

compatible. The only controversy between Saitoe *et al.*'s study and ours lies in our two dramatically different sets of *syntaxin* and *shibire* mutant data.

Null-*syntaxin* mutants and temperature-sensitive-*shibire* mutants (when at a nonpermissive temperature) are the only conditions known to completely block all transmission (both evoked and spontaneous vesicle fusion) at developing *Drosophila* glutamatergic neuromuscular junctions (NMJ). Saitoe *et al.* report no glutamate-receptor fields in these mutants. By contrast, we report that these mutants have normal glutamate-receptor fields. Specifically, we observed that every presynaptic varicosity (defined by immunohistochemical staining of synaptotagmin) had a corresponding normal postsynaptic receptor field. When no morphological or immunohistochemical presynaptic varicosity existed, we saw no postsynaptic glutamate-receptor fields – consistent with earlier observations showing that innervation is required for postsynaptic

glutamate-receptor field formation at the *Drosophila* NMJ [3]. In our hands, null *syntaxin* and *shibire^{ts}* mutants (raised at nonpermissive temperature) display fairly dramatic defects in muscle innervation. Thus, there is overall a loss of NMJ glutamate-receptors in *syntaxin* and *shibire* mutants, but this deficit reflects clearly (at least to us) the lack of NMJs.

Antibodies that recognize *Drosophila* NMJ glutamate receptors can be obtained through the University of Iowa's Developmental Studies Hybridoma Bank [product 8B4D2 (MH2B), <http://www.uiowa.edu/~dshbwww/>], and reliable methods for using them are published [1]. Likewise, both *syntaxin* and *shibire* mutants are readily obtained from the Bloomington *Drosophila* Stock Center (<http://flybase.bio.indiana.edu:82/>). Therefore, we expect the discrepancy to be resolved soon enough. In the meantime, we need to continue to focus on the fact that, despite the immense importance of glutamate-mediated transmission and intense interest in the subject, many fundamental questions

regarding glutamate-receptor field formation remain unanswered.

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Event-related brain dynamics

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Event-related potentials (ERPs) provide evidence of a direct link between cognitive events and brain electrical activity in a wide range of cognitive paradigms. It has generally been held that an ERP is the result of a set of discrete stimulus-evoked brain events. A recent study, however, provides new evidence to suggest that some ERP components might be generated by stimulus-induced changes in ongoing brain dynamics. This is consistent with views emerging from several neuroscientific fields, suggesting that phase synchronization of ongoing rhythms across different spatio-temporal scales mediates the functional integration necessary to perform higher cognitive tasks.

The event-related potential (ERP) is a summary measure of the brain's electrical activity derived by averaging the post-stimulus electroencephalogram (EEG) over a large number of trials. Underlying this averaging process is an assumption that the ERP is generated from a set of stimulus-evoked, fixed-latency, fixed-polarity brain events. In a recent article,

however, Makeig *et al.* [1] provide evidence that some components of the ERP are generated by stimulus-induced changes in ongoing brain dynamics. This is a radically different perspective, which could cast new light onto how cognitive and perceptual processes are implemented in the brain.

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Specifically, Makeig *et al.* were able to account for the generation, and attention-induced modulation, of a component of the visual ERP (the so-called 'N1' – a negative 'peak' that is typically 'maximal' at 150 ms post-stimulus) as arising from stimulus-induced 'partial phase resetting' of multiple ongoing EEG rhythms. These rhythms were identified by applying independent component analysis (ICA) to the single-trial data over a period that encompassed the N1 (using a window 50–250 ms post-stimulus), and finding

spatio-temporal modes that were consistent in their scalp topography and frequency content across subjects. These included central and posterior 'alpha' rhythms, left and right 'mu' rhythms and frontal midline 'theta' rhythms. Equivalent dipole modeling of these components suggested they originated from compact cortical domains.

Partial phase resetting

There are several key aspects to these findings. The first relates to partial phase resetting. This refers to the phenomenon that, following each stimulus presentation, the phase of an ongoing rhythm is shifted towards a particular value in relation to the stimulus [2]. Thus, looking at the distribution of phase over many stimulus presentations, one sees a pre-stimulus distribution that is approximately uniform, changing to a post-stimulus distribution that peaks about a dominant value. Communications theory [3] refers to this as phase-modulation (PM). The alternative view of the ERP – that it is generated by

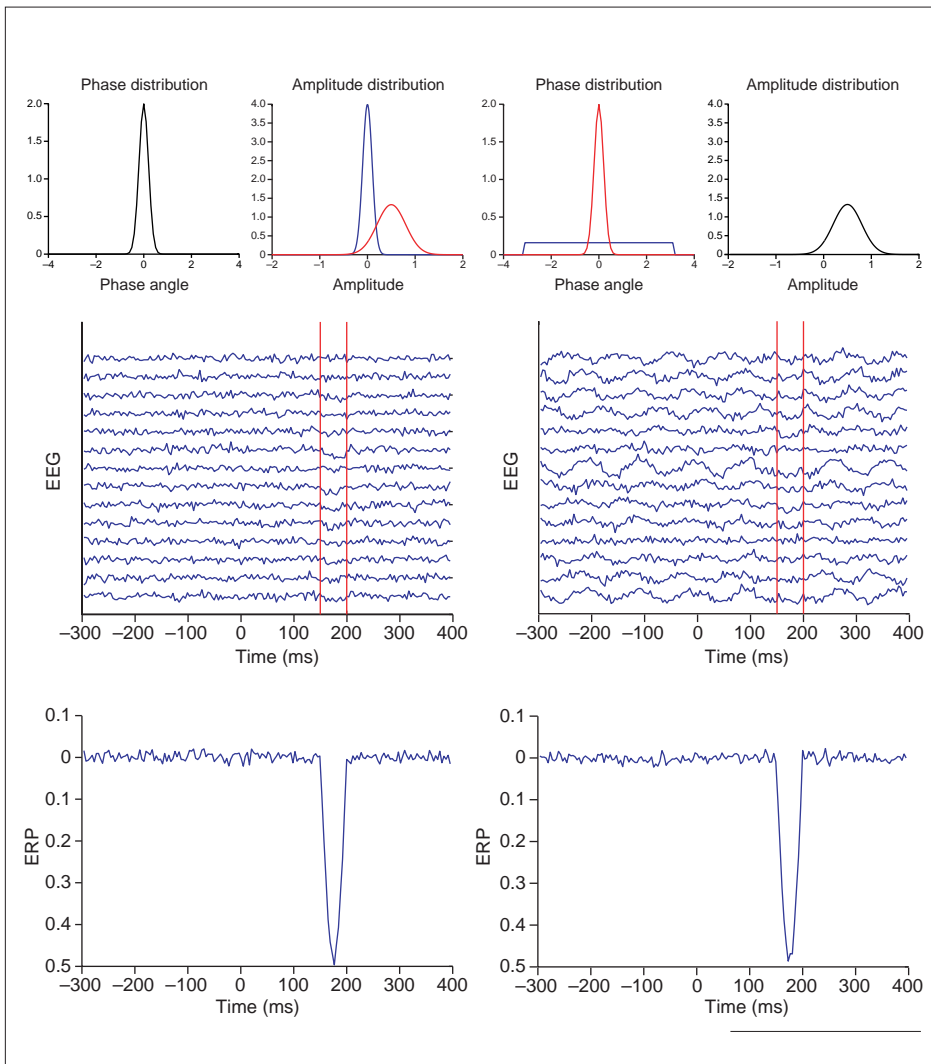


Fig. 1. How amplitude-modulated (AM) electroencephalogram (EEG) and phase-modulated (PM)-EEG can give rise to the same event-related potential (ERP). (a) In each trial and in each period (background or stimulus-induced), the amplitude and phase of each sinusoid are drawn from their respective distributions. Background distributions are shown in blue and stimulus-induced distributions in red. Black indicates the same distribution for both periods. (b) Synthetic data from 15 trials of EEG at a single electrode. On each trial, data was generated by adding Gaussian noise onto 10-Hz sinusoids. Within each trial there is a stimulus-induced period (150–200 ms post-stimulus, between the red lines), the rest of the trial constituting a background period. (c) The ERP computed from 1000 trials of such data. The AM and PM ERPs are identical (to within the noise limit). Note that these two examples show idealized AM and PM processes. Both mechanisms are likely to underlie real ERP data.

fixed-latency, fixed-polarity brain events – is generally referred to as amplitude modulation (AM) (Fig. 1).

As shown in Fig. 1, looking at the ERP in the EEG by changing the distribution of phase alone cannot necessarily reveal whether the underlying modulation is mediated by phase or amplitude. To decide whether an AM or a PM mechanism underlies the ERP, one needs to look at the spectral characteristics of single-trial EEG. If there is no stimulus-induced increase in the power band of interest (e.g. 10 Hz), then PM is the more likely mechanism. Indeed, from an inspection of data at individual electrodes, this is what Makeig *et al.* found. This echoes similar findings

by Sayers *et al.* [4] who, in a study of auditory ERPs, concluded that auditory stimuli reorganize spontaneous activity in awake behaving macaque monkeys reset the phase of ongoing motor cortical beta rhythms, in both the local field potential

and single-unit activity. Together these findings suggest that electrophysiological recordings are not purely amplitude-modulated, but rather, arise from an interaction between sensory input and ongoing dynamic brain activity.

Neural network models

The mechanisms of amplitude and phase modulation have been extensively studied in theoretical models of neuronal networks. These models describe how the activity producing a single trial of EEG can be generated from the underlying neural circuitry. Of the many studies worthy of mention, computational models such as that of Hoppensteadt and Izhikevich [7], for example, show how memory traces can be stored in the phase relationships between neurons oscillating at a given frequency. They suggest that the brain could use principles of radio communication, with the information transmitted via phase modulations. This study is representative of a larger body of work that uses the loosely coupled oscillator metaphor for neuronal dynamics.

In earlier, landmark work on the olfactory bulb, Freeman and Schneider [8] demonstrated the existence of an AM mechanism. During inhalation of a familiar odour, the EEG is a strong, almost periodic waveform, with a spatial distribution of amplitude over the bulb that is consistently different for each specific odour. These dynamics, however, take place within an inhalation–exhalation cycle where, in the exhalation stage, the EEG reverts to a chaotic ‘searching’ attractor. This whole cycle has been more recently modeled using a loosely coupled dynamical systems approach [9], in which synchronous inhalation attractors are themselves brought about by phase resetting. This could explain at a cellular level why phase resetting is partial and different on each trial: to enter a synchronous attractor basin, the system must be in an appropriate region of the dynamic manifold. The trend towards a coupled, nonlinear-systems approach suggests that a mixture of AM and PM mechanisms is involved, and that neuronal transients are better understood in dynamic terms.

Spatially distributed sources

Our discussion has focused on the modulation of activity at individual

electrode sites or local cortical areas in terms of the phase resetting of an ongoing rhythm. It is generally accepted, however, that all but the very earliest components of the ERP (such as evoked components of the auditory ERP arising <20 ms post-stimulus) are likely to arise from multiple, spatially distributed sources (e.g. Ref. [10]). This issue is addressed by a second key aspect of the Makeig *et al.* study, in which ICA was used to find a set of spatiotemporal modes underlying the N1 component. These modes were shown to be in agreement with single or symmetric equivalent dipole models situated in cortical areas that were consistent across subjects. The EEG recordings were then attributed to the partial phase resetting of these multiple spatially distributed components.

Independent component analysis is useful in this two-stage approach as it leads to a parsimonious representation of the data. An alternative, spatial-decomposition approach involves combining ERP analyses with functional magnetic resonance imaging (fMRI). This has been undertaken, for example by Di Russo *et al.* [11] who, in a visual stimulation experiment, were able to locate subcomponents of the N1 to extrastriate cortex by registering equivalent dipoles with retinotopic maps derived from fMRI. Spatial localization of the sources underlying the ERP is important, as it will allow for a more precise characterization of their dynamics.

Multiple frequencies and neuronal transients

In a recent review, Varela *et al.* [12] introduce the notion of large-scale integration, defined as communication between dynamic processes separated by >1 cm. The majority of work in this area considers the interaction between processes at the same frequency. An interesting aspect of the Makeig *et al.* study is that the N1 component was attributed to ongoing activity from multiple frequencies. This fits in with the more general framework of Friston, who describes a process whereby large-scale integration can arise from interactions among possibly different frequency components [13]. In an analysis of magnetoencephalogram (MEG) data, for example, Friston [14] observed a significant correlation between frontal

gamma activity and parietal beta activity during self-paced hand movements.

The components identified by Makeig *et al.* constitute a snapshot of brain dynamics in a particular time window (50–250 ms post-stimulus). To derive this snapshot, it is necessary to assume that the dynamics are stationary during this period. More generally, however, it is thought that brain dynamics are non-stationary, and that perception is mediated by the temporary formation of dynamic ensembles that wax and wane as one moves from one cognitive state to another. This has been demonstrated in a compelling EEG study by Rodriguez *et al.* [15], who showed that perception of an ambiguous figure was correlated with the formation of fronto-parietal gamma synchronization (200–350 ms). This was followed by a period of desynchronization and further synchronization over fronto-central sites, coinciding with a motor response. They suggest that this desynchronization period allows for the generation of a new dynamic ensemble, and a new cognitive state.

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Summary

The emergence of a single perceptual moment relies on the functional integration of many specialized brain regions. Modern imaging methods are beginning to show the underlying correlates of such integration. The study by Makeig *et al.* includes a description of one such set of correlates, which has much in common with current research in event-related EEG and MEG. Moreover, the descriptions converge with new findings in animal neurophysiology and fit in with the latest research in neural-network modeling. The key contribution of the Makeig *et al.* paper is to link the study of event-related EEG to the study of ERPs. Indeed, Makeig *et al.* envisage that these two fields will merge into the study of 'event-related brain dynamics' [16] which, when combined with new computational models and signal processing methods, could soon provide a much richer picture of the brain processes underlying human cognition.

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