cog-ni-tion *noun* \käg-ˈni-shən\

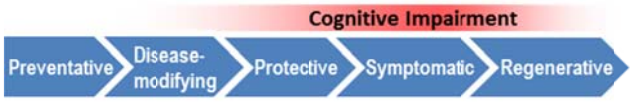
1: a mental faculty for the processing of information.

2: a group of mental processes that includes attention, memory, language, learning, reasoning, problem solving, and decision making.

OVERVIEW

Cognitive disorders such as Alzheimer's, schizophrenia, ADHD, and others take a tremendous toll on those affected, their families, and society in general.

While preventative and/or disease-modifying therapies represent the greatest potential impact, effective treatments that reduce the devastating cognitive effects would, in the interim, still provide substantial relief to the patients and support systems tasked with caring for them.



The challenge of developing effective pro-cognitive treatments is amplified by the inherent difficulty in directly measuring cognitive processing itself. This limits the ability to accurately assess the level of a patient's cognitive dysfunction or any pro-cognitive changes due to a therapeutic intervention.

The result? Either potentially effective drug candidates don't get identified in the early stage trials, or the cost of advancing a promising drug through the later stages becomes extremely time-consuming and expensive.

The solution to this dilemma would be a sensitive and reliable physiological measure of cognitive function that could be practically applied throughout the drug development process.

Fortunately, with the recent technological advancements in electronic sensor design, signal processing, and web-based data management, that solution is available now.

PHARMACOLOGICAL TREATMENTS FOR COGNITIVE DISORDERS

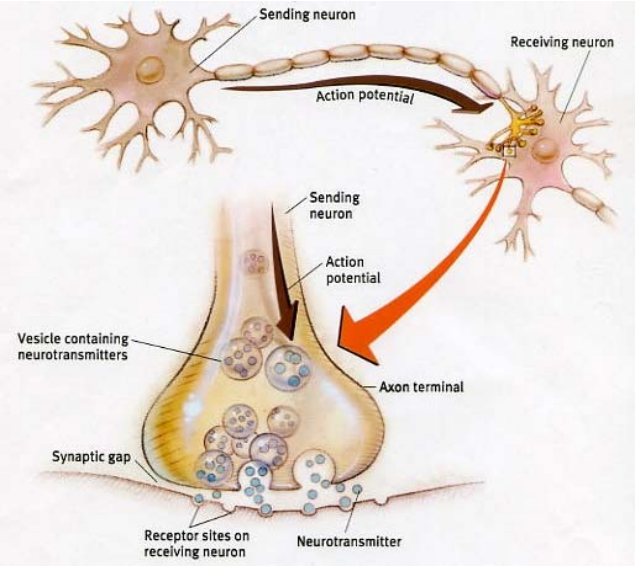
Cognitive disorders such as Alzheimer's, schizophrenia, ADHD, and others, share many common factors relevant to pharma companies endeavoring to treat these diseases:

- They manifest as deficits in various fundamental cognitive domains, e.g. attention, sensory gating, working memory, etc.
- The cognitive deficits proximal to the underlying bio-pathological processes are difficult to measure at the level of behavior.
- Patients with the same underlying disease process often present with wide variation in cognitive and behavioral symptoms.
- There are no meaningful imaging or biochemical markers of these diseases which can be used as measures of cognitive impairment.

Pharmacological Targets

Most efforts to develop treatments for the broad range of cognitive disorders have focused on (and will continue to be focused on) modulating neuronal activity through the mechanisms of neurotransmitter regulation, hormonal activity, and/or neurotrophic factors.

These targeted therapies are intended to regulate neuronal function and normalize the fundamental cognitive processes underlying the emergent behavioral symptoms.



These efforts have resulted in several therapies which have proven to be moderately effective for many patients:

- Cholinesterase inhibitors and glutamate regulators for Alzheimer's disease.
- Dopaminergic and serotonergic receptor antagonists for Schizophrenia.
- Psychostimulants for ADHD.

Many other potentially useful targets, mechanisms of action, and adjunctive therapies are under development by many companies.

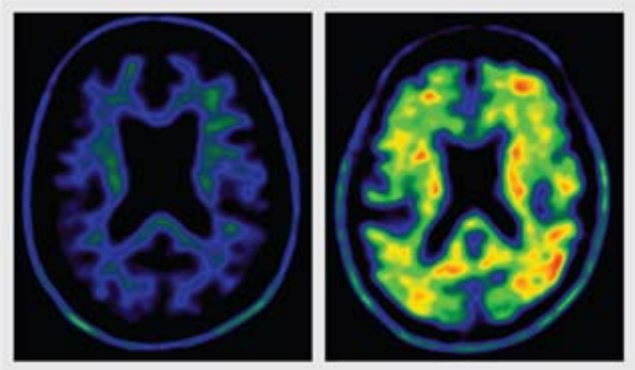
THE BIG CHALLENGE

Other than the obvious difficulty in designing safe and effective neurotherapeutic compounds, the biggest problem affecting the CNS industry has long been the lack of a practical, sensitive, and reliable physiologic measure of cognitive function, a ***cognitive biomarker***.

The Need for New Biomarkers

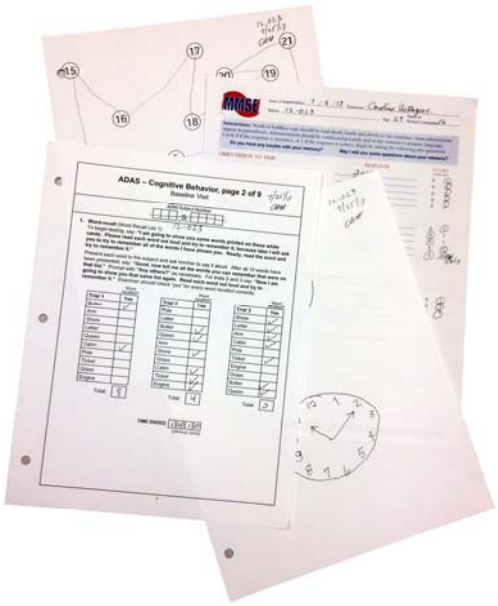
Biochemical markers, such as those which can be measured in cerebral spinal fluid, are indispensable in trying to understand certain aspects of the disease-related biopathology or the pharmacokinetics of a particular agent.

Molecular imaging can also be very useful when evaluating the biochemical/anatomical nature of disease or the proximal effects of disease-modifying therapies.



But measures of brain biochemistry and/or anatomy using molecular markers or advanced imaging techniques are not surrogates for cognitive processing and especially not for psychological function.

Standardized psychometric/psychological testing can provide useful measures at the level of behavior, and are generally required as pivotal endpoints in late stage trials. However, these tests often lack the sensitivity, reliability, and repeatability required for studies involving a reasonable number of subjects and which can be completed in an economically viable timeframe.



These psychometric/behavioral measures are also rarely useful at the early development stages when investigating potentially beneficial pharmacodynamic effects in the brain, i.e. the ability to improve synaptic function.

These measures are also difficult to use in dosing studies where short-term longitudinal effects are of interest.

A Cognitive Biomarker?

The ideal neuro-biomarker for measuring the effects of cognitive therapies would:

- Offer a direct physiologic measure of those brain processes most responsible for cognitive ability, i.e. synaptic activity.
- Give a sensitive measure of pharmacodynamic activity and dose-response.
- Be measurable in animal models—rodents and primates as well as humans—using consistent methods and with highly correlated results.
- Correlate with measures of cognitive dysfunction.
- Provide useful data when recorded longitudinally, over both short-term or long-term, i.e. rapid response to drug action, no habituation, and stable over the long term.
- Provide low intra- and inter-subject variability.
- Be insensitive to site and/or user variability.
- Be unaffected by communication or other behavioral difficulties.
- Be measured easily and cost-effectively in common clinical trial settings.

SOLUTION: NEURO-ELECTROPHYSIOLOGY

Neuro-electrophysiology Overview

An ***electroencephalogram (EEG)*** is a recording from the surface of the scalp of the electrical activity originating in the brain. The electrical field is produced as the sum of billions of neurons involved in various neuro-regulatory functions, preattentive cortical processing, and/or conscious activity.

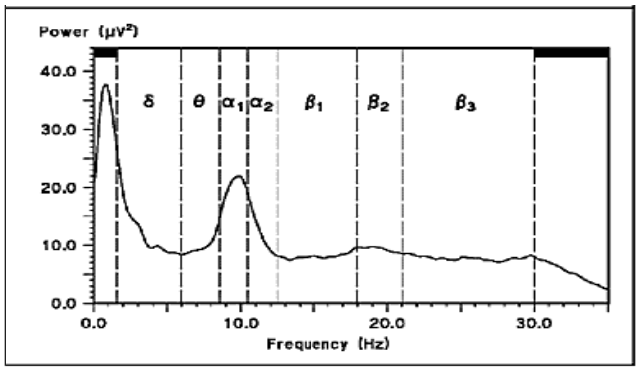
EEGs recordings provide unique advantages for use in evaluating cognitive disorders:

- A primary physiologic measure of the synchronous, large-scale synaptic activity underlying all brain functions.
- Have millisecond resolution and can thereby capture many rapidly occurring aspects of regulatory, sensory, and cognitive processing.
- Can be modulated due to the effects of psychotropic compounds and/or in response to various external stimuli.
- Can be recorded while the brain is in a resting state or while performing specific cognitive tasks.

Quantitative EEG (QEEG)

QEEG is the application of signal processing algorithms to the time-varying EEG amplitude, typically to quantify various features in the frequency domain.

One method of QEEG analysis involves Fourier transforms to evaluate EEG power in well characterized frequency bands—delta, theta, alpha, beta, and gamma.

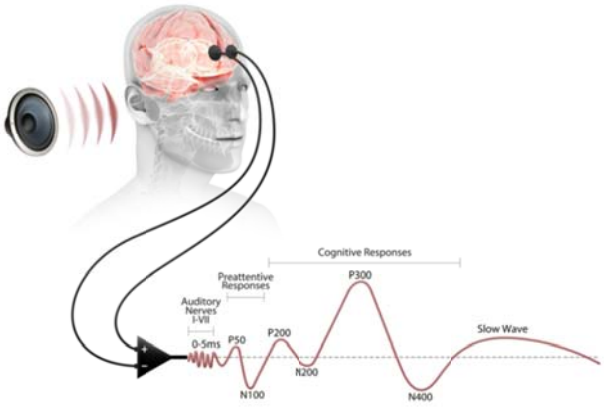


Another QEEG method is wavelet decomposition which is used to evaluate frequency specific information vs. time.

Synchrony and coherence analysis may also be performed to look at the time and phase relationships of EEG activity between different channels.

Event Related Potentials (ERP)

ERPs are part of the EEG directly related to sensory and cognitive processing of external stimuli. The stimuli can be auditory, visual, or tactile and are generally arranged in a long sequence of many repetitions. These sequences can be designed to probe specific cognitive processes such as sensory gating, selective attention, memory encoding, or semantic processing.



The early brain responses (<200ms) represent pre-attentive sensory processing of incoming stimuli whereas later time points reflect cognitive processing and evaluation of specific features of the stimulus sequence.

Since ERPs reflect the precise temporal pattern and intensity of neuronal activity, they are useful in quantifying the timing and structure of various aspects of mental function and cognition.

Cognitive Event-Related Potentials: Useful Clinical Information in Alzheimer's Disease
Katada,et al,Current Alzheimer Research, vol. 1, pp. 63–69, 2004

ERP Feature	Brain Function
P50	The P50 increase may be related to reductions in prefrontal inhibition over auditory cortical responsiveness.
P100 (P1)	If attention was maintained in a single locus, the P1 was enhanced.
N100 (N1)	When attention was shifted from one location to another, the N1 was enhanced
P200 (P2)	The early stage of sensory processing.
N2a	The storage of information in sensory memory.
P2b	Selective attention.
P3a	Orienting response.
P3b	Immediate memory attention.
P400	Encoding and maintaining information in memory process.
N400	Implicit memory, semantic memory.
P600	Verbal episodic memory processes.
NA	Pattern recognition.
RP	The earliest sensory processing prior to pattern recognition.

Auditory Steady-state Response (ASSR) Event-related Desynchronization (ERD)

Other neuro-electrophysiological measures such as ***ASSR*** and ***ERD*** employ stimulus streams and EEG recording to investigate a range of complex neurodynamic processes.

Several of these neuro-electric measures have proven useful in the evaluation of cognitive disorders and as pharmacodynamic endpoints.

One such biomarker, the *ASSR-induced gamma band entrainment synchronization measure*, has been shown to be highly correlated with schizophrenia and with the pro-cognitive effects of certain compounds used to treat the disorder.

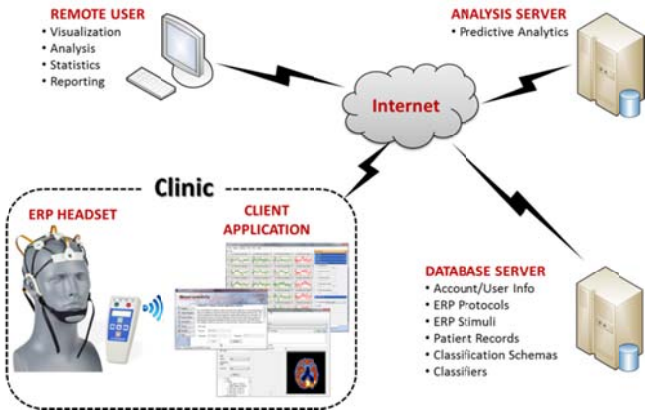
Limitations of Traditional QEEG/ERP Systems for Clinical Use

Although the potential of neuro-electric biomarkers has been known for decades, traditional QEEG/ERP systems have been plagued with a range of technical and practical limitations which have confined them to the academic research lab:

- Complex hardware with little system integration and minimal human-factors design leading to extensive training requirements and inconstant test results.
- Systems designed to be operated in an electromagnetically shielded environment and whose data quality suffers when used in a clinical or office setting.
- Software designed for electrophysiology experts and not user-friendly for non-specialists.
- Limited standardization of device settings, protocols, methods, and data analysis techniques making multi-center studies unrealistic.
- Expensive hardware limits the practicality of performing QEEG/ERP studies at large numbers of sites.
- Long setup and test administration times creates a significant burden on study subjects and staff.
- Limited functionality to aggregate data in a HIPAA-compliant manner makes data management complex and inefficient.
- Complicated data processing pipeline makes analyses of studies with large cohorts difficult, time-consuming, and expensive.

COGNISION™ Overcomes the Limitations of Previous Methods

The ***COGNISION™ System*** from Neuronetrix was designed from the outset to overcome the limitations of research-oriented methods and equipment and deliver on the promise of advanced neuro-electrophysiological techniques.



- The hardware was designed to be very patient-friendly, and easy and fast to setup and operate even for users with minimal electrophysiology training.
- The system produces exceptionally high fidelity data in normal office settings.
- The software was developed to provide the most advanced functionality through an easy and intuitive user interface.
- The system architecture supports large-scale data collection through the internet in order to facilitate the multi-center studies necessary for clinical validation.
- Modern integrated electronic packaging makes for a low-cost system for use at numerous sites in large-scale trials.
- The system implements the most scientifically validated neuro-electric protocols which can be selected from an online library and run in a fully automated way.
- The data preprocessing and analysis pipeline is predefined for each test protocol which facilitates complex analyses with minimal user input, even for studies with large "n".

These features enable researchers and pharma companies to practically and cost-effectively implement neuro-electric biomarkers throughout all stages of their clinical trials.

This enables drug development programs to leverage the sensitive physiologic measures of cognitive function provided by neuro-electric biomarkers.

reCOGNISION™: Predictive Modeling, Analysis, and Classification

In principle, simple neuro-biomarkers might be able to answer a variety of clinical questions, but in the real-world of CNS disorders, these measures rarely have the necessary levels of sensitivity and specificity to provide reliable answers for many of the important questions. Instead there may be many measures, each having low predictive value, but when combined using advanced classification algorithms, might provide the required accuracy to support the complex decisions encountered in most CNS drug development programs.

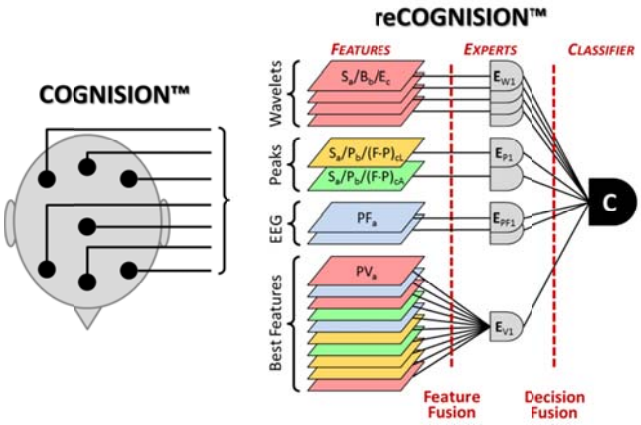
Therefore combining biomarkers is often necessary, especially for neuro-electric measures which contain useful and important information in many features of the test data.

Unfortunately, as the number of biomarkers grows, the complexity of the problem grows even faster. Advanced computerized classification software is required to address problems of this type.

The COGNISION™ System includes an advanced predictive analytic classification system called ***reCOGNISION™*** which learns to classify subject data based upon user-defined *meta-models*.

Unique advantages of reCOGNISION™:

- Any neuro-related clinical data can be used for classification.
- Allows the user to define the problem meta-model before any patient data is used.
- Uses clinical neuroscience terminology to define the meta-model.
- Large selection of classification algorithms.
- Performs feature- and decision-fusion during training.
- Handles n-class problems where n ≥ 2.
- Performs automatic rank-ordering of predictor variables.
- Performs automatic K-fold cross-validation.
- Performs automatic featurespace optimization.



reCOGNISION™ is not limited to ERP data. The application can leverage other neuro-biomarkers such as; medical histories, lab tests, MRI and PET images, genotype, and psychometric tests.

reCOGNISION™ could be an enabling technology for companies developing neuro-related therapies. Answers from reCOGNISION™ could be used to help identify drug targets, to select patients for clinical studies, to evaluate effects of therapy, and as endpoints for drug approvals.

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