Utilization of Event-Related Potentials for Drug Development

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OVERVIEW

An important and limiting factor in developing effective therapeutics to treat cognitive disorders is the high risk of failure and ensuing financial burden of clinical trials[1]. Utilization of a sensitive and reliable neurophysiological measure of cognitive activity may mitigate this risk, accelerate clinical trials, and reduce cost.

EVENT RELATED POTENTIALS

The electroencephalograph (EEG) is a direct measure of cortical activity that has been used as a surrogate measure of pharmacodynamic activity[2]. 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***.

USE IN DRUG DEVELOPMENT

As cognitive biomarkers, ERPs can be useful both in cognitive assessments and in evaluating the pro-cognitive effects of novel therapies[3]. Since ERPs reflect the precise temporal pattern of synaptic activity, they are useful in quantifying the timing and sequence of neural engagement underlying various aspects of cognition.

NEUROCOGNITIVE ASSESSMENT

As physiological measures, ERPs have several distinct advantages when compared to psychometric/behavioral measures used for cognitive assessments[4,5].

- Direct measure of the neuro-electric network activity related to fundamental information processing.
- Objective measures which are not subject to language/communication barriers, rater bias, or many psychological/behavioral confounds.
- Evaluates multiple cognitive domains with a single, brief ERP protocol.
- Measures cognitive deficits irrespective of the underlying etiology.
- Facilitates precise longitudinal assessments which detect slight changes in cognitive function related to disease progression.

PHARMACODYNAMIC EVALUATION

ERPs have additional specific advantages when compared to other common biomarkers used to assess the biological effects of novel therapeutics[6].

- Homologous measures in animals and humans provide a translational measure of pharmacodynamic activity.
- Precise measures of synaptic modulation– sensitive to target engagement and dose effects to help optimize compound selection and accelerate Go/No-go decisions.
- Evaluates pro-cognitive activity irrespective of therapeutic mechanism of action.
- Absolute measure of cognitive function provides subject stratification from a single test.
- Unaffected by learning/habituation allowing for repeated cognitive testing over short time intervals.

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