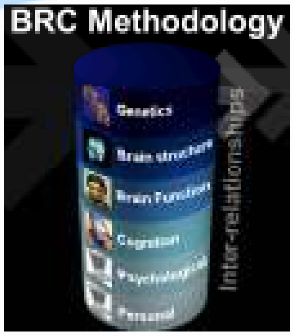
Risk Assessment for Convulsions

Brain Resource (BRC) has developed the first standardized approach to measuring the brain that brings together elements of brain functioning that are normally studied in isolation. Our approach integrates across behavioral and biological measures to obtain new insights about brain performance.



From this convergent approach, we have elucidated a number of Biomarkers that measure brain instability and the potential for convulsive risk induced by new compounds (such as glutamatergic agonists). This document summarizes these EEG-Body Arousal Biomarkers.

Our Biomarkers fall into 3 categories:

1. Measures of EEG brain function stability

There are 3 measures of EEG activity that have been shown to reflect brain instability and the potential for epileptiform phenomena.

The first measure of Brain instability is reflected in quantitative EEG variability from epoch to epoch across a selected recording period. A second measure reflects the ‘peakiness’ of Alpha activity sharpening and the increase in ‘peakiness’ of Theta activity. Alpha sharpening has been shown (including in **2.** below) to predict Grand Mal Epilepsy and Theta sharpening can result in Petit Mal Epilepsy (this reflects the lack of a dampening of brain function that is associated with enhanced brain stability). The third measure concerns overall EEG brain stability.

2. EEG Numerical Simulation Model

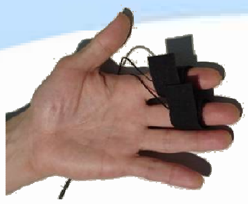
This Numerical Simulation began with Roger Sperry and Jim Wright at Caltech, over 25 years ago. A team of physicists at the University of Sydney have since worked on this model.

Brain Resource owns the IP to fit the model parameters to individual subjects. In essence, the model considers the excitatory gain in the cortex (the *Ge* parameter in the **EEG Biophysical Model** (**see the attached pdf**), as well as thalamo-cortical excitation (*GeSe* parameter).

An increase in gain excitation in either the cortex or thalamo-cortex can be considered a marker for potential brain instability, tipping toward convulsive phenomena.

3. <u>Simultaneous Measure of Arousal and EEG</u>

In Brain Resource's standardized methodology we simultaneously measure EEGs, heart rate and sweat rate. An increase in Arousal reflects an excitatory drift, and the extent of this excitatory gain can act as a global marker for the risk of brain instability.



Capabilities:

Age- and Gender-Specificity

The use of the above Biomarkers can be complimented with the use of insights obtained from our database (the Brain Research International Database (BRID)), which is the largest standardized brain database in the world. Using our database, we can determine the variance for each of these Markers particular to each age range in which the compound is being assessed (for example, for male subjects who are18-25 years old). This frame of reference allows us to determine the extent of change (for example, 1.5 Standard Deviations) that may indicate a threshold for risk for brain instability for your compound.

Dose Optimization with Risk Minimization

Using the converging evidence obtained from our above Biomarkers, we can determine <u>which</u> dose of the new compound may be most likely to pose a risk for brain instability.

Our approach offers a refined way of determining the potential convulsion *risk* from your compound, way beyond visual inspection of actual epileptiform spike and wave phenomena that may be induced in your subjects (spike and wave is in itself of course the crucial marker, but at a very late stage of brain processing).

For Risk Assessment for

Convulsion Costs, contact:

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