Chapter 36

Cognitive neurophysiology: Event-related potentials

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Abstract

Event-related potentials (ERPs) are one of the most commonly used tools to assess cognitive processing with a high temporal resolution. We provide an updated view of the cortical origins of evoked responses and discuss potential mechanisms contributing to ERP generation. In particular, we focus on the relationship between evoked and ongoing oscillatory activity and discuss the differences between ERPs and cortical activation as indexed by high-frequency activity in human intracranial electroencephalography (EEG). We highlight several possibilities for how ERPs can precisely index human perception and behavior in nontraditional approaches, such as neuronal entrainment through steady-state evoked potentials, multivariate decoding, and cross-frequency correlations. We argue that analyses of time-locked responses are beneficial to assess nonlinear and nonsinusoidal neuronal activity on a fine-grained temporal scale, since analyses in the time domain are less susceptible to artifacts than spectral decomposition techniques. Taken together, the current review provides a state-of-the-art overview of ERPs and their application in cognitive and clinical neurophysiology.

50 YEARS OF EVENT-RELATED POTENTIALS IN COGNITIVE NEUROSCIENCE

The first few years of electroencephalography (EEG) mainly focused on oscillatory activity in the alpha (8–12 Hz) and beta (13–30 Hz) ranges. About 35 years after the initial discovery (Berger, 1929), the first evoked responses, which were about 10–100 times smaller than background EEG activity, were characterized: the contingent negative variation (CNV) was first published in 1964 (Walter et al., 1964), the readiness potential (RP) in 1965 (Kornhuber and Deecke, 1965), the same year visual evoked potentials (VEPs) and the P300 component were first described (Cooper et al., 1965; Sutton et al., 1965). These discoveries initiated a very fruitful phase for human electrophysiology in the 1970s–2000s, when event-related analyses became virtually synonymous with EEG analyses. Several additional components were discovered: the mismatch negativity (MMN) was first described in 1978 (Näätänen et al., 1978), the N400 in 1980 (Kutas and Hillyard, 1980), the N2pc in 1994 (Luck and Hillyard, 1994), and the N170 in 1996 (Bentin et al., 1996). However, most of the findings were descriptive and most components were labeled according to their polarity, latency, and scalp distribution (Luck, 2014).

While ERPs serve as a precise index of cortical activity with a temporal resolution in the millisecond range, they do not provide a mechanistic understanding of brain physiology. With the discovery of synchronized gamma-band oscillations (Gray et al., 1989), the focus started to shift away from ERPs. Over the last 10–15 years several influential studies highlighted the role of rhythmic brain activity for high-level cognitive functions (Engel et al., 2001; Salinas and Sejnowski, 2001; Varela et al., 2001; Fries, 2005; Siegel et al., 2012). Notably, oscillatory analyses are more susceptible to artifacts than analyses in the time domain. Specifically, the current debate includes gamma-band activity (Brunet et al., 2014; Hermes et al., 2015a,b; Ray and Maunsell, 2015) as well as the concept of cross-frequency coupling (Aru et al., 2015; Gerber et al., 2016; Cole and Voytek, 2017), which implies that

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cortical communication is multiplexed across temporal scales that dynamically interact by selective synchronization (Canolty and Knight, 2010).

Recent evidence suggests that some of these findings might be caused by nonsinusoidal signal characteristics as well as sharp evoked transients (Aru et al., 2015; Gerber et al., 2016; Cole and Voytek, 2017; Cole et al., 2017), which were readily visible in the time domain (Vaz et al., 2017). Hence, time domain analyses have regained importance for understanding cortical physiology. A recent review argued that the discovery of the fundamental cardiac physiology and ECG (electrocardiogram) would have never been possible in the frequency domain (Cole and Voytek, 2017). Only inspection in the time domain clearly delineated the P-wave from the QRS-complex and the T-wave, which in turn could be related to distinct stages of one heartbeat. Importantly, the polarity of these waves contained all the information to infer directionality and spread along predefined anatomical structures.

In this chapter, we provide an updated perspective on the physiologic basis of ERPs. We discuss the origin, function, and clinical applicability of two exemplary components, the MMN and the P300. In addition, we highlight several studies that demonstrated how ERPs could be used to index top-down control and how ERPs relate to ongoing brain dynamics and cortical activation. Therefore we discuss different mechanisms of ERP generation and review evidence regarding where ERPs are being generated in the cortex. Crucially, we highlight several methodological limitations and provide an updated perspective on how ERPs can be used in cognitive and clinical neurophysiology. We focus on recent methodological developments, such as neuronal entrainment by steady-state evoked potentials, multivariate decoding, and event-related cross-frequency correlations. We believe that these techniques are likely to gain importance in light of several constraints of spectral analyses. Hence, ERPs combined with state-of-the-art methodology will likely remain one of the essential tools in cognitive neurophysiology to elucidate cortical physiology and behavior.

**TYPICAL ERPS AND THEIR ALTERATIONS IN NEUROPSYCHIATRIC DISORDERS**

Evoked potentials are used in a variety of clinical contexts (Walsh et al., 2005; Lascano et al., 2017). For example, visual evoked potentials (VEPs) are informative in diagnosing optic neuritis and multiple sclerosis; TMS-evoked motor potentials (MEPs) provide insights for motor neuron diseases and spinal cord conduction; and brainstem auditory evoked potentials (BAEPs) reliably assess auditory pathways. It has been hypothesized that ERPs that are typically observed in cognitive experiments might be useful as biomarkers to detect early stages of neuropsychiatric diseases and index disease progression (Duncan et al., 2009; Morlet and Fischer, 2014; Kapppenan and Luck, 2016; Kremláček et al., 2016; Michie et al., 2016; Seer et al., 2016). In theory, high temporal resolution and low operating expenses make scalp EEG an ideal tool to screen for neuropsychiatric diseases. Despite substantial effort in these areas, no definitive relationship between cognitive ERPs and neuropsychiatric diseases has been established to date. Here, we focus on two of the most widely studied components, the mismatch negativity (MMN) and the P300, to illustrate the classic ERP findings in cognitive and clinical neurophysiology. Please note that there are many more components that might be useful in clinical contexts, including the N170 for face processing (Feuerriegel et al., 2015; Yovel, 2016), the event-related negativity (ERN) for error detection (Wessel, 2012; Ulssperger et al., 2014), or the N400 (Kutas and Federmeier, 2011; Mohammad and DeLisi, 2013), which indexes word processing and semantic memory.

**Mismatch negativity**

The MMN was first described in the auditory domain (Näätänen et al., 1978), but can also be observed in other sensory modalities and constitutes an automated slow cortical response to infrequent deviant stimuli (Fishman, 2014; Sussman and Shafer, 2014). The MMN is normally assessed as the difference wave of deviant and standard stimuli over fronto-central EEG leads and peaks around 150–250 ms (Näätänen et al., 1978, 2014). Converging intracranial evidence located the MMN to primary sensory as well as inferior frontal areas (Edwards et al., 2005; Rosburg et al., 2005). Functionally, the MMN is highly context dependent and might reflect a deviation from a template-matching process to a memory trace (Fishman, 2014; Näätänen et al., 2014; Bartha-Doering et al., 2015). The MMN constitutes a reflexive response that can be elicited largely irrespective of the current cognitive state, which makes it ideal for passive screening in clinical environments (Duncan et al., 2009). For example, a reduced MMN has repeatedly been observed in schizophrenic patients and in neurodegenerative disorders such as Alzheimer’s disease (Todd et al., 2013; Bartha-Doering et al., 2015; Michie et al., 2016). In addition, the presence of an MMN in coma patients has been shown to be a reasonably good predictor of recovery of consciousness (Morlet and Fischer, 2014). Previously, only auditory and somatosensory evoked potentials, which peaked at around ~20–30 ms, had been used for coma diagnoses.
However, the MMN and passive auditory oddball paradigms, which include a higher cognitive component, might prove beneficial in prediction of coma outcome given that their generation involves more complex, long-range, top-down network interactions (Brown et al., 2011). For example, coma awakening is well correlated with the presence of a clear P300 or an MMN response and might provide a signal that the cortical network architecture is still intact (Morlet and Fischer, 2014). In contrast, early-evoked potentials, such as the N20, can only index the function of primary sensory areas and bottom-up signaling to some extent (Boly et al., 2011; Rosanova et al., 2012), but do not allow inferences about cortical networks underlying higher cognitive functions.

**P300**

P300 summarizes a family of frontal and parieto-temporo-occipital positive components that emerge around 300 ms and index the detection and discrimination of task-relevant targets and cues (Polich, 2007). The more frontal P3a has been linked to bottom-up attention and novelty processing, while the posterior P3b might signal more top-down control of attention and memory processing (Friedman et al., 2001; Polich and Criado, 2006; Polich, 2007). The P300 has been widely studied, because both its amplitude and latency seem to provide relatively stable markers to index classification accuracy and speed (Friedman et al., 2001; Polich, 2007). In contrast to early evoked potentials (P100/N100), the P300 involves bilateral cortical regions and its amplitude is maximal over midline EEG leads (Soltani and Knight, 2000).

So far, no consensus has been reached as to what the P300 actually reflects. Both cortical activation and inhibition have been debated. Recent intracranial evidence showed that electrodes exhibiting strong P300 responses did not show a strong high-frequency activity response (HFA; see the following), thus supporting the inhibition hypothesis (Szczepanski et al., 2014; Kam et al., 2016). HFA is generally thought to reflect cortical activation and has been shown to index cortical spiking activity (Ray and Maunsell, 2011; Rich and Wallis, 2017; Watson et al., 2017). Furthermore, HFA positively correlates with the fMRI BOLD signal (Hermes et al., 2017). However, there is only minimal overlap between electrodes that exhibit a strong HFA response and electrodes that have a clear ERP component, which supports the notion that distinct cortical generators contribute to the generation of these electrophysiologic signatures (Dürschmid et al., 2016; Kam et al., 2016). To date, it remains unknown how population activity and the timed interplay of inhibitory or excitatory neurons contribute to ERP generation. However, it is unlikely that ERPs signal cortical activation given their inconsistent relationship to surrogate makers of spiking activity (Kam et al., 2016). Future studies in humans taking advantage of single neuron recordings to estimate the excitatory-inhibitory balance will have the potential to address these outstanding questions (Fried et al., 2014; Voytek and Knight, 2015).

Given that the P300 is a prominent component with large amplitude, it requires very few trials to be reliably estimated against background activity. Therefore it has been employed in a variety of clinical contexts (Duncan et al., 2009; Morlet and Fischer, 2014; Kremláček et al., 2016; Seer et al., 2016) and used for noninvasive brain-computer interfaces (Birbaumer, 2006; Cecotti, 2011). The P300 appears to be reliably reduced in schizophrenic patients (Duncan et al., 2009). In contrast, the P300 in patients with Parkinson’s disease (PD) is variable and depends on medication and deep brain stimulation (DBS) settings, PD subtype, and disease duration (Seer et al., 2016). In addition, the P300 has been used to track a healthy development. For example, children with attention deficit hyperactivity disorder (ADHD) have comparable smaller P300 amplitudes, while autistic children often also exhibit delayed peak latencies (Duncan et al., 2009).

Taken together, several lines of research have indicated the usefulness of ERP analyses to assess neuropsychiatric diseases. While a number of guidelines have been proposed (Duncan et al., 2009; Kappenman and Luck, 2016), the field has not reached a consensus yet and the sheer variety of tasks, settings, recording environments and equipment, study populations, and analysis techniques makes it difficult to compare across studies. Ultimately, a better understanding of the neural underpinnings and origins of ERPs will be necessary to make use of them in clinical settings (Sussman and Shafer, 2014; Sussman et al., 2014).

**TOP-DOWN CONTROL OF SENSORY ERPs**

The lesion approach in cognitive neuroscience takes advantage of the high temporal resolution of EEG to link behavioral deficits to impaired neuronal processing in the millisecond range (Szczepanski and Knight, 2014). Here, we review several studies that successfully employed this method to make inferences about top-down guided behavior in the human brain. We focus on lesions in the prefrontal cortex (PFC), given that substantial evidence from imaging and invasive recordings tightly linked the PFC to goal-directed top-down control (Miller and Cohen, 2001; Szczepanski and Knight, 2014; Helfrich and Knight, 2016).
Several studies demonstrated that early ERP amplitudes are decreased ipsilaterally to a circumscribed dorsolateral prefrontal cortex (DLPFC) lesion in the visual (Barceló et al., 2000; Yago et al., 2004; Voytek et al., 2010) or the auditory domain (Knight et al., 1981; Bidet-Caulet et al., 2015) and indexed impaired behavioral performance. In addition, it has been shown that the later responses, such as the novelty P300, are markedly reduced in response to unexpected novel stimuli (Knight, 1984; Yamaguchi and Knight, 1992; Løvstad et al., 2012). In the case of predicted events, DLPFC lesion patients do not exhibit the usual behavioral benefits from predictive cues, which was reflected in prolonged P300 peak latencies (Fogelson et al., 2009). Hence, ERP components may serve as a precise index of top-down control on a fine-grained temporal scale.

THE ORIGIN OF EVENT-RELATED POTENTIALS

Substantial invasive and noninvasive evidence demonstrated that the ERP at scalp level reflects the summation of independent cortical sources (Halgren et al., 1980; Soltani and Knight, 2000; Edwards et al., 2005; Rosburg et al., 2005; Kam et al., 2016). In particular, intracranial recordings from patients with intractable epilepsy provided insights into the neuronal underpinnings of ERPs (Halgren et al., 1980; Edwards et al., 2005; Rosburg et al., 2005; Dürschmid et al., 2016; Kam et al., 2016). We review two lines of research in this domain. The first one entails a direct comparison of ERPs as observed on the cortex and observed at scalp electrodes. The second approach takes advantage of the discovery of broadband high-frequency activity (HFA or high gamma) in the human brain in the range from 70 to 150 Hz (Crone et al., 1998). It has been demonstrated that amplitude changes in this frequency range closely correlate with spiking activity of single neurons and might serve as a surrogate marker of cortical activation (Ray and Maunsell, 2011). Several studies taking advantage of higher digitization rates of new EEG amplifiers (>1000 Hz) have begun to unravel the relationship of cortical activation and ERP generation.

Comparison of extra- and intracranial ERPs

Early clinical recordings had a limited sampling rate of <256 Hz, which did not permit reliable estimation of HFA; therefore most of the intracranial reports in the 1980s and 1990s focused on ERPs. In particular, Halgren et al. delineated the cortical origins of the P300 in a series of seminal papers (Halgren et al., 1980, 1982, 1998). They concluded that bilateral parietal, dorsolateral prefrontal, orbitofrontal, and anterior cingulate areas contribute to the scalp ERP (Halgren et al., 1998). In addition, they showed that later ERP components were not lateralized, while early evoked responses exhibited a contralateral preference.

Rosburg et al. took advantage of simultaneous intracranial and extracranial EEG recordings and showed that most intracranial electrodes that exhibited a scalp-like MMN were located around the superior temporal lobe, and only a minority were over inferior frontal areas (Rosburg et al., 2005). A related study extended these findings and demonstrated that auditory ERPs mainly arose from the posterior Sylvian fissure, but that MMN-like responses were more pronounced over more anterior temporal regions (Edwards et al., 2005). This is in line with several other studies describing the most pronounced effects along the superior temporal gyrus (Liégeois-Chauvel et al., 1994; Yvert et al., 2005; Nourski et al., 2013). Notably, the study by Edwards et al. also examined HFA responses, which partially overlapped with the ERP findings.

Relationship of cortical activation and ERPs

HFA tracks behavior on a trial-by-trial basis with high precision and several studies have begun to assess the relationship of HFA and ERPs. It has been observed that electrodes that show ERPs on the cortex do not necessarily exhibit HFA (Fig. 36.1) (Edwards et al., 2005; Szczepanski et al., 2014; Dürschmid et al., 2016).

Kam et al. addressed the relationship between the P300 and HFA in an auditory and a visual target detection task (Kam et al., 2016). They found that (I) more frontal electrodes show HFA than a P300, (II) an equal number of parietal electrodes exhibits HFA or a P300, but crucially (III) the overlap between HFA-responsive and P300-positive electrodes was minimal. This has been interpreted that separate neuronal mechanisms contribute to P300 and HFA generation and that the P300 does not necessarily index cortical activation. Furthermore, they demonstrated that (IV) the P300 at single intracranial recordings did not resemble the P300 at scalp level. A classic scalp-like P300 only became evident when P3 time courses from multiple electrodes were averaged (Fig. 36.2). This finding supported the idea that multiple cortical ERP generators contribute to the scalp potential.

Likewise, it has been demonstrated that HFA over frontal but not sensory areas is more sensitive to unpredicted deviants than the ERP (Fig. 36.3) (Dürschmid et al., 2016). Taken together, several intracranial studies demonstrated that the overlap of electrodes exhibiting HFA and the ERP is minimal and that it is likely that these features index different cortical processes, but the exact relationship and physiologic function are unknown.
THE RELATIONSHIP OF ERPs AND ONGOING BRAIN ACTIVITY

ERPs are small in comparison to large fluctuations as observed in ongoing brain activity. Several lines of research have demonstrated that ongoing brain activity exhibits a rich spatiotemporal structure, which indexes instantaneous cortical excitability and thereby shapes evoked response based on the brain state at stimulus presentation (Klimesch et al., 2007c; Barry, 2013). A common approach is to divide ongoing activity into several frequency bands to extract prestimulus phase and/or amplitude and then determine their impact on subsequent ERPs.

Ongoing brain activity vs evoked brain activity

For decades, ongoing brain activity has been largely ignored and the background EEG was considered to mainly reflect noise, which could be attenuated through time-locked averaging. Early reports suggested that the phase of band-limited ongoing activity might play a role for subsequent behavior and cortical responses (Callaway and Yeager, 1960; Lesèvre and Rémond, 1967; Trimble and Potts, 1975). Recent work has systematically investigated the relationship of ongoing activity and evoked potentials.

For example, in a series of studies Barry et al. demonstrated the importance of the prestimulus delta, theta, and alpha phases for the subsequent ERP generation (Barry et al., 2004; Barry, 2013). In particular, they showed that cortical negativity (half wave below zero) as well as negative driving (falling flank of the sine wave) in multiple frequency bands in the range from 1 to 13 Hz modulated early (N100) and later components (P300). The artificial subdivision into narrow frequency bands did not take into account whether a true oscillation was present (Sauseng et al., 2007). Therefore, these phase effects need to be interpreted with caution and might be spuriously introduced by narrow-banded filtering of ongoing broadband brain activity without a true oscillation (Aru et al., 2015). Work by the Klimesch group focused on the role of ongoing alpha dynamics for subsequent ERP generation. They demonstrated that prestimulus phase alignment in the alpha band predicts the P100 amplitude (Fellinger et al., 2011) as well as amplitude and latency of the P100/N100 complex (Gruber et al., 2005). Furthermore, prestimulus amplitudes have been shown to inversely correlate with the amplitude and latencies of early evoked potentials, such as the P100 component (Klimesch, 2011; Himmelstoss et al., 2015). This has been interpreted in light of the alpha inhibition hypothesis (Klimesch et al., 2007b; Jensen and Mazaheri, 2010; Klimesch, 2011), which postulates that states of high alpha power block out irrelevant information by decreasing the instantaneous cortical excitability. Crucially, their findings suggested that slower components such as the N170, P2, or ERN are associated with increased phase-locking in slower frequency bands (delta: 1–4 Hz, theta: 4–7 Hz (Fell et al., 2004; Freunberger et al., 2007; Yeung et al., 2007; Han et al., 2015)).

Phase-resetting as a mechanism of ERP generation

Most of the evidence for the relationship between prestimulus activity and subsequent ERPs has been correlative in nature. Hence, it remains unclear if phase and
power only modulate evoked dynamics or if they causally contribute to their generation. In particular, it has been fiercely debated whether evoked dynamics are added on top of the background EEG or whether an endogenous phase reset and subsequent phase alignment of low-frequency oscillations explain most of the ERP (Penny et al., 2002; Sauseng et al., 2007). Evidence has been presented in favor of (Makeig et al., 2002) and against (Shah et al., 2004; Mazaheri and Jensen, 2006) this idea. To date, no definite conclusion has been reached, which is largely due to methodological limitations (Krieg et al., 2011; Xu et al., 2016). In order to extract the instantaneous phase, the signal needs to be band-limited by either band-pass filtering or a Fourier or wavelet transformation (Bruns, 2004). However, all of these techniques will render transient evoked activity sinusoidal, since commonly used filters are acausal, i.e., filtering at a certain time point depends on both the signal in the past and in the future. Therefore, it is inevitable that evoked signals smear into the prestimulus baseline and bias phase estimates towards nonuniform distributions before target onset (Zoefel and Heil, 2013; Iemi et al., 2017). Hence, the ERP, which reflects a rather sharp transient, will necessarily show up in multiple frequency bands and introduce spurious phase-locking. Therefore, it remains difficult to disentangle true phase-resetting from spurious phase-alignment due to the evoked potentials. One way to circumvent this issue is the use of causal filters, which only consider the past of the signal and not the future (Zoefel and Heil, 2013) and a set of criteria that might help to determine true phase-resetting has been introduced (Sauseng et al., 2007).

### Steady-state visual evoked potentials and neuronal entrainment

The rapid presentation of sensory stimuli gives rise to repeated EPRs, which partially overlap in time. It has
been argued that the brain might entrain its ongoing activity to the external rhythm after several cycles (Herrmann et al., 2016) and that this rhythm keeps on cycling after the offset of the external stimulus train (Mathewson et al., 2012; Spaak et al., 2014; Notbohm and Herrmann, 2016; Notbohm et al., 2016). This approach has been used to investigate the causal relationship of prestimulus activity for evoked activity after the offset of the stimulus train and subsequent perception of near-threshold targets (Herrmann et al., 2016). However, it has been argued that this effect does not constitute real phase alignment but is rather the result of the superposition of single evoked responses (Capilla et al., 2011; Keitel et al., 2014). While this is an obvious concern for neuronal data, it cannot explain the typically observed phase-dependent modulation after stimulus offset (Mathewson et al., 2012; Spaak et al., 2014; Notbohm and Herrmann, 2016). Recently, Xu et al. used this technique to disentangle the contribution of the prestimulus phase to ERP generation (Xu et al., 2016). They found that neither the evoked nor the phase resetting model fully explained the ERP. This is in line with several reports that indicated that the ERP has evoked components that are being influenced by prestimulus oscillatory brain activity (Fell et al., 2004; Shah et al., 2004; Sauseng et al., 2007; Min et al., 2007; Klimesch et al., 2007a,c).

These findings helped to shed new light on one of the most studied psychological paradigms, the so-called attentional blink, where a preceding target in a rapid visual stream masks the detection of a second target (Zauner et al., 2012). Crucially, the masking depends on the frequency of stimulus presentation and is most pronounced if presented at around 8–15 Hz and has been attributed to entrainment in the alpha range (Zauner et al., 2012; Shapiro et al., 2017). Hence, the...
rhythmic presentation of the stimuli gives rise not only to a steady-state evoked potential, but also entrains the underlying alpha generators to the stimulus presentation rate (Spaak et al., 2014; Notbohm and Herrmann, 2016; Notbohm et al., 2016). This entrainment through steady-state visual evoked potentials (SSVEPs) had direct functional consequences for perception.

In a separate line of research, SSVEPs have been used to frequency-tag overlapping stimulus streams (Norcia et al., 2015). The cortex exhibits a frequency-following response, i.e., an ongoing oscillation is not a prerequisite for the observation of a peak in the power spectrum, as long as the sensory stimulus stream provides an exogenous rhythmicity (Herrmann, 2001; Keitel et al., 2010). While the superposition of evoked responses impeded the analyses in the time domain, the two streams can be disentangled in the frequency domain. A robust finding is that attention to one of the streams enhances the evoked amplitude, but not the amplitude of the ignored stream (Baldauf and Desimone, 2014). Hence, frequency-tagging and SSVEPs allow a reliable estimate of the focus of attention and have been used in a variety of cognitive experiments.

**METHODOLOGICAL CONSIDERATIONS:**

**STATISTICAL TESTING OF ERPs**

ERPs are a simple and cost-effective tool, which can be easily set up in clinical and basic science lab environments. However, several methodological limitations apply in addition to the limited spatial resolution and they have been addressed in introductory tutorials, guidelines, and books (Handy, 2005; Luck, 2014). Here, we discuss a major caveat, which has been part of recent scientific debate: namely, what is an appropriate way to test ERP differences (Luck and Gaspenlin, 2017)?

The spatial extent of clusters can be approximated at scalp or source level. One of the most straightforward and most commonly employed methods is the surface Laplacian or current source density, which is calculated at sensor level (Carvalhaes and de Barros, 2015; Kayser and Tenke, 2015a,b). The algorithm transforms the scalp-recorded EEG into radial currents by local re-referencing. While this approach slightly improves the spatial specificity, it is still a two-dimensional representation of a more complex underlying pattern. Another possibility is to project the sensor level data into source space based on adaptive spatial filtering. The linearly constrained minimum variance (LCMV) beamforming (Van Veen et al., 1997) or the low-resolution brain electromagnetic tomography approach (LORETA) (Pascual-Marqui et al., 1994) are among the most commonly used tools. However, there is not a single solution to the inverse problem and, therefore, all source projection methods remain equivocal, but the visualization on 3D-rendered brains helps to identify cortical regions contributing to scalp-level ERPs.

**NEW VISTAS FOR EVENT-RELATED NEURONAL ACTIVITY**

With the discovery of neuronal oscillations, ERP analyses have been sidelined in favor of more sophisticated spectral analysis techniques. In particular, metrics of synchronization between different regions and/or different frequencies have been used to explain behavior on a trial-by-trial level (Salinas and Sejnowski, 2001;
However, spectral techniques only estimate activity and artificially render nonsinusoidal neuronal activity sinusoidal (Cole and Voytek, 2017). The raw voltage trace contains rich spatiotemporal information, which might not be accessible by trial-averaged ERPs or spectral estimates. Hence, we highlight different possibilities as to how some of the rich information in single-trial ERPs can be used to make inferences about cognitive functions (Stokes and Spaak, 2016).

**Figure 36.4.** Multivariate decoding on ERPs. (A) A decoder was trained to identify items held in working memory (WM). While univariate tests between conditions did not reveal prominent differences in the ERPs at single electrodes, multivariate decoding from several posterior electrodes enabled Wolff et al. to correctly identify the item in WM in the first 200 ms. The discriminability was above chance for nearly 800 ms. (B) A second noninformative strong visual impulse stimulus reinstated the decodability above chance. This was interpreted as evidence that a memory representation might be encoded in an activity-silent state: i.e., there were no ERP differences between conditions, but the spatiotemporal network configuration still provided information about the item held in WM. Figure reproduced with permission from Wolff MJ, Ding J, Myers NE et al. (2015). Revealing hidden states in visual working memory using electroencephalography. Front Syst Neurosci 9: 123. https://doi.org/10.3389/fnsys.2015.00123 under the Creative Commons Attribution (CC BY) license.

**Multivariate approaches and single-trial decoding**

ERPs contain rich spatiotemporal information that is often reduced by averaging across trials, sensors, and subjects to obtain grand-average waveforms. Multivariate pattern classification approaches take advantage of the fact that every different time point is associated with a certain unique spatial distribution of activity (Stokes et al., 2015). A decoding algorithm is trained on a certain number of trials and then applied to the remaining trials and the classification accuracy at any given time point is extracted (Blankertz et al., 2011). Performance above chance indicates that the spatiotemporal patterns contained information to reliably discriminate two conditions. This approach reduces the dimensionality into a single time course per participant and provides additional insights into the temporal dynamics of an observed effect (Fig. 36.4). This technique has recently been used to decode items held in working memory (Wolff et al., 2015). Crucially, after a delay period the decodability returned to zero. A brief noninformative visual impulse stimulus then elicited an evoked response, which again contained information about the item held in working memory that was not detectable with univariate tests. In this case, this has been interpreted as evidence for “activity-silent” working memory, where information is encoded in a current network state (Stokes, 2015; Wolff et al., 2015; Rose et al., 2016).

**Event-related cross-frequency correlations**

ERPs have several spectral components, mainly covering frequencies below 20 Hz, but might also have high-frequency contributions. More sophisticated methodologies and invasive recordings now allow reliable estimating of high-frequency gamma activity (>40 Hz) (Gross et al., 2013). Previous EEG studies on gamma-band oscillations were often contaminated by microsaccadic artifacts (Yuval-Greenberg et al., 2008; Keren et al., 2010), which closely resembled gamma-band activity, but several methods to attenuate these artifacts have been introduced in recent years (Keren et al., 2010; Carl et al., 2012; Hipp and Siegel, 2013).

It has been suggested that the correlation or coupling between low- and high-frequency components might be differentially modulated depending on the cognitive state...
Normally, cross-frequency interactions are calculated across time and then compared across different trials (Canolty et al., 2006; Tort et al., 2008). Recently, a method for event-related cross-frequency coupling has been proposed to track the time course of cross-frequency correlations. In a standard oddball task, Voytek et al. demonstrated that the correlation between alpha phase and gamma amplitude was greater for targets than for standards (Voytek et al., 2013). Importantly, this difference was detected in the first 250 ms, a time frame where no ERP differences are obvious in an oddball task and the P300 effect only emerges later (Polich, 2007). Hence, cross-frequency correlations might provide additional information into the temporal dynamics of evoked responses. However, a number of recent reports urged caution in interpreting cross-frequency metrics, which require a number of careful control analyses, such as the absence of power differences, equal number of trials, and the presence of oscillatory activity (Aru et al., 2015; Gerber et al., 2016; Cole and Voytek, 2017).

Assessing nonsinusoidal neuronal activity in the time domain

Spectral techniques that are used to capture event-related dynamics might easily render sharp transient evoked activity sinusoidal by band-pass filtering or Fourier or wavelet transforms (Bruns, 2004). Hence, all subsequent analyses that are being carried out on frequency-domain transformed data must be carefully interpreted and cross-checked with the underlying raw traces to ensure that oscillatory brain activity was actually present (Aru et al., 2015). In the case of ERPs, multiple scenarios are likely where no sinusoidal oscillation was present before the evoked response (Sauseng et al., 2007). Therefore it has been argued that the shape of the waveform might actually hold more physiologically relevant information than a frequency decomposition of the signals (Cole and Voytek, 2017). This framework has been first suggested for the analysis of nonsinusoidal oscillatory activity but might also have merits to gain additional insights into ERPs. In addition to amplitude measures and latency analyses, evoked activity could be described according to the waveform shape, the symmetry, the rise time, or the steepness of the slope.

CONCLUSIONS

For more than half a century, event-related analyses have provided a unique opportunity to study temporal dynamics of conscious cognitive processes on a fine-grained temporal scale (Luck, 2014). While the exact physiologic mechanisms that give rise to ERPs are still largely unknown, multiple studies favored a mixed model of evoked responses plus phase resetting (Fell et al., 2004; Min et al., 2007; Sauseng et al., 2007; Krieg et al., 2011; Han et al., 2015; Xu et al., 2016). In addition, several recent intracranial studies provided insights into the cortical origins of ERPs, suggesting that ERPs do not necessarily overlap with areas of cortical activation (Szczepanski et al., 2014; Kam et al., 2016). We also reviewed several novel methods and techniques, which allow extracting more information from ERPs than could usually be obtained from grand-average difference waveforms. While spectral analysis techniques have been widely popular over the last 10 years, they only provide estimates of oscillatory activity and are susceptible to artifacts, which are obvious in the time domain (Cole and Voytek, 2017; Vaz et al., 2017). Therefore, we believe that ERPs will remain one of the essential tools for image cognitive processes with a high temporal resolution needed to understand cortical information processing and transfer. In addition, ERPs are of particular relevance for a variety of clinical applications in both neurology and psychiatry and will likely gain more importance in the future. Diagnostically, ERPs are routinely used to, for example, infer optic nerve damage in MS (visually evoked potentials), where increased latencies and/or reduced amplitudes are commonly observed. Likewise, somatosensory-evoked potentials are being used to assess ascending spinal pathways, while transcranial magnetic stimulation over motor cortex is often used to assess the integrity of the corticospinal tract and is routinely used to aid in diagnosis of motor neuron disorders, such as amyotrophic lateral sclerosis.

ERP data collection is fast and cost effective and modern EEG systems allow experimenters and clinicians to collect ERPs in the patient room or in the ICU, making ERPs ideally suited for long-term monitoring. ERPs can be used to track patient arousal states with high temporal resolution to, for example, delineate a reversible coma from a vegetative state (Boly et al., 2011; Morlet and Fischer, 2014; Sussman and Shafer, 2014). Furthermore, ERPs might be helpful to index the instantaneous cortical excitability, which is altered in epilepsy as well as in neuropsychiatric disorders, such as schizophrenia (Kremláček et al., 2016). In particular, ERPs in task-related designs that allow the assessment of both sensory-evoked and cognitively relevant potentials are likely to gain importance in the future, since these components, such as the MMN or P300, allow making inferences about cortical networks that go beyond simple sensory processing.

Therapeutically, ERPs have been used in a variety of brain-computer interfaces, for which they are ideally suited given their prominent amplitude in comparison...
to the background activity and the fact that it only takes a few trials (four to six) to successfully train the classification algorithm. This approach allows, for example, ALS patients to communicate with their environment (Krusienski et al., 2008; Guger et al., 2009).

Taken together, ERPs are an elegant way to assess a variety of clinically relevant cognitive functions and we foresee that their application in clinical neurophysiology will likely increase over the next decade. In particular, several lines of research are beginning to clarify the neural underpinnings that contribute to the generation of ERPs and to converge on the idea that ERPs can be used to noninvasively index cortical function with high temporal resolution.

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REFERENCES


COGNITIVE NEUROPHYSIOLOGY: EVENT-RELATED POTENTIALS


