Cognitive neurophysiology: Beyond averaging

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Averaging of repeated responses to sensory stimuli is the standard approach in cognitive electrophysiology. This procedure can give rise to inappropriate interpretations in some situations, because two factors contribute to the average ERP responses: the amplitude of the responses during the individual experimental trials, and the concentration of the phases (phase-locking) across responses. Larger post-stimulus single-trial amplitudes compared to prestimulus baseline are thought to correspond to a stimulus-related increase of postsynaptic potentials or/and activation of an increased amount of neural assemblies. But the functional interpretation of an enhanced inter-trial phase-locking is unclear. BOLD responses are probably related to single-trial EEG amplitudes, but not to the phase concentration across trials. Therefore, separation of amplitude and phase contributions is indispensable to avoid misinterpretations and to gain a deeper understanding of the relation between event-related EEG and fMRI.

The standard statistical approach in cognitive electrophysiology is repeated recording of electroencephalographic (EEG) responses to sensory stimuli involving different perceptual or cognitive tasks. These EEG responses are then selectively averaged for different classes of stimuli or tasks resulting in so-called average event-related potentials (ERPs). The amplitudes of different ERP components are believed to indicate the strength of the postsynaptic potentials in a neural population, together with the amount of neural assemblies participating in the processing of certain tasks. However, this approach provides incomplete, or, in some cases, misleading results, because averaged ERPs reflect more than just how many neurons are being recruited (e.g. Makeig et al., 2004).

In principle, two factors contribute to the average ERP responses: First, the amplitude of the responses during the individual experimental trials, and second, the concentration of the phases across responses, which is often called “phase-locking”. Here, phase means the angle corresponding to the momentary deflection of the EEG at a certain time point within the trial, for instance 90° for the peak or 270° for the trough of a sine oscillation. Although this fact has been acknowledged for a long time (e.g. Basar, 1980; Sayers et al., 1974), separation of these two aspects underlying average ERPs is still being done only in rare cases.

The contribution of these two factors can, for instance, be quantified by wavelet-based techniques (Daubechies, 1990), which recently have been introduced into EEG analysis (e.g. Lachaux et al., 1999; Tallon-Baudry et al., 1996). These methods allow the extraction of amplitude and phase information for single trials with both high time and frequency resolution. In the extreme case of a completely random phase distribution across trials, the individual responses would cancel each other out and no average ERP response would be observable. Otherwise, a pronounced ERP component can either be produced solely by a strong increase of phase concentration across trials or by a moderate increase of phase concentration combined with a distinct amplitude enhancement.

Accordingly, two conflicting theories have tried to explain the genesis of averaged ERPs (e.g. Shah et al., 2004). One hypothesis claims that ERPs originate from an event-related activation of neural assemblies distinct from background dynamics (“the evoked model”). This may involve both an amplitude increase, as well as an enhancement of phase concentration across trials, because the additional activity may occur with a defined phase after stimulus presentation. An alternative hypothesis states that ERPs are solely produced by increased phase concentration caused by a stimulus driven reset of ongoing oscillatory activity (“phase resetting model”). At present, there is a lively debate whether additive responses or rather pure phase reset play the dominant role in ERP generation (e.g. Hanslmayr et al., 2007; Klimesch et al., 2004; Makeig et al., 2002; Makinen et al., 2005; Mazaheri and Jensen, 2006; Shah et al., 2004). At least late ERPs appear generally to depend on both mechanisms (Fell et al., 2004).

An enhancement of single-trial EEG amplitudes due to stimulus presentation is thought to correspond to increased postsynaptic potentials or/and activation of an increased amount of neural assemblies compared to baseline (e.g. Lopes da Silva, 1993). The interpretation of an increased inter-trial phase concentration is less obvious. First of all, an enhancement of phase concentration indicates that the timing of stimulus processing exhibits less inter-trial variability because increased phase locking corresponds to a decreased variability of ERP latencies. The functional significance of this effect is not clear. It has been suggested that ERP components...
provide a threshold controlling the excitability of cortical networks (Elbert and Rockstroh, 1987; Schupp et al., 1994). According to this framework, precise timing of ERP phase may reflect inhibition or facilitation of neural firing occurring exactly at the right time point within the required sequence of neural processing.

The analysis of depth-ERPs recorded in presurgical epilepsy patients offers a unique opportunity to examine phase and amplitude contributions at the locus of ERP generation, as well as to avoid influences by projections of multiple generators to different scalp positions. The following example illustrates that the traditional interpretation of ERP findings based on conventional averaging may be extremely misleading. In a continuous recognition paradigm, words were subsequently presented on a screen (Grunwald et al., 1998). Hereby, each word appeared twice during the course of the experiment. Patients had to indicate for each word whether it was presented for the first (new word) or for the second time (old word). At the same time, EEG was recorded with depth electrodes from within the mediotemporal lobe.

**Fig. 1.** Mediotemporal EEG recordings in presurgical epilepsy patients performing a continuous word recognition paradigm (adapted from Fell et al., 2004). Above: Averaged ERPs recorded from within the anterior mediotemporal lobe for correctly recognized old words and correctly identified new words, depicting the AMTL-N400 as the dominant component. Below: Phase locking (phase concentration) and power (squared amplitude) changes at different frequencies (2 to 48 Hz) associated with the AMTL-N400. The plots show color-coded phase locking and power values, which have been normalized with respect to a prestimulus baseline [-200 to 100 ms] and have been transformed into dB scale (10 * log_{10}). The frequency [Hz] is represented in y direction, while time [ms] relative to the onset of word presentation is depicted in x direction. The phase-locking index quantifies the degree of variability of phases across trials. Positive values indicate that phases are less variable compared to baseline, while negative values express that phases are more variable than during baseline. The power changes represent the averages of the squared oscillatory amplitudes across trials. The oscillatory amplitudes correspond to the maximum deflection of the oscillation, which is given by the norm of the complex wavelet transformed EEG at a certain time point.
The conventional analysis based on ERP averaging revealed a negative ERP component with a latency around 400 ms, which is known to be generated within the anterior parahippocampal gyrus (McCarthy et al., 1995), the so-called anterior mediotemporal N400 (see Fig. 1). This AMTL-N400 is larger for correctly recognized new words than for old words (e.g. Grunwald et al., 1998). Accordingly, the traditional interpretation would be that more neural assemblies participate in the processing of new compared to old words. However, when separating amplitude and phase contributions by single-trial analysis one recognizes that the old–new effect is produced by a stronger phase concentration for new words (Fell et al., 2004; see Fig. 1). Thus, the recruitment of additional neural assemblies is not necessary to observe this effect. In contrast, single-trial amplitudes are clearly larger for old than for new words, most prominently in the lower theta range (2–5 Hz). Therefore, interpretations of this finding based on ERP averaging are both inappropriate and misleading.

Such examples are crucial with respect to the evaluation of parallel EEG and imaging investigations, for instance EEG/fMRI studies. It has been shown that the blood oxygen level dependent (BOLD) fMRI response is not only correlated with neural firing, but even somewhat better with local field potentials (LFPs), i.e. the microscopic constituents of EEG and ERPs (e.g. Kayser et al., 2004; Logothetis et al., 2001). This is not surprising, since postsynaptic potentials have been estimated to be the dominant energy user in the brains of primates (Attwell and Laughlin, 2001). However, recent data indicate that the haemodynamic response to neural activity is not initiated by signals arising from the energy deficit of the tissue but, rather, is driven locally by fast glutamate-mediated signaling processes (e.g. Attwell and Iadecola, 2002; Takano et al., 2006). Furthermore, BOLD responses may not only be related to the activity of pyramidal neurons, which represent the main source of scalp recorded EEG, but may also reflect the activity of interneurons (Lauritzen, 2005). Even inhibitory interneurons have been shown to produce vasodilator substances (e.g. Cauli et al., 2004). Probably as a consequence of these and other factors, the neurovascular relationship is not strictly linear, but incorporates nonlinear effects. For instance, hemodynamic responses were shown to continue increasing beyond the saturation of neural activity (Devor et al., 2003; Sthel et al., 2004).

In any case, phase shifts in the ERP response will only have a negligible influence on the phases of the BOLD responses because of the different time scales of ERPs and fMRI signals (milliseconds versus seconds). Consequently, it must be assumed that the fMRI signal is correlated (if at all) to single-trial amplitude changes, but rather not to variations in phase concentration.

But things are probably far more complicated. A recent study using ongoing stimulation by a movie clip has shown, that BOLD responses are positively correlated to ongoing LFP power in the gamma range above 30 Hz, but are negatively correlated to the frequency bands below 20 Hz, with the most negative correlation between BOLD responses and the 5–10 Hz LFP band (Mukamel et al., 2005). This finding is supported by the outcome of several EEG/fMRI investigations demonstrating a negative correlation between BOLD signals and the ongoing alpha EEG (e.g. Goldman et al., 2002; Goncalves et al., 2006; Moosmann et al., 2003; Laufs et al., 2003). These data are in accordance with a recently suggested “heuristic” elaborating that BOLD increases are related to shifts of the EEG spectral profile towards higher frequencies, while BOLD decreases are related to shifts towards lower frequencies (Kilner et al., 2005). However, it is yet an open question whether these results concerning ongoing EEG activity can be directly transferred to event-related responses.

For the above case, this means that the increased single-trial amplitudes in the theta range for old compared to new words may actually correspond to decreased BOLD activity for old words (or increased BOLD activity for new words). However, this effect may partly be compensated by the more extended event-related increase in the gamma range above 20 Hz for old versus new words (see Fig. 1). Interestingly, an fMRI study implementing a similar word recognition paradigm indeed found increased BOLD activity within the left parahippocampal gyrus for new compared to old words (Jessen et al., 2001). Although such an outcome had been expected based on the old–new effect reported for averaged mediotemporal ERPs (e.g. Grunwald et al., 1998; Halgren and Smith, 1987), the actual implications are probably far from trivial, as described above.

In conclusion, the comparison between averaged ERPs and fMRI findings has to be regarded with caution. Among others, one reason for discrepancies between EEG and fMRI effects could be that averaged ERPs depend on inter-trial phase concentration, which is not correlated to fMRI signal changes. Furthermore, recent studies addressing the relation between ongoing EEG and BOLD signals suggest that the sign of the correlation depends on the EEG frequency band. Thus, single-trial techniques, which allow separation of phase and amplitude effects, not only facilitate a better evaluation of ERP recordings. Such an approach will be essential in order to achieve a deeper understanding of the relation between event-related EEG and fMRI.

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References


