EEG/ERP Biomarker Qualification Consortium
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Standardized EEG/ERP battery for measuring drug effects in CNS trials using end-to-end automated analytic pipeline

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Introduction

Many investigational compounds are designed to have acute effects on cortical networks. In early-phase interventional trials with these compounds it is critically important to determine if the drug being trialed crosses the blood-brain barrier, reaches the intended cellular target, and modulates neurotransmission. Given that primary brain function is inherently electrophysiological, electroencephalographic (EEG) measures are the most direct and potentially useful biomarkers to measure these pharmacodynamic effects.

Numerous EEG techniques have been developed in CNS drug trials to quantify functional aspects of brain networks, including background states, attentional activity, and fundamental cognitive processes. To a degree, this has led to "an embarrassment of riches" where investigators are free to design different EEG/ERP paradigms and procedures to answer a wide range of study-specific questions. This has led to numerous methodological approaches, enabling investigators to tailor EEG/ERP methods to address specific study questions. However, this methodological flexibility has created challenges for the pharmaceutical community in comparing, contrasting, and synthesizing data across studies, thereby complicating the process of deriving broader insights into drug mechanisms and their effects across clinical populations.

To address these challenges, the EEG/ERP Biomarker Qualification Consortium (erpbiomarkers.org) was established which aimed to develop, validate, document, and provide structure to EEG/ERP investigations so that standardized methods could be efficiently implemented across many CNS drug trials.

This report describes a large-scale subject assessment workflow and data-analysis pipeline developed by the Consortium to specifically address widespread implementation challenges with EEG/ERP assessments. The key concepts which drove the direction of the Consortium's efforts are:

1. Breadth of application of EEG/ERP paradigms and features across drug mechanism-of-action and indications.
2. Strict standardization of methods and techniques to allow data from different studies to be compared/contrasted.
3. Streamlined implementation of cumbersome procedures to facilitate efficient multi-site scalability.
4. Hyper-automation of the complex analytical processes so that results can be evaluated in near-realtime.

Selection of a Standardized EEG/ERP Test Battery

The first step for the Consortium was to select a specific panel of EEG/ERP paradigms that would have broad application based on the following criteria:

1. All paradigms must have broad scientific reporting, support, and validation.
2. Selected paradigms should target a range of distinct brain networks in both passive and active modes.
3. Each paradigm should produce multiple, well-defined features that are expected to be identifiable in diverse study populations.
4. The features should be sensitive to broad classes and mechanisms of action of CNS compounds.
5. The complete battery should be able to be practically performed within an approximately 1-hour testing session to ensure that the measures are related to drug effects at Cmax (see Figure 1).

Table 1 describes the 4 paradigms that were selected for inclusion in the standardized EEG/ERP testing sessions. The table also references the published exemplar which was generally followed for each paradigm.

Table 1. EEG/ERP Test Descriptions

EEG/ERP Test	Paradigm	Stimulus	Sequence
Duration-Deviant (MMN)[a]	Auditory Oddball	Standard= 1000Hz, 50ms, 90%, 85dB Deviant= 1000Hz, 100ms, 10%, 85dB	Stimuli presented in pseudorandom order so that between 6 and 12 standards are presented between deviants for a total of 2000 stimuli. The interstimulus interval was 600ms.
Auditory Steady-State Response (ASSR)[b]	Stimulus Train	500ms duration, 40Hz white noise click trains, 85dB	Click trains presented every 1000ms for a total of 200 repetitions.
Resting-state EEG[c]	Eyes Closed	n/a	Subjects were instructed to rest with their eyes closed for 5 minutes of EEG recording.
Active Auditory Oddball (P300)[d]	Auditory Oddball	Standard= 1000Hz, 100ms, 80%, 85dB Deviant= 2000Hz, 100ms, 20%, 85dB	Stimuli presented in pseudorandom order so that 2-5 standards are presented between deviants for a total of 300 stimuli. The interstimulus interval is randomized between 2500-3000ms. Subjects are instructed to press a button on the handset as soon as possible each time they hear the deviant (target) stimulus.

a: Light G, et al, Characterization of neurophysiologic and neurocognitive biomarkers for use in genomic and clinical outcome studies of schizophrenia. PloS one. 2012;7(7):e39434.
b: Light G, et al, Gamma band oscillations reveal neural network cortical coherence dysfunction in schizophrenia patients. Biological Psychiatry. 2006;60(11):1231-1240.
c: Jobert M, et al, Guidelines for the recording and evaluation of pharmaco-EEG data in man: the International Pharmaco-EEG Society (IPEG). Neuropsychobiology. 2012;66(4):201-220.
d: Polich J, et al, Neuropsychology and neuropharmacology of P3a and P3b. International Journal of Psychophysiology. 2006;60(2):172-185.

Primary Feature Parameters

The EEG/ERP time-series data (μV vs Time) can be analyzed in numerous ways, including frequency band power, peaks in the frequency spectrum, ERP waveform peaks, etc. The result of each analytical method is called a "feature parameter" (see Table 2).

The feature parameters that are included in the standardized EEG/ERP test battery were selected based on the following criteria:

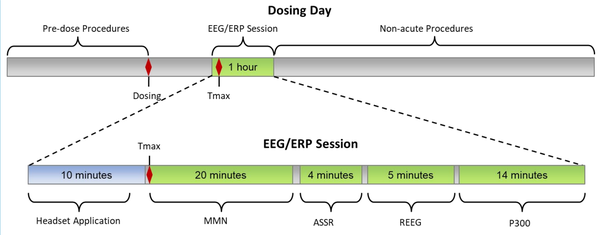
1. Commonly reported in the scientific literature.
2. Have sufficient ICC to be useful in studies with small "n".
3. Shown to be impaired in certain CNS disorders.
4. Can be modulated by various interventions.

Table 2. Primary EEG/ERP Feature Parameters

Feature Parameter	Significance
Delta Power	Associated with cortical plasticity in awake subjects. Can also indicate brain dysfunction. Increased activity is often present postictal and could represent reduced seizure activity.
Gamma Power	Linked to cognitive function, perception, sensory integration, and brain connectivity. Believed to indicate the synchronization of neural networks, particularly in the cerebral cortex
Peak Alpha Frequency	An indicator of neural processing speed and efficiency. Reflects factors such as age, cognitive ability, and overall brain health.
MMN Amplitude	A neural marker of change detection performance. Represents a preattentive form of sensory discrimination enabling a reorienting response to salient stimuli.
P3a Amplitude	Associated with an involuntary attention shift to novel or unexpected stimuli. Amplitude represents the strength of this attentional shift.
ASSR Intertrial Coherence	A measure of phase synchrony of cortical oscillations. Represents the level of organized network activity and cortical communication.
ASSR Evoked Power	Measures the strength of resonate responses in the auditory cortex and is modulated by GABAergic and glutamatergic inputs. Influenced by attention, expectation, etc.
P3b Amplitude/Latency	Index of working memory whose amplitude represents the level of engagement of attention resources directed to the task. The latency indexes stimulus processing where shorter latencies are associated with superior cognitive performance. Together, the P3a amplitude and latency is an objective measure of cognitive function.

Implementation in Interventional Trials

Many investigational compounds are designed to have acute effects on cortical networks. In early-phase interventional trials it is important to determine if the study drug crosses the blood-brain barrier, reaches the intended target, and modulates neurotransmission. Given that brain function is inherently electrophysiological, EEG measures are the most direct and potentially useful biomarkers to measure these pharmacodynamic effects.



The EEG/ERP session can be efficiently implemented to capture PD effects after dosing, generally around Tmax, as compared to placebo. Additionally, since the session only requires one hour, within-subject effects can be investigated using a "pre-dose" vs "post-dose" session on the same study day.

Validation Studies

A validation trial (NCT04025502) was performed by the Consortium where 80 healthy subjects and 80 subjects with Schizophrenia were tested at 4 sites during 2 separate visits using the EEG/ERP testing session described here. All procedures and methods were designed to simulate a standard early-phase interventional trial.

An additional validation trial (NCT04928703) was performed with 24 healthy subjects across 3 visits. Each subject was dosed with ketamine during 2 visits and a placebo during 1 visit, in randomized order.

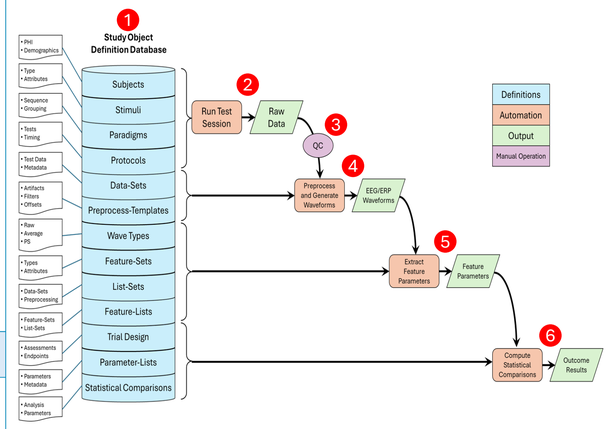
The trial results demonstrated:

1. The selected test battery could be performed at common clinical trial sites in healthy subjects and patients during a 1-hour time window
2. Several relevant EEG/ERP biomarkers were significantly impaired in a clinical population with respect to healthy subjects
3. The biomarkers demonstrated sufficient test-retest reliability and dynamic range to be useful pharmacodynamic measures in early-phase trials.
4. The biomarkers could be consistently collected, even when the subjects have been administered ketamine.
5. The biomarkers could be used to detect effects from a sub-anesthetic dose of ketamine.

Data Collection and Analysis Waterfall

Raw data collected during standard EEG recording sessions, or especially during complex ERP sessions, requires significant cleaning, preprocessing, and feature extraction analytics. These analytic processes also requires a complex data management effort to define the relationships between subjects, study arms, timepoints, testing paradigms, feature definitions, analytic methods, etc.

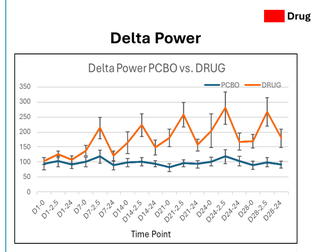
To perform these procedures in an efficient way the Consortium developed a predefined, fully-automated, data management and analysis "waterfall", which executes all functions without human intervention. This ensures that no bias is introduced by users endeavoring to clean and preprocess the data based on their own expertise or experience. This explicitly defined and standardized pipeline ensures data consistency across different trials and trial sites.



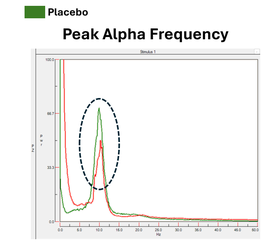
1. The backbone of the data and analytical architecture is the SQL database schema which logically defines all study workflows, data definitions, data relationships, and analytical processing steps. This predefined study schema is exposed to users through a web-based UI employing standard clinical study concepts, terminology, and language. The data and metadata definitions include subjects, arms, assessments, timepoints, interventions, EEG/ERP paradigms, data cleaning attributes, analysis algorithms, feature parameters, statistical comparisons, and other study-related data objects. The predefined workflows are composed of modules that include all tasks, events, and processes necessary to efficiently schedule, run, clean, analyze, and report all EEG/ERP assessments and endpoints. This database is updated in realtime as new subjects are enrolled at different sites, assessments performed, or other study data is created.
2. EEG/ERP testing sessions, which include the 4 separate paradigms (see Table 1), are scheduled to be performed with the designated subject at the predetermined time using the Schedule of Assessments UI. Each of the 4 paradigms are then sequentially performed in an automated process.
3. Upon completion of the testing session, the raw EEG/ERP data from each paradigm is automatically uploaded to the online database where they are flagged for review by a Quality Specialist. The quality review involves automated and semi-automated processes with manual confirmations. The detailed results of the quality review are captured in the database for documentation purposes.
4. Upon quality approval, the raw EEG/ERP data are automatically submitted to the cleaning, preprocessing, and waveform generation module. This module calls predefined preprocessing and analysis workflows to produce high-quality waveforms from each paradigm, based on the specific requirements of each feature parameter definition. The generated waveforms can also be used for visualization of individual subject waveforms, comparisons of subject waveforms, group waveforms, and/or comparisons of group waveforms. The visualization workflow can also be stored in the database for rapid access.
5. Feature parameters are the numeric values used to perform statistical comparisons and to evaluate and report endpoint results. The feature parameters can be values of peak amplitudes or latencies from time-series data or frequency spectrums. They can also be frequency band powers, coherence values, or values calculated by other means. The feature parameters are calculated by executing complex analytic algorithms on fully preprocessed EEG/ERP waveforms. These algorithms are completely predefined before any data is collected so that as data is collected, QC'd, and preprocessed all feature parameters can be immediately calculated and made available for statistical analysis.
6. Before a study even begins, the important statistical comparisons of EEG/ERP endpoint data can be defined. With the appropriate unblinding procedures in place, the statistical comparisons can be generated at any point during the study as part of an interim analysis or at the end of the study. Monitoring comparisons during a study can facilitate adaptive designs where study design changes can be performed based on interim results.

Real-world Results of Pharma-sponsored Trials

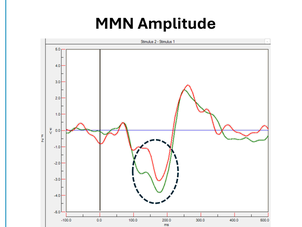
This EEG/ERP testing battery has already been implemented in several pharma-sponsored trials at multiple sites. Statistically significant measures of drug effects have been measured with various feature parameters across several drug mechanisms.



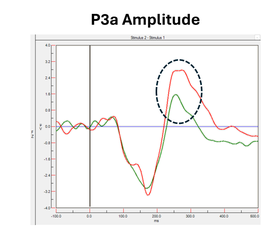
Drug Mechanism	Sodium Channel Blocker
Indication	Epilepsy
Study Phase	1
Subject Population	32 Healthy Subjects
EEG/ERP Paradigm	Resting EEG



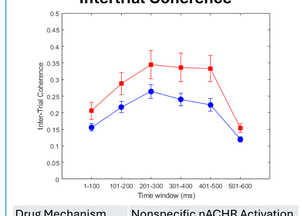
Drug Mechanism	NMDAR Antagonist
Indication	Healthy
Study Phase	1
Subject Population	24 Healthy Subjects
EEG/ERP Paradigm	Resting EEG



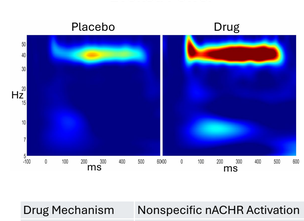
Drug Mechanism	α7 nACHR Activation
Indication	Healthy
Study Phase	1
Subject Population	24 Healthy Subjects
EEG/ERP Paradigm	Passive Oddball



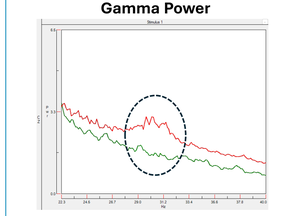
Drug Mechanism	Ketamine Blockade
Indication	Healthy
Study Phase	1
Subject Population	22 Healthy Subjects
EEG/ERP Paradigm	Passive Oddball



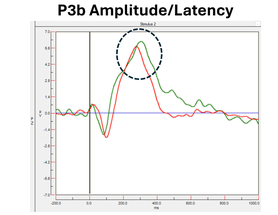
Drug Mechanism	Nonspecific nACHR Activation
Indication	Schizophrenia
Study Phase	POC
Subject Population	24 Subjects w/Schizophrenia
EEG/ERP Paradigm	ASSR



Drug Mechanism	Nonspecific nACHR Activation
Indication	Schizophrenia
Study Phase	POC
Subject Population	24 Subjects w/Schizophrenia
EEG/ERP Paradigm	ASSR



Drug Mechanism	NMDAR Antagonist
Indication	Healthy
Study Phase	1
Subject Population	24 Healthy Subjects
EEG/ERP Paradigm	Resting EEG



Drug Mechanism	NMDAR Antagonist
Indication	Healthy
Study Phase	1
Subject Population	24 Healthy Subjects
EEG/ERP Paradigm	Active Oddball