

A teal-colored horizontal band with a faint, light blue background graphic of an EEG waveform and electrode placement diagram. The diagram shows a series of numbered electrodes (1-14) and connecting lines, with a vertical double-headed arrow indicating a measurement or range.

# Referenced-EEG<sup>®</sup> (rEEG<sup>®</sup>) An Introductory Guide for Physicians

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## Overview

When treating patients with treatment-resistant neurobehavioral disorders, medication selection using objective physiologic data can add information of value to the physician's development of an effective treatment plan. The CNS Response, Inc. database contains data tracking the responses of over 1825 patients whose Referenced EEG (rEEG<sup>®</sup>) biomarkers were correlated with long-term medication treatment outcomes (average 405 days).

Referenced EEG (rEEG<sup>®</sup>) correlates medication response with the abnormal quantitative EEG features within the database. Our goal is to provide patient specific correlative information to aid in planning the pharmaco-therapeutic dimension of treatment plan for your patients. rEEG<sup>®</sup> includes the process of recording, transmitting, processing, comparing the EEG to a clinical outcomes database, and reporting digital EEG studies using CNS Response's procedures and methods. This document provides information about the rEEG<sup>®</sup> process including:

- Conventional EEG limitations
- Types of examinations available
- Patient exclusionary criteria
- Patient inclusion criteria
- Use of medications
- Patient state during recording
- Sending EEG data to CNS Response
- Analysis and interpretation
- rEEG<sup>®</sup> report content and report delivery options
- Scoring clinical improvement for follow up studies
- Compatible digital EEG instruments

One should read this introductory guide in conjunction with other information provided by CNS Response. For questions or information not included in this guide, please call CNS Response at (888) 545-2677.

## Conventional Electroencephalogram (EEG)

The CNS Response rEEG<sup>®</sup> is a tool only appropriate for patients without significant neurological disorders such as epilepsy, brain tumors and strokes.

### **Patients with significant neurological disorders cannot be tested.**

To prevent inappropriate analysis, the EEG submitted for rEEG<sup>®</sup> is first screened for gross abnormality by a board-certified electroencephalographer. The rEEG<sup>®</sup> baseline report will contain this review. In those cases where there is a major EEG abnormality, rEEG<sup>®</sup> analysis is not appropriate. The electroencephalographer will describe the abnormality that is

preventing rEEG<sup>®</sup> analysis and provide his telephone number for the referring physician's invited follow up discussion. In cases where the EEG abnormality is moderate or nonspecific, rEEG<sup>®</sup> analysis will be performed and the report will note the presence of these abnormalities. rEEG<sup>®</sup> analysis does not require that EEG testing include evocative procedures for epileptic abnormalities [e.g., awake/sleep transitions, hyperventilation, photic stimulation] as in routine clinical EEG testing.

**If significant neurological disturbances are suggested by examination of the rEEG<sup>®</sup>, the database analysis may not be completed and the examining physician's comments on the EEG findings will be forwarded in lieu of a rEEG report.**

Occasionally, the EEG recording contains electrical activity that is not directly generated by neuronal activity in the brain and this is termed "artifact". Artifacts may be caused by body movement, jaw clenching, eye blinking, sweating, swallowing, and by 60 Hz interference from the recording facility's electrical service, as well as other physiological and environmental events. These artifacts may focally or globally obscure brain activity and limit interpretation of certain periods during the recording. Recordings with such artifacts may not be suitable for rEEG<sup>®</sup> analysis. Two minutes of artifact free data must be present in the record in order for rEEG<sup>®</sup> analysis to be completed.

## Types of Examinations Available

Two fundamentally different examinations can be performed. One examination, **Type I**, requires the patient to be medication free. It establishes a baseline of understanding of the brain's functioning. A second type of examination, **Type II**, occurs after the patient has been medicated and allows comparison to the baseline.

If the patient is medication free for at least five half-lives of any previous medication thought to cross the blood-brain barrier or otherwise affect brain function, a **Type I** examination is appropriate. This requirement includes freedom from psychotropic and non-psychotropic medications, supplements other than daily vitamins, alcohol or drugs of abuse. Hormone replacements such as insulin, thyroxine or oral contraceptives do not need to be discontinued. The patient also cannot be malnourished.

Under some circumstances, CNS Response may be willing to analyze rEEG<sup>®</sup> data of a currently medicated patient. This Type 1(m) test must be pre-approved by CNS Response. The resulting report is an opinion and not a completed rEEG<sup>®</sup> statistical analysis. If CNS Response is willing to do such a test, the resulting report may provide insight into how to proceed. This is an area where there is limited data and little predictive power. The test takes quite a bit of time and must be done manually outside of our normal process. It should only be considered as an option of last resort.

Follow-up EEG recordings, **Type II**, can track changes produced by the administration of a single medication or, at most, two medications according to the **Type II** examination procedure. The medication or medications must be among those found on a Type I report. **Type II** examination reports the impact of medication and

pathophysiologic processes on the EEG data.

When **Type II** examination follows a **Type I** examination, it is possible to observe the absolute changes attributable to medication and appreciate the spectrum of actions on the EEG of a given medication or combination of medications. These effects can be compared to the set of initially comparable individuals and their response to the same medication or medications. When the data for the current patient and the reference group within the outcomes database are substantially similar, this further validates the electro physiologic characteristics of the medication.

## When rEEG® is Not Appropriate

1. If any of the following are true:
  - Intramuscular depo-neuroleptic therapy within the preceding twelve months
  - History of craniotomy with or without metal prostheses
  - History of cerebrovascular accident
  - Spikes or other seizure activity on the conventional EEG
  - Current diagnosis of seizure disorder
  - Diagnosis of dementia
  - Mental retardation
  - Current use of marijuana, cocaine, hallucinogens or other drugs of abuse
  - Alcohol in the last three days
  - Significant abnormality of the CBC, chemistry or thyroid function tests, including TSH until corrected
  - Severe encephalopathy due to multiple causes, such as head injury, anoxia, encephalitis, dementia, and other causes
  - Recent ECT treatments
  - Active suicidal intention
2. If substance abuse is a clinical concern, only submit a rEEG® study after the Urine Drug Screen (UDS) is negative for the requisite time for the agents of concern according to the 5 half-lives chart.
3. If a patient cannot safely remain medication-free and (and street drug-free) for five half-lives of the current agent(s) prior to rEEG® examination.

## When rEEG® is Appropriate

When a patient does not meet any of the exclusion criteria AND

1. is between 6 and 90 years of age
2. is medication free or can safely become medication free
3. has been diagnosed with any non-psychotic psychiatric disorder
4. has had two or more unsuccessful medication trials
5. is treatment naïve
6. has reservations about pharmacotherapy
7. values shorter path to likely treatment success

## Use of Medications in a Type I Examination

All medications that penetrate a patient's blood-brain barrier can influence the EEG. However, some "medications" such as thyroid, insulin, or estrogen are really replacement of natural hormones and do not require discontinuation prior to baseline examination. If you have any questions, please call CNS Response at 888.545.2677.

All other medications **must be avoided prior to the Type I** examination. Similarly, in a Type II examination all substances that are not of interest must be discontinued so as not to confound the results. Use of non-prescription agents such as analgesics, herbal and naturopathic agents, food supplements and vitamins must also be discontinued for 5 half-lives or two weeks if the half-life is unknown or cannot be determined. Please call CNS Response at 888.545.2677 if you have any doubt as to whether any substance needs to be discontinued and/or for how long.

## Importance of completing rEEG® Requisition Form

The rEEG® Requisition Form, which can be downloaded at <http://www.cnsresponse.com/>, orders the rEEG® analysis and specifies its completion. The ordering physician must fill the form out completely and sign it. The physician should deliver a copy of this form to CNS Response and to the EEG testing professional. At the EEG testing appointment, the EEG professional must confirm that the patient has been medication free consistent with the history identified on the form and has not taken any substances (including over-the-counter, NSAIDs, aspirin, caffeine, nicotine, alcohol, etc.) in the interim. As the prescribing physician, your written instructions will be essential in directing your patients in this process.

You are referred to the CNS Response Taper Procedure for an example of how Daniel Hoffman, M.D. has developed and implemented tapering of psychotropic medications.

The EEG recording professional must confirm that the patient has appropriately complied by initialing the Requisition Form and faxing it to CNS Response at 866.294.2611. An EEG record can be rEEG® processed only upon receipt of an EEG completed Requisition Form. If it is discovered that the patient has not appropriately complied, the EEG test must be rescheduled. A list of “5 half-lives for Common Medications” can be downloaded at <http://www.cnsresponse.com/>. CNS Response updates this spreadsheet on a routine basis. If you encounter a medication that is not listed, we will be happy to assist you in finding the information and we will add it to the list.

## Patient State

Recordings are technically suitable for medication response correlation ONLY when free of artifact [e.g., body movement, jaw clenching, swallowing, EKG, eye movement, etc.] and if the patient is awake and alert. EEG recorded during mild patient drowsiness will be edited from the record prior to analysis. It is important to instruct the patient to get a good night’s rest prior to the day of testing. Further, it is useful to explain to the patient the need to remain motionless, awake and alert during testing. The technician will monitor the EEG for loss of alertness while the recording is in progress. Diminution of posterior alpha activity accompanied by an increase in slow activity, loss of occasional eye movement, and loss of blinking are usually indications of diminished alertness. When these signs are noted, the patient will be prompted to increase alertness. If this is unsuccessful, the patient will need to be rescheduled for a time when alertness can be maintained.

## Sending EEG Data

The recorded EEG file should be uploaded to our secure ftp site at: 72.19.246.114. First time users, please call CNS Response Customer Support at (888) 545-2677 or email at [support@cnsresponse.com](mailto:support@cnsresponse.com) so that a specific folder with a login and password may be created just for your use. Due to the size of these files and the inconsistency of dial-up service, we strongly recommend a high-speed Internet connection. The EEG file may also be delivered via CD-ROM. This should be sent to our central office in Costa Mesa:

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## Analysis and Interpretation

Our board certified physician electroencephalographers will interpret the conventional EEG data as part of a **Type I** analysis unless other arrangements are made. If the recording is medically and technically appropriate, our technicians select segments/epochs for further

analysis. During the data selection process, our technicians select two minutes of artifact-free data for comparison to the reference population.

## Report Content and Delivery Options

A **Type I** rEEG® report contains information about how other patients who had similar EEG abnormalities responded to psychotropic medications. The report contains information on the pharmaceutical group(s) as well as individual agents that are associated with positive clinical and neurophysiological outcomes.

A **Type II** rEEG® report comments on the change in rEEG® correlations from a **Type I** examination. A Type II cannot be completed without a valid **Type I** test as baseline.

You can select to have copies of these reports sent to you via secure email or fax. A permanent copy will follow via US mail.

## Digital EEG Systems Compatible with rEEG® Reporting Services

Recordings must be made in **digital format** using all electrodes in the International 10/20 System of electrode placement. It is also desirable to record A1 and A2 if it is possible on your machine. This will allow CNS Response to re-montage the data during EEG analysis. Many commercially available digital EEG machines can be used for rEEG® recording. Machines that are supported by Insight or which have the capability to export EDF or EDF90 file formats are acceptable. In order to verify that the machine will produce files that are acceptable prior to an actual patient's EEG being recorded, CNS Response requires that a test EEG file be uploaded and checked through our translations prior to recording patient EEG for analysis.

For a complete list of compatible machines, please check:

<http://www.eeg-persyst.com/web/FormatsSupported.html#notSupported>

## CNS RESPONSE CONTACT INFORMATION

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