ERP Biomarkers for Alzheimer's Disease:

Diagnosis, Disease Progression, and Drug Development

Sarah A. Berg, PhD, Director of Neuroscience, Neuronetrix

OVERVIEW

Event-related potentials (ERPs) are part of the 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***. Numerous research studies have helped establish ERPs as a useful cognitive biomarker for the diagnosis of dementia, tracking disease progression, and evaluating the pro-cognitive effect of therapeutics.

ALZHEIMER'S DISEASE (AD)

The diagnosis of Alzheimer's disease is confirmed histo-pathologically upon autopsy by identification of the build-up of amyloid plaques in the medial temporal lobe[1]. However, the diagnosis of AD in living patients is primarily obtained on the basis of behavioral impairments and dementia[2]. These cognitive deficits, particularly with regards to working memory, are the hallmark of AD.

Traditionally, psychometric/behavioral measurements are used to assess cognitive function. However, behavior is essentially an emergent property of cortical processing. Even the simplest behavioral response involves cortical processing at multiple stages including allocation of attention, sensory information processing, stimulus classification, storage in immediate memory, and response selection[3]. Due to compensatory mechanisms and neural plasticity, deficits in synaptic activity and subsequent abnormalities in cortical synchronization and processing can occur far before the overt manifestation of behavioral impairments. The resulting delay in diagnosis can lead to loss of valuable time for disease-modifying treatments.

It can be argued, then, that cortical activity is more closely related to the underlying disease processes of AD than behavior. Thus, compared to neuropsychological tests, measurements of cortical processing and synaptic activity via ERP measurements should have fewer confounds and therefore be a more sensitive and robust biomarker for the diagnosis of dementia disorders. One such ERP paradigm that has been shown to have clinical utility is the auditory oddball paradigm.

AUDITORY ODDBALL ERP 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. This protocol elicits a waveform that consists of a series of ERP components which produce positive and negative deflections in the ERP waveform (Figure 1). This waveform provides a direct measure of cortical synaptic activity which indexes sensory and cognitive processes. The P3 component (a positive deflection ~300ms after the target tone) reflects attention and working memory processes and has been shown to be useful in detecting clinically relevant changes in cognitive function[4].

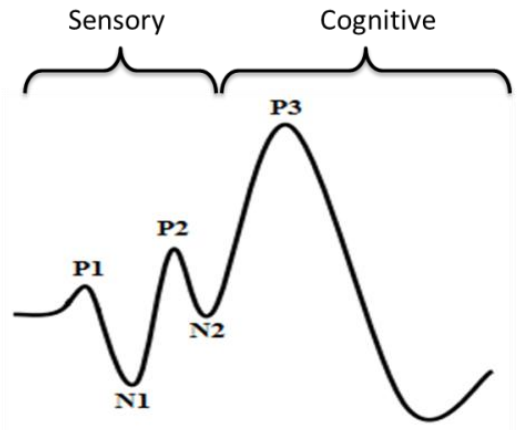

Figure 1: ERP waveform adapted from Polich 2007

DIAGNOSIS AND DISEASE PROGRESSION

Several studies have demonstrated the utility of ERPs in early evaluation and detection of AD. Abnormalities in the standard ERP waveform are present not only among individuals with cognitive deficits[5] but also before the behavioral manifestation of cognitive impairment. As such, ERPs have been shown to be a reliable preclinical biomarker to identify individuals who will develop AD[6,7]. Reduced P3 amplitude as well as increased P3 latency have been observed among individuals diagnosed with AD when compared to age-matched controls[8–10]. Additional features of the ERP waveform, including wavelet decomposition[11] and the amplitude and latencies of other peaks observed

in the ERP waveform[7], have also been used to identify individuals with AD. Additionally, ERPs are sensitive enough to distinguish between different types of dementia with a high degree of sensitivity and specificity[12].

As a reliable biomarker, the ERP waveform can track changes in cognitive function during the progression and treatment of AD. ERP abnormalities have been shown to predict which individuals with mild cognitive impairment will convert to AD[13–17]. The decline in cognitive function observed in the progression of AD has been shown to correlate to increased P3 latency.

Variability observed in ERP features has been shown to be comparable (and in some cases superior) to that of other routinely employed clinical assays[3]. Additional research has shown that ERPs can be used to classify individuals with AD with an accuracy that exceeds that of community physicians and approximates the performance achieved at university hospital-based evaluations[11]. These data support the clinical utility of ERPs as a useful biomarker for AD.

TREATMENT RESPONSE AND DRUG DISCOVERY

Since ERPs reflect synaptic activity mediating cognitive function, they are a sensitive measure of target engagement and can be used to assess any nootropic mechanism of action[18]. Therefore, a simple, inexpensive, auditory ERP test eliciting a robust P3 can be used to evaluate the efficacy of novel AD drugs irrespective of the therapeutic target. A series of studies assessing effects of acetylcholinesterase inhibitors on AD patients suggests that reduced P3b latency could be used as a reliable marker of improved cognitive function in clinical trials[19–21].

COGNISION™ EEG/ERP SYSTEM

Current limiting factors in the widespread use of ERPs are the cumbersome, elaborate, and expensive apparatus required to obtain quality ERP data and the need for trained specialists to analyze and interpret these results. The COGNISION™ System overcomes these limitations by integrating the complex hardware and software subsystems into an inexpensive, easy-to-use, handheld system for automated ERP testing and analysis. All data collected is uploaded to an online HIPAA-compliant database for further analysis, significantly simplifying data acquisition, storage, and analysis.

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