Event-related Potential Biomarkers:

The 2-Deviant Oddball Paradigm, ERP Features and Significance

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OVERVIEW

Event-related potentials (ERPs) are part of the electroencephalogram (EEG) generated by sensory and cognitive processing of external stimuli. As such, ERPs provide a real-time physiological measure of fundamental cognitive processes, i.e. a cognitive biomarker. ERPs have been used extensively in research to assess neural abnormalities which subserve cognitive deficits associated with many neurological disorders including Alzheimer's disease, schizophrenia, ADHD, and traumatic brain injury. These studies have demonstrated that ERP features provide valuable diagnostic information as well as aiding in the evaluation of pro-cognitive therapeutics.

ERP WAVEFORM

The ERP waveform (Fig. 1) provides microvolt-level measures of electrical activity for an ensemble of cortical neurons on a millisecond time scale. The early brain responses (<200ms) represent pre-attentive sensory processing of incoming stimuli whereas later time points reflect cognitive processing and evaluation of those stimuli. Since ERPs reflect the precise temporal pattern and intensity of neuronal activity, they are useful in quantifying the timing and sequence of various aspects of cognition.

2-DEVIANT AUDITORY ODDBALL PARADIGM

In this ERP protocol, an unexpected (distractor) tone is played occasionally during a stimulus sequence of frequent (standard) and infrequent (target) tones. The subject is instructed to respond when the infrequent target tone is heard. The protocol elicits a waveform that consists of a series of ERP features (positive and negative deflections in the waveform) that can be used to assess sensory and cognitive processing.

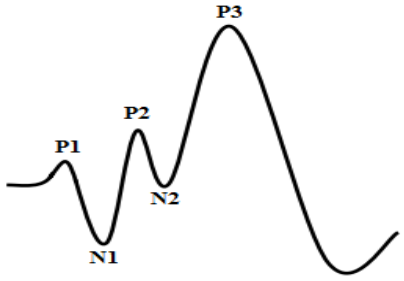

Fig. 1: ERP waveform adapted from Polich 2007

ERP FEATURES

Mismatch Negativity (MMN): is obtained by subtracting the ERP of the standard tone from the distractor tone. It is a negative deflection which occurs ~100-200ms after stimulus onset and is an index of auditory sensory memory and sound discrimination accuracy. The MMN is a pre-attentive process which compares incoming stimuli to that of previously heard stimuli and is elicited when there is a deviation between what is expected versus what is heard. It has a fronto-central distribution which arises from the auditory cortex[3] and may reflect NMDA receptor activity[4].

P3a: is a positive deflection in the ERP waveform elicited by the distractor tone. It has a latency of ~250-400ms and has been associated with brain activity related to the engagement of attention and the processing of novelty[5]. This component has a fronto/central distribution[6] and is primarily generated by frontal lobe and hippocampal activity[7]. It has been shown to be modulated primarily by dopaminergic activity[8].

ERP Feature	Distribution and Stimulus	Cognitive Process	Neurobiological Generators	Clinical Implications[1,2]
MMN[3]	Fz ~ Cz > Pz Distractor–Std	Sensory Memory Passive Attention	Auditory Cortex, Temporal Lobes	↓ A: SCZ, MS, AD
P3a	Fz < Cz > Pz Distractor Tone	Attention Switching, Orienting Response	Frontal Lobe, Hippocampus	↑ A: ADHD
P3b	Fz < Cz < Pz Target Tone	Attention and Working Memory	Temporal, Parietal areas	↓ A & ↑ L: AD, SCZ, AUT ↓ A: ADHD, TBI

A: amplitude, L: latency, SCZ: schizophrenia, AD: Alzheimer's disease, ADHD: attention deficit/hyperactivity disorder, TBI: traumatic brain injury, MS: multiple sclerosis, AUT: autism

P3b: is a positive deflection in the ERP waveform elicited by the target tone with a latency of ~300-500ms. It reflects the strength of memory formed during encoding and storage processes. The amplitude has been shown to correlate to memory updating and allocation of attention[6] whereas the latency reflects classification speed[9] and is proportional to the time required to detect and process an attended stimulus[10]. P3b is primarily generated by temporal-parietal processes and has been shown to be mediated by norepinephrine activity[11].

DIAGNOSTIC UTILITY

Many disorders which are characterized by cortical synaptic dysfunction contributing to deficits in sensory and cognitive processing can be assessed and characterized with ERPs. While the underlying biological substrates mediating these cognitive deficits varies among disease states, the abnormalities in cortical synaptic activity and resulting behavioral deficits can be quantified on a neurophysiological basis with the use of ERPs. The cortical distribution as well as alterations in peak amplitudes and latencies aid in the differentiation of abnormalities associated with various pathological conditions. Accordingly, ERPs can be used as an adjunct to current diagnostic criteria.

ERPs have been proposed as biomarkers for Alzheimer's and schizophrenia[12-13]. There is also accumulating evidence that ERPs can aid in the diagnosis and treatment evaluation of cognitive deficits associated with ADHD, dyslexia, autism, multiple sclerosis, traumatic brain injury, and substance use disorders[14-16].

PHARMACOTHERAPY EVALUATION

ERPs have several distinct advantages when assessing the ability of novel therapeutics to enhance cognitive function. ERPs have homologous measures in animals and humans thereby providing a translational measure of pharmacodynamics activity. Functionally, ERPs provide a precise measure of synaptic modulation sensitive to target engagement and dose effects which helps optimize compound selection and accelerate Go/No-go decisions[17]. Additionally, ERPs can evaluate the pro-cognitive efficacy of therapeutics irrespective of the mechanism of action. As an absolute measure of cognitive function, ERPs provide subject stratification from a single test.

Overall, the 2-deviant oddball ERP paradigm can provide a more complete clinical picture of many neurological disorders critical to both clinicians and the pharmaceutical industry, leading to improved patient outcomes.

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