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Event-Related Potentials

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Synonyms

ERPs

Definition

Event-related potentials are a general class of electrical brain potentials that are embedded in the electroencephalogram and that display a stable time relationship to a definable sensory, cognitive, or motor event.

Principles and Role in Psychopharmacology

Electroencephalography is one of the most popular psychophysiological methods in clinical and preclinical research and provides a recording that reflects the global electrical activity of the brain – the EEG. A limitation of the EEG is that it represents the summation of all the electrical activity at a given moment in time, making it difficult to isolate the activity associated with individual neurocognitive processes. A more powerful method for the study of isolated neurocognitive processes focuses on the specific EEG responses to particular sensory, cognitive, or motor events. Such specific responses are called event-related potentials (ERPs), to denote the fact that they are associated with specific events. The ERP is difficult to see in the EEG recorded for a single event. To isolate an ERP, one must collect the EEG of a large number of trials with the event of interest, time-lock the corresponding signals to the onset of this event, and then average the signals. The averaging process filters out all EEG activity that is not related to the event of interest and isolates the ERP – the systematic response of the EEG to the event (Luck 2005).

Properties of ERP Components

ERPs consist of a series of peaks and troughs that are referred to as ERP components (Fig. 1a). The naming of these components often reflects their polarity (P for positive, N for negative voltage) and their order of occurrence (e.g., P1 is usually the first negative component) or typical timing in milliseconds after the event (e.g., P300). Apart from their polarity and latency, ERP components can be characterized in terms of their general scalp distribution (Fig. 1b). The relationship between the voltage distribution observed over the scalp and the brain regions giving rise to this pattern is by no means transparent. This is because there is, in principle, an infinite number of cortical source configurations that can produce the same scalp distribution – a methodological problem known as the inverse problem. Nonetheless, the scalp distribution can be used to infer or test coarse hypotheses about a rather localized neuronal population or multiple, anatomically distributed populations that

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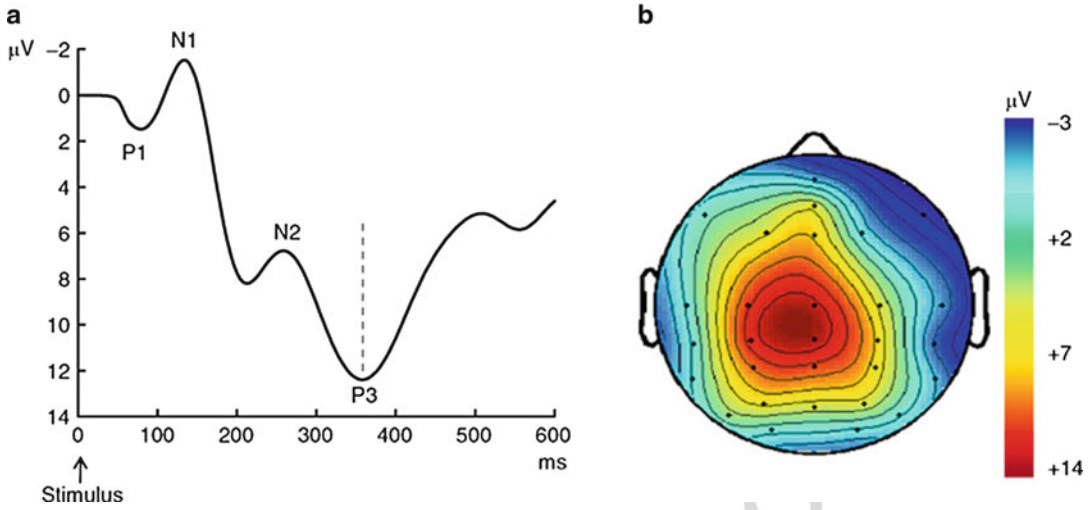

Fig. 1 (**a**) Typical stimulus-evoked average ERP waveform. The abscissa indicates time from the onset of the stimulus, and the ordinate indicates the microvolt value for a specific electrode. Negative voltage is plotted upwards by convention. (**b**) Typical voltage distribution over the scalp, corresponding with the P3 peak latency

generate an ERP component. This can be achieved using source localization techniques, which limit the number of possible source configurations by making simplifying assumptions about the physics of the brain and head tissues, as well as the nature of the active neuronal populations (Handy 2005; Luck 2005).

One must exercise great caution when using ERP component measures for drawing conclusions about underlying neural processes. One difficulty is that ERP components can reflect the combined activity of multiple, relatively independent, underlying or *latent* components that are overlapping in time and/or location. In that case, the neural process of interest typically corresponds with only one of those latent components. Furthermore, differences between experimental conditions or groups in the scalp distribution of a component need not necessarily represent the involvement of different neural sources but may also reflect different relative contributions of the same sources. Techniques such as principal component analysis can sometimes be useful in identifying latent ERP components and their contributions to the observed ERP over the scalp. However, these techniques have significant limitations (Handy 2005; Luck 2005; Picton et al. 2000). Another potential pitfall concerns the variability in timing of some ERP components. Not only can there be large variability of the average component latency across individuals or groups but also substantial variability in the timing of single-trial ERP components. Both cases may pose significant problems for the investigator, because an increase in latency variability results in a decrease in peak amplitude of the average (across individuals or trials). For example, two experimental conditions that differ in latency variability may appear to differ in component amplitude when examined in an average ERP, even when this is not the case in the single-trial waveforms. Investigators should take this possibility into account when examining and measuring ERP components (Picton et al. 2000). Indeed, sometimes it pays off to attempt to measure single-trial estimates of an ERP component and use the trial-to-trial variability in component latency or amplitude to address scientific questions.

In view of the above considerations, it is not useful to define a particular ERP component in terms of its polarity, latency, and scalp distribution. Peak latency and scalp distribution may differ between trials, conditions, and individuals, and even the polarity of a component may vary depending on the placement of the reference electrode. Modern definitions of ERP components acknowledge that

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a component may occur at different times under different conditions and emphasize that two components are the same if they arise from the same neuroanatomical structure(s) and represent the same cognitive function (Luck 2005).

The Physiological Basis of ERP Components

Little is known about the physiological basis of ERP components. It is widely accepted that ERP components reflect the intracortical currents induced by excitatory and inhibitory postsynaptic potentials, which are triggered by the release of neurotransmitters. If many individual neighboring neurons with a similar orientation receive a similar excitatory or inhibitory input at approximately the same time, then the summation of the resulting postsynaptic potentials results in a measurable voltage at the scalp (Luck 2005). Thus, ERP components reflect the postsynaptic effects of neurotransmitters such as glutamate and GABA and indirect modulatory effects from neuromodulators such as norepinephrine, dopamine, and serotonin. Biophysical considerations suggest that the contribution of subcortical structures to the scalp-recorded EEG is small, and hence, most ERP components reflect primarily cortical activity. Whether an ERP component has a positive or negative polarity depends on many neurophysiological and nonphysiological factors and is little informative about the neural origin or functional significance of the component (Handy 2005).

With regard to the origin of ERP components, an important distinction can be made between traditional and synchronized oscillation theories of ERP generation (Klimesch et al. 2007). According to the traditional view, ERP components reflect phasic bursts of activity in one or more brain regions that are triggered by experimental events of interest. As explained above, this view treats the ongoing EEG as background noise that obscures the ERP signal of interest and deals with that noise through data-averaging procedures. The synchronized oscillation hypothesis challenges this approach and instead proposes that ERP components are generated when an event leads to the resetting of the phase of ongoing oscillations in the EEG, such that peaks and troughs in the oscillatory waveform become aligned to the resetting event. When aligned in this way, oscillatory peaks and troughs in the ongoing EEG are evident in the ERP waveform, even in the absence of transient bursts of neural activity. Empirically distinguishing between these two theories has proven difficult for a variety of methodological reasons.

ERP Components as Markers of Mental Processes

The study of ERPs has been of great importance for our understanding of mental processes, by augmenting traditional, behavioral measures such as reaction speed and accuracy (Rugg and Coles 1995). This approach is based on the assumption that changes in a certain cognitive process are selectively expressed in a particular component of the ERP. Then, if it has been established that ERP component X reflects cognitive process Y, one can investigate whether an experimental manipulation or mental state/trait (e.g., psychopathology) affects process Y by measuring its effect on component X. In particular, an effect on the component amplitude suggests a change in process Y or a change in the input to this process. For example, patients with obsessive-compulsive disorder exhibit an increased amplitude of the error-related negativity, an ERP marker of internal error detection. This finding confirms previous notions of a dysfunctional action-monitoring circuit in obsessive-compulsive disorder. Furthermore, an effect on the peak latency of component X suggests that the manipulation or mental state/trait has changed the duration of processes preceding and including process Y. In contrast, an effect on reaction speed in the absence of an effect on the peak latency of component X suggests a change in the duration of processes *following* process Y. For example, it is well known that the presentation of a warning signal can speed up the reaction to an

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imperative stimulus. ERP researchers have increased our understanding of this phenomenon by showing that the benefit in reaction speed is largely restricted to the time interval between an early ERP marker of spatial attention shifts and an ERP marker of hand-specific motor preparation, the lateralized readiness potential.

Of course, the logic outlined above depends on the validity of any given ERP component as a marker of a specific mental process. In the past decades, a large amount of research has focused on validating ERP components, and although there are many ongoing debates in the scientific literature, significant progress has been made in refining hypotheses about the functional significance and neural origin of ERP components (Key et al. 2005; Rugg and Coles 1995). This is particularly true for early ERP components such as the P1 and N1 (Fig. 1a). It is generally held that these components reflect aspects of stimulus encoding in modality-specific perceptual areas, such as visual or auditory cortex. Voluntary or involuntary changes in the amount of attention paid to a particular stimulus lead to amplitude modulations of the P1 and N1 components. Another prominent example of a "sensory" ERP component with a source in modality-specific perceptual areas is the mismatch negativity. This is a negative deflection with a typical latency of 100–250 ms that occurs in response to an odd stimulus in a sequence of stimuli, regardless of whether the subject is paying attention to the sequence.

Some other prominent ERP components are not sensory in nature but reflect central cognitive processes. Important examples are the N2 and P3 components (Fig. 1a), both of which are sensitive to contextual variables, such as the relationship between the eliciting stimulus and the subject's goal of the task and the subjective probability and novelty of the stimulus. The scalp distribution and latency of these components are highly variable across different task contexts. The N2 has been associated with various mental processes, including response inhibition and conflict detection. The P3 is thought to reflect updating of contextual memory representations or temporal filtering of motivationally significant stimuli and its latency is thought to index the end of stimulus evaluation processes. Another cognitive ERP component is the error-related negativity, a negative deflection immediately following erroneous responses that is clearly visible in the response-locked ERP. There is much evidence that the error-related negativity reflects the response of the dopamine system to unfavorable outcomes and events. Finally, there are a number of ERP components that are directly related to motor processes. The most important example is the Bereitschaftspotential or readiness potential, a measure of activity in the motor cortex that is leading to voluntary muscle movement. A derived measure, the lateralized readiness potential, reflects the relative activation of the left and right motor cortex and this has been very important for the study of covert aspects of motor preparation (Rugg and Coles 1995).

Investigating Drug Actions Using ERPs

One use of ERP methodology in psychopharmacology is to investigate the effects of a drug on specific neurocognitive processes (Carozzo et al. 2006; Pogarell et al. 2006). To that end, researchers examine whether and how the drug changes the corresponding ERP components. This often allows for more detailed conclusions than examining behavioral measures alone. For example, ethanol, which has sedative effects, has been found to decrease P3 amplitude, whereas caffeine increases P3 amplitude, suggesting that these drugs affect high-level stimulus-encoding processes. Another example concerns the P50 wave, an ERP component that is used for the assessment of sensory gating – the habituation of responses to repeated stimuli. In healthy subjects, there is an inhibition of responsiveness, that is, a diminished P50 to repetitive stimuli – an adaptive mechanism to prevent overstimulation. The NMDA receptor antagonist ketamine and the antipsychotic haloperidol disrupt P50 suppression, indicating that these drugs modulate sensory gating. Another ERP measure, the

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loudness dependence of the auditory evoked potential (LDAEP), has been proposed as a valid indicator of central serotonergic function in humans. This measure is assessed using the N1/P2 component of the auditory evoked potential and reflects the reactivity of the auditory cortex. Thus, this ERP measure is used as a marker of neuromodulatory function, rather than a cognitive function.

Investigating ERPs Using Drug Actions

Since ERPs reflect functional aspects of neurotransmitters and neuromodulators, drugs affecting particular neurotransmitter or neuromodulator systems are used to investigate the role of these systems in the generation of ERP components (Carozzo et al. 2006; Pogarell et al. 2006). A limitation of this approach is that most available drugs are not selective for a single system, which complicates the interpretation of the results. One exception is a class of drugs, selective serotonin reuptake inhibitors (SSRIs), which selectively increases the amount of serotonin in the brain. Accordingly, SSRIs have often been used to investigate the role of serotonin in the generation of different ERP components. Using this approach, it has been shown that serotonin affects the LDAEP strongly, but is not involved, for example, in the generation of the P3, which is modulated by cholinergic, dopaminergic, and noradrenergic drugs. The mismatch negativity is blocked by NMDA receptor antagonists, indicating that the mismatch negativity critically depends on glutamatergic neurotransmission. These and many other findings have led to an increased understanding of the neural basis of ERP components. This, in turn, has informed theories of their functional significance. For example, the finding that the error-related negativity is modulated by dopaminergic drugs has strengthened existing views that link this ERP component to the literature on dopaminergic reward-prediction errors.

The Role of ERPs in Psychiatry: Sensitivity and Specificity

ERPs are not only important research instruments but are also useful as clinical instruments in neuropsychiatry (Pogarell et al. 2007). ERPs can be used in the diagnostic work-up of a wide range of neuropsychiatric disorders as well as in monitoring the course of the disorders and the prediction of treatment responses. To be useful in the diagnostic work-up, an ERP component has to be sensitive enough to detect the disorder but also sufficiently specific for the disorder to rule out alternative explanations.

Alzheimer's disease is consistently related to smaller P3 amplitudes and prolonged P3 latencies. Using the P3 component, Alzheimer's patients can be diagnosed with high sensitivity and specificity (up to 88.5 %). Furthermore, the P3 is effective in both monitoring and predicting the treatment response of Alzheimer's patients to cholinesterase inhibitors. Thus, the P3 may be an important instrument not only in the diagnostic work-up but also in the monitoring and prediction of the treatment response in Alzheimer's disease. This tool is still underutilized in the clinic, presumably because the P3 has not been generally accepted as a valid biomarker for Alzheimer's disease. Schizophrenic patients also show a decreased P3 amplitude. However, this is generally considered a trait marker rather than reflecting the neurological pathology causing schizophrenia, because the P3 amplitude reduction is not affected by neuroleptic medication and can also be found in remitted schizophrenics, relatives of schizophrenic patients, and other subjects at risk of developing schizophrenia. Thus, the P3 amplitude may be a sensitive marker but is not a specific marker for schizophrenia and is therefore not used in the diagnostic work-up. However, there are indications that in schizophrenic patients, the P3 may predict treatment response.

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Advantages and Limitations of Event-Related Potentials

The major advantage of ERPs is their fine temporal resolution (on the order of milliseconds), indicating that ERPs reflect what is happening in the brain at the very same moment. Another advantage of ERPs is that electroencephalography is noninvasive and cheap compared with other brain imaging methods. An additional convenience is that there are clear and widely agreed-upon guidelines for how ERP studies should be conducted, analyzed, and reported (Picton et al. 2000). The primary limitation of ERPs is that it is not possible to determine the neuroanatomical generator of an ERP component from the measured scalp potentials alone. Furthermore, the geometrical orientation of neurons must be more or less parallel in order to detect the neural activity at the scalp. Signals from structures located deep within the brain are particularly hard to measure. Finally, during the averaging procedure for isolating the ERP from the EEG, all activity that is not time-locked to the event of interest is lost. In order to examine that information, other electrophysiological methods are needed.

Cross-References

- ▶ Attention
- ▶ Caffeine
- ▶ Electroencephalography
- ▶ Psychophysiological Methods

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