatory input by shunting inhibition.

In order to further explain how pulsed inhibition could be reflected in the neuronal firing of pyramidal cells and subsequently the MEG signal, we constructed a simple model (Figure 9). In this model, 500 pyramidal cells are modulated by a 10 Hz inhibitory signal. The signal serves to silence the firing of the pyramidal cells in a phasic manner. As a consequence a pattern of rhythmic pulsing emerges. The MEG signal is thought to be produced by the dendritic current in the pyramidal cells. Thus the inhibition results in an MEG signal having amplitude asymmetry. This model might also explain the inverse relationship between the alpha activity and the BOLD signal (Goldman et al., 2002; Goncalves et al., 2006; Laufs et al., 2006; Ritter et al., 2009; Scheeringa et al., 2009; Yuan et al., 2010). In the example in Figure 9, the firing rate is highest (e.g., 0.4–0.6 s) when the “10 Hz signal” is low compared to when the “10 Hz signal” is high (e.g., 0.8–1.0 s). Since firing rate is linked to the BOLD signal, it would have a negative relationship to the alpha activity.

Interestingly, amplitude asymmetry can emerge from even very simple models of oscillatory activity. In 1976, Lopes da Silva et al. proposed a computational model that could account for certain features of the alpha activity. The model was composed of thalamocortical relay neurons coupled with inhibitory interneurons (Lopes da Silva et al., 1976; Stam et al., 1999a). As seen in Figure 10, this model produced alpha oscillations with amplitude asymmetry (even though this was not essential for the authors). This underscores that amplitude asymmetry is a natural phenomenon that easily can arise from physiological models of oscillatory activity. In fact, we posit that amplitude asymmetry is the norm and amplitude symmetry is the exception.

EVIDENCE SUPPORTING RHYTHMIC PULSING CROSS-FREQUENCY PHASE-AMPLITUDE COUPLING

The rhythmic pulsing view fits conceptually well with recent evidence that the power of gamma oscillations is phase-locked to posterior alpha activity. Gamma oscillations have long been implicated in neuronal processing in various tasks (Fell et al., 2003;

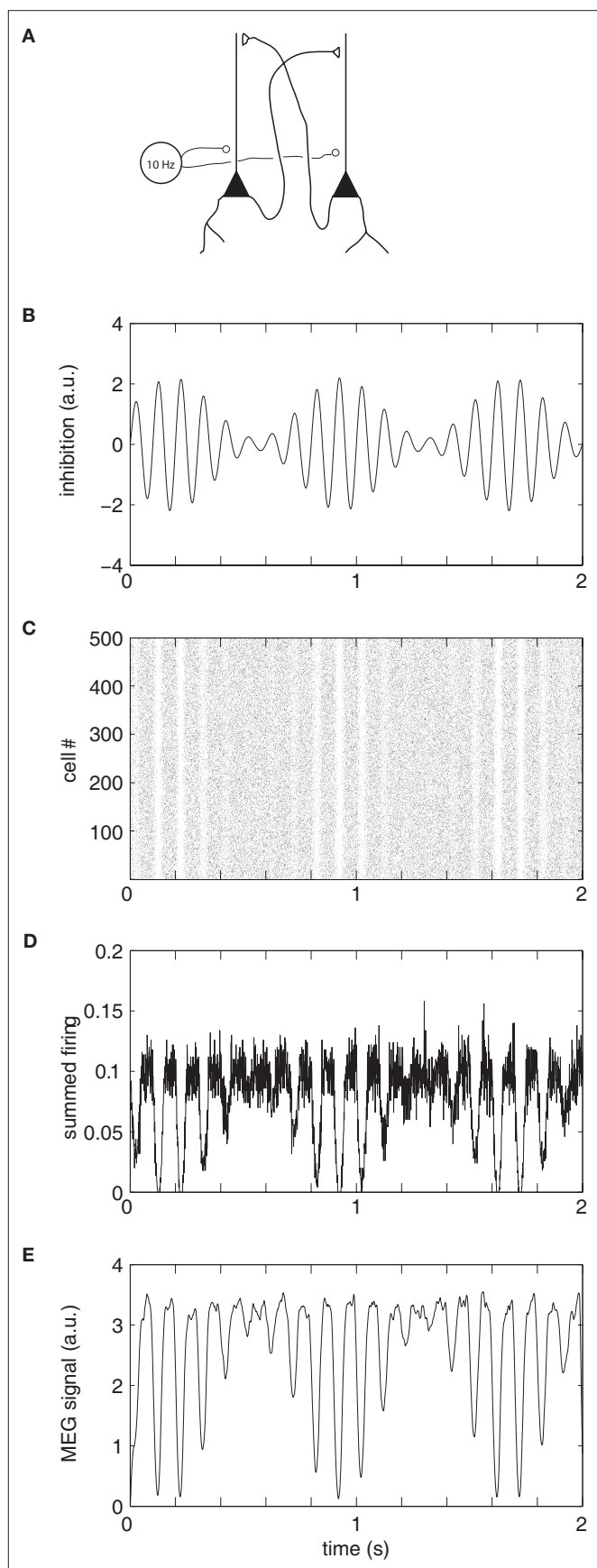


Lachaux et al., 2005; Womelsdorf et al., 2006; Fries et al., 2007; Jensen et al., 2007). One of the models proposed for explaining this interaction entails the amplitude fluctuations of alpha activity to be asymmetric (**Figure 11**). According to this model the gamma burst responsible for visual processing can only occur at alpha phases when the inhibition is sufficiently low (i.e., the trough). When the alpha inhibition is very weak, gamma can occur over the entire cycle of alpha. Such a model of alpha phase to gamma power interaction is consistent with many studies that have found a decrease in alpha to accompany and increase in gamma (Basar et al., 2001; Jokisch and Jensen, 2007; de Lange et al., 2008; Shahin et al., 2009). However, it must be noted that although we conjecture that amplitude asymmetry fits readily with phase-power

coupling across oscillations, it is not necessary for oscillations to be amplitude asymmetric to exhibit phase-power relationships. Moreover a direct functional link between alpha phase and gamma power still remains to be empirically determined.

ONGOING ALPHA AMPLITUDE AND INHIBITION

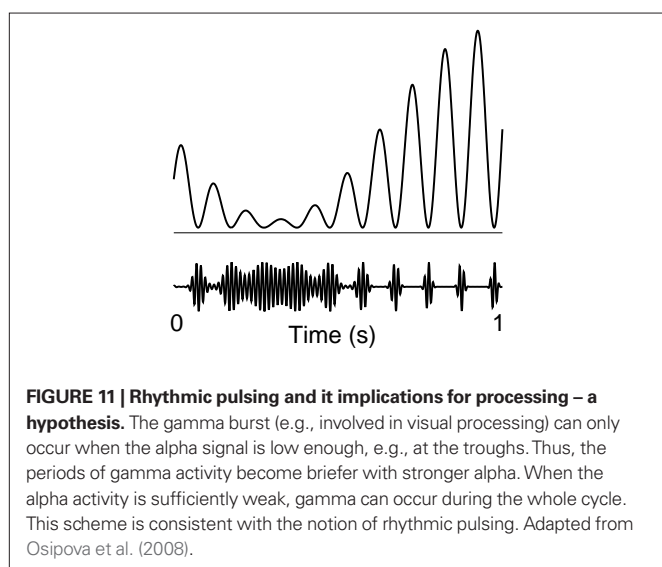
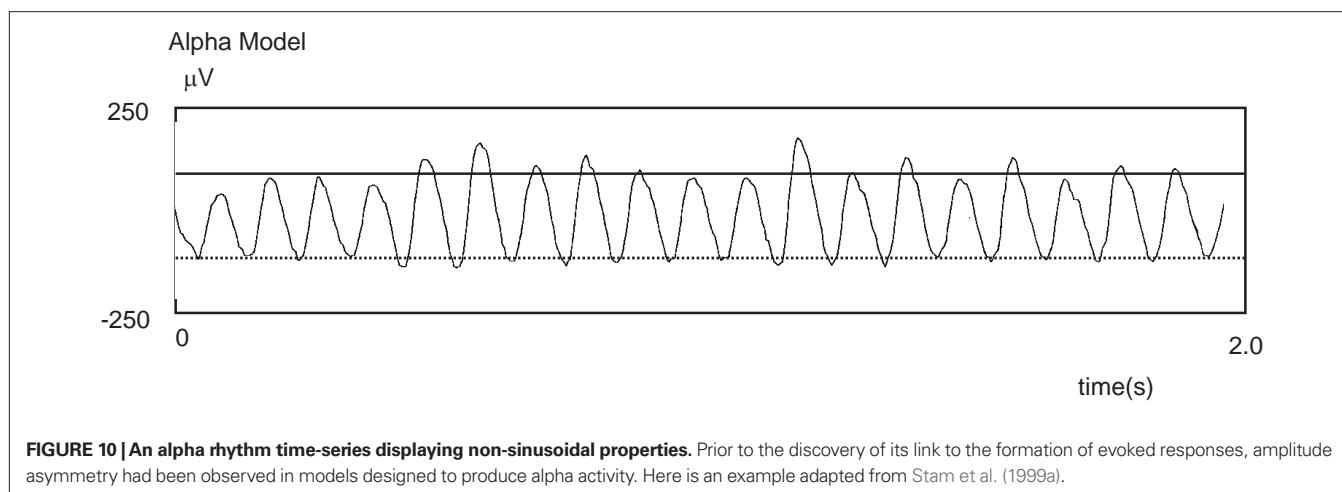
Klimesch et al. (2007a) recently proposed the inhibition-timing hypothesis where alpha oscillations play an important role in the brain's capacity to process information. They postulated that a reduction in the amplitude of the ongoing alpha activity reflects a state of comparatively high excitability, whereas high amplitudes reflect a state of inhibition (comparatively low excitability).



In fact it was first suggested almost 80 years ago that that the cortex exhibits cyclic changes between maximal and minimal responsiveness (Bishop, 1933). Since then a number of studies have showed an influence of the phase of the ongoing alpha activity on processing of visual stimuli (Callaway and Yeager, 1960; Varela et al., 1981). Two very recent EEG studies by Mathewson et al. (2009) and Busch et al. (2009) have reported a functional link between the phase of the pre-stimulus alpha oscillations and conscious perception by using threshold stimuli. The authors conjecture that the alpha inhibition is limited to parts of the cycle, generating a form of “pulsed inhibition.” We suggest that this pulsed inhibition occurs as a function of the amplitude asymmetric property of the ongoing oscillations.

Evidence supporting the inhibitory nature of alpha activity has been found in a number of studies that demonstrate an increase or decrease in the amplitude of alpha activity depending on the visual stream engaged in a given task. (Worden et al., 2000; Thut et al., 2003, 2006; Kelly, et al., 2006; Jokisch and Jensen, 2007; Medendorp et al., 2007; Rihs et al., 2007; Romei et al., 2007, 2008; van Dijk et al., 2008; Zhang et al., 2008). The functional role of alpha in defining the brain state does not seem to be restricted to visual tasks. A recent study has found alpha power lateralization at parieto-occipital sites to be modulated by the direction of auditory attention to continuous speech in space (Kerlin et al., 2010). In a working memory study on maintaining pitches, alpha activity from left superior temporal areas increased during the retention interval (van Dijk et al., 2010a). This temporal alpha activity, possibly being the tau-rhythm (Lehtela et al., 1997) is likely to reflect inhibition of the left auditory cortex in order to allocate resources to the right auditory cortex involved in pitch processing. In a somatosensory working memory task, the alpha activity decreased in the primary sensorimotor cortex contralateral to the engaged hand while it increased in the ipsilateral hemisphere (Haegens et al., 2010). In summary these studies are consistent with the idea that the functional inhibition of a region in the cortex is mediated by increasing oscillatory activity in the alpha band (8-13 Hz) (Jensen and Mazaheri, in press).

FIGURE 9 | A simple model explaining how pulsed inhibition is reflected in neuronal firing of pyramidal cells and subsequently the MEG signal. (A) Pyramidal cells are mutually synaptically coupled. The synaptic currents produce the MEG signal. We here assume a Poisson distribution of firing which is phasically silenced by an inhibitory GABAergic signal. **(B)** The signal at 10 Hz exercises an inhibitory drive silencing the firing of the pyramidal cells in a phasic manner. The magnitude of the inhibition is modulated by an arbitrary slower signal. **(C)** A raster diagram showing the firing of 500 pyramidal cells. The bouts of inhibition serve to silence the firing. In periods when the inhibition is low, the firing will persist (e.g., 0.4–0.6 s). **(D)** The summed firing of all the pyramidal cells (summed using a $\Delta t = 1$ ms sliding time window). **(E)** Each spike was convolved with an alpha-function ($\alpha(t) = (t/\tau) e^{1-(t/\tau)}$, where $\tau = 5$ ms) in order to approximate the post-synaptic current. These post-synaptic currents were then averaged over the pyramidal neurons. The “MEG signal” (arbitrary units, arbitrary offset) is proportional to the total dendritic current. Note that the inhibition results in a rhythmically pulsed MEG signal with amplitude asymmetry.



OPEN QUESTIONS AND CAVEATS FOR FUTURE RESEARCH

RELATIONSHIP BETWEEN OSCILLATIONS AND BOLD

Understanding the relationship between the brain's ongoing oscillations and evoked activity is quite important to the field of human electrophysiology since it is bound to lead to a fundamentally better understanding of how the signals measured by MEG/EEG link to cognition. Moreover understanding this relationship can extend beyond the realm of EEG and MEG research because evoked responses provide a critical link between the hemodynamic response measured by the fMRI and the underlying temporal dynamics of neuronal activity. There are now a number of studies that have correlated the amplitude of alpha activity with the BOLD signal (Goldman et al., 2002; Goncalves et al., 2006; Laufs et al., 2006; Ritter et al., 2009; Scheeringa et al., 2009; Yuan et al., 2010). However, the relationships between the pre-stimulus phase and amplitude of the ongoing alpha activity and the stimulus evoked BOLD have thus far not been investigated. If a relationship between pre-stimulus alpha phase and BOLD is demonstrated it would support the phasic aspect of the alpha oscillations and demonstrate that alpha activity has direct con-

sequences for neuronal excitability. Moreover, the combination of brain stimulation by transcranial magnetic stimulation (TMS) with EEG can provide real-time information on the phasic aspects of cortical reactivity (Thut and Miniussi, 2009; Miniussi and Thut, 2010). Indeed, recent studies have found that the phase of the spinal beta rhythm in which the input (a TMS pulse) arrives modulated the gain of this input (Maki and Ilmoniemi, 2010; van Elswijk et al., 2010).

WHAT ABOUT OTHER RHYTHMS?

The mechanism behind amplitude asymmetry of oscillatory activity need not be specific to alpha oscillations. The unidirectional primary currents in pyramidal cells could also be responsible for asymmetry in other frequencies bands as well. There is a body of research pointing to delta oscillations serving a fundamental role in the active input selection at primary sensory cortex level (Lakatos et al., 2007, 2008; Schroeder and Lakatos, 2009). According to this view the phase of the delta rhythm serves as a master controller of neuronal excitability. The relationship between delta phase and alpha activity needs to be explored. For example delta activity might reflect a top-down regulations of the alpha activity. Thus the time course of delta active could be comparable to the ERPs/ERFs produced by the modulation of the amplitude asymmetric alpha activity. The late occurring slow evoked responses can be viewed as the link between electrophysiology and cognition. These responses have been found to index working memory capacity (Vogel et al., 2005), long-term memory encoding and recognition (Sanquist et al., 1980; Takashima et al., 2006; Rugg and Curran, 2007), action monitoring (Kilner et al., 2004), language comprehension (Kutas and Hillyard, 1980; Hagoort and Brown, 2000), response preparation (Walter et al., 1964), and novelty detection (Soltani and Knight, 2000). Yet the exact physiological mechanism for how these responses are generated is still unknown.

Future work is required in order to investigate if the principle of amplitude asymmetry and the generation of evoked responses can be generalized to frequency bands beyond the alpha range. Averaging epochs of amplitude asymmetric oscillations will result in an evoked response with a shape that is similar to the time course of amplitude suppression of the oscillation. A number of

studies have now shown that modulations in oscillatory activity at various frequency bands to occur at the same time window as cognitive evoked responses such as the Dm, P300, N400, and P600 effect (Klimesch et al., 1996; Mazaheri and Picton, 2005; Davidson and Indefrey, 2007). It would of interest to see if the mechanism of amplitude asymmetry plays a role in the formation of these responses.

If the mechanism underlying these responses is revealed to be explained by amplitude asymmetry of ongoing oscillations, it would in no way discount the value of conventional ERP/ERF analysis.

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- could be construed as a potential conflict of interest.

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