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**(54) METHOD FOR CLASSIFYING PHYSIOLOGIC BRAIN IMBALANCES USING QUANTITATIVE EEG**

VERFAHREN ZUR KLASSIFIKATION PHYSIOLOGISCHER GEHIRNUNAUSGEGLICHTENHEITEN MITTELS QUANTITIVEM EEG

PROCEDE DE CLASSIFICATION DES DESEQUILIBRES PHYSIOLOGIQUES DU CERVEAU UTILISANT L'ELECTROENCEPHALOGRAPHIE QUANTITATIVE

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(73) Proprietor: **CNS Response, Inc.**  
**Long Beach, CA 90804 (US)**

(72) Inventor: **SUFFIN, Stephen**  
**Sherman Oaks, CA 91401 (US)**

(74) Representative: **MacDougall, Donald Carmichael et al**  
**Marks & Clerk LLP**  
**19 Royal Exchange Square**  
**Glasgow**  
**G1 3AE (GB)**

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**EP 1 253 853 B1**

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**Description****BACKGROUND OF THE INVENTION**

5 [0001] Many researchers continue to attempt to employ neurophysiologic techniques, such as electroencephalography (EEG), magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single photon emission computerized tomography (SPECT), as well as others, to guide therapeutic outcome in psychiatry. For example, the neurophysiologic technique of EEG measures the electrical activity of the brain as a function of time varying spontaneous potentials (SP) through a number of electrodes placed at standard locations on the scalp. The neurophysiologic information obtained through EEG analysis is recorded as sets of traces of the amplitude of SP referenced over time for scalp electrodes that are referenced electrically. This analog EEG information can then be visually analyzed and interpreted for signal abnormalities.

10 [0002] In the 1970's, quantitative analysis of the EEG signal provided rapid easy access to measurements that extended the EEG method beyond qualitative visual detection of signal abnormality. Quantitative EEG (QEEG) studies involve the multi-channel acquisition, processing, and analysis of brain activity often but not exclusively by computers. An example of an EEG/QEEG instrument is the Easy Writer II system, available from Caldwell Laboratories, Inc. (Kennewick, Washington).

15 [0003] In one version of EEG/QEEG recordings, nineteen or more electrodes are commonly placed at standard locations on the scalp using the International 10/20 Placement System. A multi-channel recording of the brain's activity in an awake, eyes-closed, or "background" state is then recorded and analyzed often by use of Fast Fourier Transform (FFT) signal processing. Signal processing of the raw EEG permits measurement and quantification of multiple characteristics of brain electrical activity. In this process, artifacts due to muscle or eye movement or environment noise are rejected, leaving only valid information suitable for further analysis.

20 [0004] John E.R., "Principles Of Neurometrics" Am J EEG Tech USA 30:251-266 (1990) is a general review article describing the basic concept of quantitative electroencephalography (QEEG). Actual data is provided demonstrating that QEEG parameters change with age and/or some psychiatric disorders.

25 [0005] Suffin et al., "Neurometric Subgroups In Attentional and Affective Disorders and Their Association with Pharmacotherapeutic Outcome" Clinical EEG 26:76-83 (1995), provides data showing that without regard to DSM-III-R diagnosis, there were robust correlations between QEEG patterns, responsivity to selected pharmacologic agent class (es), and clinical outcome.

30 [0006] Although technical and methodological guidelines for versions, of EEG/QEEG extraction have been presented, studies that do not observe these essential guidelines are common. In addition to guideline non-conformance, the practice of ignoring the composite nature of psychiatric imbalances is commonplace. As a result, typical EEG/AEEG findings have not always been repeatable, and use of these versions of QEEG in psychiatric assessment and treatment is minimal.

35 [0007] Current behavioral definitions of psychiatric disorders do not correlate well with response patterns to medical treatment. Since psychiatric imbalances are behaviorally defined, they do not demonstrate a consistent relation with individual neurophysiological information, such as from EEG/QEEG or other neurophysiological techniques such as MRI, fMRI, PET, SPECT or other related techniques. However, if neurophysiological information were used as the independent variable and medication response is analyzed as the dependent variable, a connection between neurophysiology and the clinical outcome of treatment may be observed.

40 [0008] There is a need to develop clinical methods for using neurophysiological information as an independent variable and medication response as the dependent variable in order to probe the connection between neurophysiology and treatment outcome. Given such methods, the relationship between observed neurophysiologic abnormality, neurophysiologic intervention, and neurophysiologic treatment outcome in a given patient can be gauged.

45 [0009] There also is a need to develop a method for comparing quantified neurophysiologic information so that pattern differences between individual patients and reference groups can be catalogued and further, for classifying the neurophysiologic information of symptomatic patients according to anticipated treatment response and outcome measures.

[0010] There is a further need to develop a method for treating physiologic brain imbalances using neurophysiologic information. Supplemental to these treatment-associated needs, there is a need to develop a method for guiding clinical testing for new chemical, electrical, magnetic other interventions to treat physiologic brain imbalances, and for identifying new uses for known interventions.

50 [0011] Finally, there is a need to develop a method for the remote assessment and treatment of physiologic brain imbalances using neurophysiologic information.

**SUMMARY OF THE INVENTION**

55 [0012] These and other needs are met by the present invention which is defined in claim 1. Some preferred features are defined in the dependent claims.

**BRIEF DESCRIPTION OF THE FIGURES****[0013]**

- 5 **Figure 1** depicts an algorithm for local and remote clinical assessment of physiologic brain imbalances, particularly as relating to the technique of EEG/QEEG.
- Figure 2** depicts an algorithm for using neurophysiologic information, preferably EEG/QEEG information, to assess physiologic brain imbalances and make treatment recommendations.
- 10 **Figure 3.1** depicts an algorithm for making monotherapy, or single drug therapy, recommendations using the method of the present invention.
- Figure 3.2** further depicts the process of multi-drug therapy using the method of the present invention.
- Figure 4** depicts an algorithm for making multiple agent therapy recommendations using the method of the present invention for drugs that are in electrotherapeutic classes 1 and 2.
- 15 **Figure 5** depicts an algorithm for making multiple agent therapy recommendations using the method of the present invention for drugs that are in electrotherapeutic classes 2 and 3.
- Figure 6** depicts an algorithm for making multiple agent therapy recommendations using the method of the present invention for drugs that are in electrotherapeutic classes 1 and 3.
- Figure 7** depicts an algorithm for making multiple agent therapy recommendations using the method of the present invention for drugs that are in electrotherapeutic classes 1, 2, or 3.
- 20 **Figure 8** depicts various medication prediction pathways for treating physiologic brain imbalances.
- Figure 9** depicts a composite QEEG antidepressant responsive spectrum.
- Figure 10** depicts a composite QEEG stimulant responsive spectrum.
- Figure 11** depicts a composite QEEG anticonvulsant lithium/responsive spectrum.
- Figure 12** depicts a composite QEEG spectrum of patients treated for attentional disorders.
- 25 **Figure 13** depicts a composite QEEG spectrum of patients treated for affective disorders.
- Figure 14** depicts a composite QEEG spectrum of patients by age, treated for affective disorders.

**DETAILED DESCRIPTION OF THE INVENTION**

- 30 **[0014]** The present invention relates to a method for classifying physiologic brain imbalances using neurophysiologic information, more preferably quantified neurophysiologic information, which includes information derived from EEG/QEEG. The present invention also relates a method for comparing quantified neurophysiologic information to establish pattern differences between individual patients and asymptomatic or symptomatic reference populations. The present invention additionally relates a method for assessing patients with physiologic brain imbalances using multivariate neurophysiologic outcome measurements, to guide choice of treatment modality. Finally, the present invention relates a method for the remote assessment and treatment of physiologic brain imbalances using neurophysiologic techniques such as QEEG or quantitative SPECT.
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**Definitions**

- 40 **[0015]** The terms used in this specification have the meanings and preferred embodiments as provided unless specified otherwise.
- [0016]** "Neurophysiologic information" is the information obtained from the measurement of electronic or chemical impulses caused by brain function, using the techniques of EEG/QEEG, MRI, FMRI, PET, SPECT, and the like.
- 45 **[0017]** "Quantified neurophysiologic information" is neurophysiologic information that has been analyzed to determine one or more numeric scale parameters characterizing the neurophysiologic information. For example quantified electroencephalography (QEEG) involves any quantification of a qualitative EEG spectrum including but not limited to measurement of the peak heights and relationships of paroxysmal and nonparoxysmal events in the EEG spectrum. An embodiment of QEEG is the digitized, fast Fourier transformed analysis of multichannel recordings from the nineteen or more electrodes placed according to the international 10/20 placement system described in the "Background of the Invention".
- 50 **[0018]** A "paroxysmal event" is a brief sudden disturbance in the background EEG, often consisting of short duration spikes and waves, which are often but not always accompanied by a sudden voluntary or involuntary muscle movement.
- [0019]** A "nonparoxysmal event" is an artifact-free background EEG, the artifacts being the short duration spikes and waves indicative of a paroxysmal event.
- 55 **[0020]** "QEEG" means quantitative electroencephalography either of the broad scope understood by the term "quantified neurophysiologic information" or by the specific embodiment obtained by digitized fast Fourier transform analysis. This term is used in both senses in this application, the choice being indicated by the context of the discussion or by

the use of the term "general QEEG" to indicate the broad scope term or by the term "FFT QEEG" to indicated the specific embodiment.

[0021] "Neurometric analysis" is the quantification of the brain's electrophysiological function referenced to a group of "normal" or asymptomatic age-matched controls using quantified neurophysiologic information.

[0022] A "physiologic brain imbalance" means a quantifiable deviation in the neurophysiologic functioning of a patient as compared to a reference population of "normal" or asymptomatic individuals or groups. "Normal" or "asymptomatic" individuals or groups are those who do not exhibit behavioral or physiologic indicia of brain imbalance.

[0023] "Multivariate outcome measurements" are quantitative output measurements collected from combinations of univariate neurophysiologic measurements collected from various regions of the brain. For one of the preferred techniques, the QEEG technique, multivariate outcome measurements are collected from combinations of QEEG electrodes for each frequency band of the EEG spectrum. For the QEEG technique, the multivariate measurements of the present invention are derived from measurement of absolute power ( $\mu V^2$ ) in each band of the EEG spectrum; relative power (percentage power in each channel) in each band of the EEG spectrum; coherence (a measure of synchronization between activity in two channels) in each band of the EEG spectrum; and symmetry (the ratio of power in each band of the EEG spectra between a symmetrical pair of electrodes).

[0024] "Behavioral diagnosis" is diagnosis of mental illness based on behavioral indicia, as observed by psychiatrists and other health care professionals and codified by the Diagnostic Statistical Manual (DSM), now in its fourth edition (American Psychiatric Association. Diagnostic and Statistical Manual of Mental Imbalances. DSM IV, Fourth Edition. Washington, DC: American Psychiatric Association), or the International Classification of Diseases (ICD) (posted at <http://cedr.lbl.gov/icd9.html>, last visited Jan. 26, 2000) or similar classification systems.

[0025] "Behaviorally defined forms of mental illness" are forms of mental illness that manifest themselves in behavioral pathologies and abnormalities as defined by the DSM or ICD.

[0026] "Behavioral indicia of physiologic brain imbalances" are the diagnostic indicators of psychiatric or neurologic disorders as defined by the DSM or ICD.

[0027] "Behaviorally diagnosed brain pathologies" are physiologic brain imbalances that manifest themselves in the behaviorally defined forms of mental illness.

[0028] "Non-behaviorally diagnosed brain pathologies" are physiologic brain imbalances that do not manifest themselves in the behaviorally defined forms of mental illness but nonetheless are observable by physiological analysis or long term psychotherapy demonstrating a thought disturbance for example, a paranoia.

[0029] "Z scores" are uniform differential probability scores. Z-scores are calculated by dividing the difference between an observed value and the mean for the expected "normal" value by the standard deviation of the expected "normal" value.

[0030] A "responsivity profile" is a treatment response profile that relates to how patients with physiologic brain imbalances respond to various methods of treatment.

[0031] A "treatment modality" is a way of treating a physiologic brain imbalance.

[0032] An "electrotherapeutic drug class" is a grouping of drugs based on a designated neurophysiologic effect. For the preferred QEEG technique, drugs are grouped according to their effects on quantitative multivariable outcome measurements collected from combinations of EEG electrodes for each region of the EEG spectrum.

#### I. Classifying and Comparing Quantified Neurophysiologic Information to Establish Differences Between Individual Patients and Reference Groups

[0033] Neurophysiologic information, preferably EEG information, gives rise to objective, precise, and statistically useful information about the brain, and to the abnormal or pathologic brain functions that may manifest themselves in the behavioral symptoms, or "indicia" of mental or neurological illness. EEG/QEEG allows for the comparison of individual patient quantified neurophysiologic information with quantified neurophysiologic information from a reference population.

[0034] Quantified neurophysiologic information distinguishes medication effects on brain function. Medications produce differential changes in the quantified neurophysiologic information that are measurable across physiologic brain imbalances, defined as psychiatric or neurological syndromes. Based in part on observations of medication effects on neurophysiologic information, general classifications have been developed that group psychiatric or neurological imbalances based on quantified neurophysiologic information such as EEG/QEEG information. Classification methods have been developed that group psychotropic or neurotropic medications according to EEG/QEEG changes in "normal" or asymptomatic individuals. In psychiatry, for example, observation of abnormal patterns of behavior is the independent variable that is primarily used to catalogue and diseases of the brain.

[0035] Without neurophysiological information regarding physiological deviations in brain function, drug treatment of psychiatric and neurologic imbalances has proven difficult. The well-known heterogeneity of medication response associated with major psychiatric illnesses supports the hypothesis that variable neurophysiology is involved.

[0036] In contrast, the classifying method of the present invention involves the comparison of individual patient neurophysiologic information, preferably quantified neurophysiologic information, with neurophysiologic information, pref-

erably quantified neurophysiologic information, drawn from reference populations of asymptomatic and symptomatic individuals. The use of multivariable measurements based on neurophysiologic information, preferably quantified neurophysiologic information, described below, provides a way to determine if the use of a treatment modality is likely to improve the clinical status of a patient.

5 **[0037]** According to the invention, the classifying and comparing method includes an exploration of clinically relevant physiologic features that characterize brain imbalances. Of the quantitative neurophysiologic technologies available such as MRI, FMRI, PET, and SPECT as well as others, the neurophysiologic method of EEG/QEEG is a practical clinical tool because it is non-invasive, includes a well-replicated normative database, has a potential for broad distribution, and is easily adapted to a variety of clinical settings.

10 **[0038]** Preliminary to the practice of the invention EEG information is collected from electrodes placed at standard locations on a patient's scalp using, by convention, the International 10/20 System for electrode placement. The information is digitized and then undergoes fast Fourier transform (FFT) signal processing to yield a QEEG spectrum. In addition to quantifying the power at each frequency averaged across the QEEG spectrum for each electrode, FFT signal processing of the raw EEG signal provides measurement and quantification of other characteristics of brain electrical activity.

15 **[0039]** The QEEG spectrum is divided into four frequency bands: delta (0.5-3.5 Hz); theta (3.5-7.5 Hz); alpha (7.5-12.5 Hz); and beta (12.5-35 Hz). The spectrum also includes the results from each of the EEG electrodes represented as quantitative output measurements for each frequency band. These include absolute power in each band ( $\mu V^2$ ); relative power in each band (percentage power in each channel); coherence (a measure of synchronization between activity in two channels); and symmetry (the ratio of power in each band between a symmetrical pair of electrodes).

20 **[0040]** The relationship between these univariate measurements and brain activity is believed to be as follows. Absolute power is the average amount of power in each frequency band and in the total frequency spectrum of the artifact-free EEG information from each electrode, and is believed to be a measure of the strength of brain electrical activity. Relative power is the percentage of the total power contributed for a respective electrode and a respective frequency band, and is believed to be a measure of how brain activity is distributed. Symmetry is the ratio of levels of activity measured between corresponding regions of the two brain hemispheres in each frequency band and is believed to be a measure of the balance of the observed brain activity. Coherence is the degree of synchronization of electrical events in given regions of the two hemispheres and is believed to be a measure of the coordination of the observed brain activity. According to the invention, it is believed that these four univariate measures of EEG information can be used to characterize physiological brain imbalances, which manifest themselves in various behavioral pathologies.

25 **[0041]** Using these univariate measures, univariate Z scores, or uniform differential probability scores are calculated. Univariate Z-scores for each quantitative output measurement for each electrode are calculated, by dividing the difference between an observed value and the mean for the expected "normal" value by the standard deviation of the expected "normal" value. The "normal" values are provided by a commercially available database such as NxLink (<http://www.bi-of.com/nxlink.html>; last visited Jan. 25, 2000). The Z transformation process scales all relevant information into units of probability (or units proportional to probability), yielding a uniform scale in all dimensions which can simplify further comparisons and evaluations of relationships between features.

30 **[0042]** An EEG/QEEG instrument, such as the Spectrum 32, manufactured by Caldwell Laboratories, Inc. (Kennewick, WA), can readily execute these univariate neurometric Z transformations. This instrument contains age-defined norms in databases of age regression expressions defining a distribution of features as functions of age in a normal population. The instrument extracts from the database the mean value and the standard deviation to be expected for each feature of a group of "normal" subjects the same age as a patient. It automatically evaluates the difference between the value of each feature observed in the patient and the age-appropriate value predicted by the database age regression expressions. The instrument subsequently evaluates the probability that the observed value in the patient belongs to the "normal" group, taking into account the distribution of values in the "normal" group. A completely analogous process can be accomplished using a family of different digital EEG machines and commercially available neurometric software, such as that available from NxLink, Inc.

#### 50 **IA. Profile of a Patient's Neurophysiologic Information**

**[0043]** Preliminary to the practice of the method of the present invention, a profile of a patient's univariate QEEG data is constructed. The purpose of the profiling step is to collect univariate Z scores. This method includes the steps, depicted in **Figure 1**. **Figure 1** summarizes the acquisition and analysis process for both conventional (or on-site) and remote (or off-site) treatment plans. As is described in a later section, remote treatment involves the transmittal of digitized EEG information from a "remote" clinical setting to a center of expertise.

55 **[0044]** As a preliminary step to the method of the present invention, an ordinary EEG is obtained by acquiring and recording a patient's digitized EEG (*steps a-b*). Univariate neurophysiologic features are extracted from the digitized EEG (*step h-j*). These univariate neurophysiologic features include measures of absolute power, relative power, coher-

ence, and symmetry for each of the electrodes of the International 10/20 System that are placed on a patient's scalp are derived. These univariate neurometric features are compared to QEEG information collected from individuals who are clinically assessed to be asymptomatic for physiologic brain imbalances. A Z score is computed for each measure.

[0045] As indicated earlier, the Z scores are uniform differential probability scores that represent deviations from the composite normal QEEG information of a commercially available neurometric database, such as the NxLink database mentioned above. The neurometric database is constructed from the QEEGs of individuals from 6 to 92 years of age and incorporates information from every electrode used by convention in the international 10/20 System for electrode placement. The database contains over 1000 quantitative univariate EEG measures. The Z score that is obtained by comparing an individual patient's QEEG information with the information for the reference asymptomatic population represents the patient's statistical deviation from the reference-asymptomatic database. That is, if a patient's Z score for a particular measure does not statistically deviate from the reference asymptomatic population, the patient would be determined to be "asymptomatic" for that measure. However, if a patient's Z score is found to statistically deviate from the reference population for a particular measure, the patient would be determined to be symptomatic for that measure.

**IB. Developing QEEG Multivariables**

[0046] A preliminary step to the method of the invention involves the extraction of univariate measures from a patient QEEG and subsequent comparison to composite information from the asymptomatic reference population (*c.f.*, *Step j* of **Figure 1**). However, according to the invention, multivariate measures based upon the univariate measurements are made. To this end, *step j* of **Figure 1** additionally involves the extraction of multivariate measures from a patient's EEG/QEEG. The multivariables described in **Chart 1.1** are formulated according to the method of the present invention for assessing and making treatment recommendations. The set of multivariate features summarized in **Chart 1.1** were constructed using neurophysiologic descriptors that successfully compress the univariate data described above without distorting the informational content of the univariate measures. It is believed that the analysis of multivariable deviations from the statistical normal set of signals provides a precise system for recognition of a multitude of physiologic brain imbalances that are unrecognized from univariate signal analysis. **Chart 1.2** lists the EEG electrodes or pairs of electrodes from which the numeric magnitude of each of the multivariable descriptors are determined. These electrodes or pairs of electrodes are identified according to their names under the International 10/20 electrode locating system.

**Chart 1.1**

<b>Multivariate QEEG Descriptors</b>			
<b>Name</b>	<b>Description</b>	<b>Name</b>	<b>Description</b>
RMAD	Relative power Monopolar Anterior Delta	CABL	Beta - Left
RMPD	Posterior Delta	CABR	Beta - Right
RMAT	Anterior Theta	QMAA	Frequency Monopolar Anterior Delta
RMPT	Posterior Theta	QMPT	Posterior Delta
RMAA	Anterior Alpha	QMAT	Anterior Theta
RMPA	Posterior Alpha	QMPT	Posterior Theta
RMAB	Anterior Beta	QMAA	Anterior Alpha
RMPB	Posterior Beta	QMPA	Posterior Alpha
CEAD	Coherence interhemispheric Anterior Delta	QMAB	Anterior Beta
CEPD	Posterior Delta	QMPB	Posterior Beta
CEAT	Anterior Theta	AADL	Asymmetry Intrahemispheric Delta - Left
CEPT	Posterior Theta	AADR	Delta - Right
CEAA	Anterior Alpha	AATL	Theta - Left
CEPA	Posterior Alpha	AATR	Theta - Right
CEAB	Anterior Beta	AAAL	Alpha - Left
CEPB	Posterior Beta	AAAR	Alpha - Right
AEMD	Asymmetry interhemispheric Monopolar Delta	AABL	Beta - Left

EP 1 253 853 B1

(continued)

Multivariate QEEG Descriptors			
Name	Description	Name	Description
AEMT	Theta	AABR	Beta - Right
AEMA	Alpha	CEBD	Coherence interhemispheric Bipolar Delta
AEMB	Beta	CEBT	Theta
AEBD	Asymmetry interhemispheric Bipolar Delta	CEBA	Alpha
AEBT	Theta	CEBB	Beta
AEBA	Alpha	RBDL	Relative power Bipolar Delta Left
AEBB	Beta	RBDR	Delta - Right
CADL	Coherence intrahemispheric Delta - Left	RBTL	Theta -Left
CADR	Delta - Right	RBTR	Theta - Right
CATL	Theta - Left	RBAL	Alpha - Left
CATR	Theta -Right	RBAR	Alpha - Right
CAAL	Alpha - Left	RBBL	Beta- Left
CAAR	Alpha - Right	RBBR	Beta - Right

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Chart 1.2  
Electrode Composition of Multivariables

Multivariable	Electrodes																					
	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
RMAD	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
RMPD	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	
RMAT	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
RMPT	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	
RMAA	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
RMPA	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	
RMAB	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
RMPB	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	
CEAD	FP1/FP2	F3/F4	F7/F8	C3/C4								FP1/FP2	F3/F4	F7/F8	C3/C4							
CEPD	T3/T4	T5/T6	P3/P4	O1/O2								T3/T4	T5/T6	P3/P4	O1/O2							
CEAT	FP1/FP2	F3/F4	F7/F8	C3/C4								FP1/FP2	F3/F4	F7/F8	C3/C4							
CEPT	T3/T4	T5/T6	P3/P4	O1/O2								T3/T4	T5/T6	P3/P4	O1/O2							
CEAA	FP1/FP2	F3/F4	F7/F8	C3/C4								FP1/FP2	F3/F4	F7/F8	C3/C4							
CEPA	T3/T4	T5/T6	P3/P4	O1/O2								T3/T4	T5/T6	P3/P4	O1/O2							
CEAB	FP1/FP2	F3/F4	F7/F8	C3/C4								FP1/FP2	F3/F4	F7/F8	C3/C4							
CEPB	T3/T4	T5/T6	P3/P4	O1/O2								T3/T4	T5/T6	P3/P4	O1/O2							
QMAD	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
QMPPD	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	
QMAT	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
QMPT	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	
QMAA	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
QMPA	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	
QMAB	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4	Fp1	Fpz	Fp2	F3	FZ	F4	F7	F8	C3	Cz	C4
QMPPB	T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2		T3	T4	T5	T6	P3	Pz	P4	O1	Oz	O2	

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(continued)

Electrode Composition of Multivariables										
Multivariable	Electrodes									
	FP1/FP2	F3/F4	F7/F8	C3/C4	T3/T4	T5/T6	P3/P4	O1/O2		
AEMD	FP1/FP2	F3/F4	F7/F8	C3/C4	T3/T4	T5/T6	P3/P4	O1/O2		
AEMT	FP1/FP2	F3/F4	F7/F8	C3/C4	T3/T4	T5/T6	P3/P4	O1/O2		
AEMA	FP1/FP2	F3/F4	F7/F8	C3/C4	T3/T4	T5/T6	P3/P4	O1/O2		
AEMB	FP1/FP2	F3/F4	F7/F8	C3/C4	T3/T4	T5/T6	P3/P4	O1/O2		
AADL	FP1/FP2	F3/F4	F7/F8	C3/C4						
AADR	T3/T4	T5/T6	P3/P4	O1/O2						
AATL	FP1/FP2	F3/F4	F7/F8	C3/C4						
AATR	T3/T4	T5/T6	P3/P4	O1/O2						
AAAL	FP1/FP2	F3/F4	F7/F8	C3/C4						
AAAR	T3/T4	T5/T6	P3/P4	O1/O2						
AABL	FP1/FP2	F3/F4	F7/F8	C3/C4						
AABR	T3/T4	T5/T6	P3/P4	O1/O2						
CADL	FP1/FP2	F3/F4	F7/F8	C3/C4						
CADR	T3/T4	T5/T6	P3/P4	O1/O2						
CATL	FP1/FP2	F3/F4	F7/F8	C3/C4						
CATR	T3/T4	T5/T6	P3/P4	O1/O2						
CAAL	FP1/FP2	F3/F4	F7/F8	C3/C4						
CAAR	T3/T4	T5/T6	P3/P4	O1/O2						
CABL	FP1/FP2	F3/F4	F7/F8	C3/C4						
CABR	T3/T4	T5/T6	P3/P4	O1/O2						
RBDL	FP1/FP2	F3/F4	F7/F8	C3/C4						
RBDR	T3/T4	T5/T6	P3/P4	O1/O2						
RBTL	FP1/FP2	F3/F4	F7/F8	C3/C4						
RBTR	T3/T4	T5/T6	P3/P4	O1/O2						

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Electrode Composition of Multivariables									
Multivariable	Electrodes								
RBAL	FP1/FP2	F3/F4	F7/F8	C3/C4					
RBAR	T3/T4	T5/T6	P3/P4	O1/O2					
RBBL	FP1/FP2	F3/F4	F7/F8	C3/C4					
RBBR	T3/T4	T5/T6	P3/P4	O1/O2					
AEBD	C3Cz/C4Cz	T3T5/T4T6	P3O1/P4O2	F7T3/F8T4					
AEBT	C3Cz/C4Cz	T3T5/T4T6	P301/P402	F7T3/F8T4					
AEBA	C3Cz/C4Cz	T3T5/T4T6	P301/P402	F7T3/F8T4					
AEBB	C3Cz/C4Cz	T3T5/T4T6	P301/P402	F7T3/F8T4					
CEBD	C3Cz/C4Cz	T3T5/T4T6	P301/P402	F7T3/F8T4					
CEBT	C3Cz/C4Cz	T3T5/T4T6	P301/P402	F7T3/F8T4					
CEBA	C3Cz/C4Cz	T3T5/T4T6	P301/P402	F7T3/F8T4					
CEBB	C3Cz/C4Cz	T3T5/T4T6	P301/P402	F7T3/F8T4					

[0047] The variables in **Chart 1.1** are represented by four letter abbreviations. The first two or three letters of the abbreviations are primary designators. The primary designators RB, RM, CA, CE, QM, AA, and AE indicate what type of QEEG measurement is referenced. For example, the primary designator "RM" is relative monopolar power. "RB" is relative bipolar power. "CA" is intrahemispheric coherence. "CEB" is interhemispheric bipolar coherence. "QM" is monopolar frequency. "AA" is intrahemispheric asymmetry. "AE" is interhemispheric asymmetry.

[0048] The one or last two letters of the multivariable abbreviations are secondary designators. The secondary designators indicate the groups of electrodes and frequency bands from which the measurements are drawn. Measurements are drawn from electrodes in the anterior or ("A"), posterior ("P") regions of the scalp, the left ("L") or right ("R") sides of the scalp. Measurements are made in the delta ("D"), theta ("T"), alpha ("A"), or beta ("B") frequency bands.

[0049] According to **Chart 1.1**, "RMAD" (relative power monopolar anterior delta) is the relative monopolar power in the delta frequency measured at the electrodes located on the front half of the scalp. Similarly, "RBDL" is the relative bipolar power measured by the electrodes in the left half of the scalp for the delta frequency band. "CABL" is intrahemispheric coherence measured from the electrodes in the left region of the scalp in the beta frequency band. "CADR" is the intrahemispheric coherence measured at the electrodes in the right region of the scalp for the delta frequency band. "AED" is monopolar asymmetry measured interhemispherically in the delta frequency band.

**IC. Calculating Z Values for Multivariables**

[0050] As indicated previously, preliminary to the method of the present invention, Z values are determined for each of the univariate variables in the neurometric information set by either Spectrum 32 or NxLink software. According to the invention, these univariate variables are then aggregated into the composite multivariate clinical descriptors, according to the description provided in **Chart 1.1**, using special weighting functions for the electrodes of interest.

[0051] The weighting functions are mathematical transforms that are empirically derived from patient data. Using the weighting functions allows for the scaling of multivariables that are derived from measurements from different numbers of electrodes or pairs of electrodes, called components. **Table 1** summarizes the mathematical weighting functions of the present invention.

**Table 1**

Multivariable Weighting Functions and Transforms		
Name	Description	Transform & Weighting Function
RMAX <sup>a</sup>	Relative power Monopolar Anterior	$12/10 \sum_{10}^1 RMA?1..RMA?n$
RMPX <sup>a</sup>	Relative power Monopolar Posterior	$12/11 \sum_{11}^1 RMP?1..RMP?n$
QMAX <sup>a</sup>	Frequency Monopolar Anterior	$12/10 \sum_{10}^1 QMA?1..QMA?n$
QMPX <sup>a</sup>	Frequency Monopolar Posterior	$12/11 \sum_{11}^1 QMP?1..QMP?n$
CEAX <sup>a</sup>	Coherence interhemispheric Anterior	$\sqrt[3.6]{\sum_n^1 CEA?1^3...CEA?n^3}$

EP 1 253 853 B1

(continued)

Multivariable Weighting Functions and Transforms		
Name	Description	Transform & Weighting Function
AEMA <sup>a</sup>	Asymmetry interhemispheric Monopolar	$\sqrt[3.6]{\frac{1}{n} \sum AEM?1^3 \dots AEM?n^3}$
AEBX <sup>a</sup>	Asymmetry interhemispheric Bipolar	$\sqrt[3.6]{\frac{1}{n} \sum AEB?1^3 \dots AEB?n^3}$
AAYX <sup>a</sup>	Asymmetry intrahemispheric	$\sqrt[3.6]{\frac{1}{n} \sum AA??1^3 \dots AA??n^3}$
CEBX <sup>a</sup>	Coherence interhemispheric	$\sqrt[3.6]{\frac{1}{n} \sum CEB?1^3 \dots CEB?n^3}$
RBYX <sup>a</sup>	Relative power Bipolar	$\sqrt[3.6]{\frac{1}{n} \sum RB??1^3 \dots RB??n^3}$
CAYX <sup>a</sup>	Coherence intrahemispheric	$\sqrt[3.6]{\frac{1}{n} \sum CA??1^3 \dots CA??n^3}$
<sup>a</sup> X= D, T, A, B; <sup>a</sup> X= D, T, A, B; Y = L, R		

**[0052]** Using the weighting functions summarized in **Table 1**, patient specific neurophysiologic data is obtained. The following embodiment illustrates the process for the determination of the magnitude of a particular multivariable for an individual patient. The value of the multivariable CEAD [Coherence interhemispheric Anterior Delta] for a patient is given in its algorithmic form in **Table 2**.

**Table 2**

Sample Calculation of Clinical Multivariate CEAD Measure				
	Component 1	Component 2	Component 3	Component 4
<b>Electrode pair</b>	Fp1/Fp2	F3/F4	F7/F8	C3/C4
<b>Univariate Z Score</b>	-0.982	-1.036	-1.230	-0.249
<b>Weighting Function, C<sup>3</sup></b>	-0.947	-1.112	-1.861	-0.015
<b>Collect Terms</b>				
<b>Fp1/Fp2 + F3/F4</b>		-2.059		
<b>F7/F8 + C3/C4</b>				-1.876
<b>Square Collected Terms</b>		4.239		3.520
<b>Sum of Squares</b>	7.760			
<b>Sign Correction<sup>a</sup></b>	-1			

EP 1 253 853 B1

(continued)

Sample Calculation of Clinical Multivariate CEAD Measure				
	Component 1	Component 2	Component 3	Component 4
CEAD	-8			
<sup>a</sup> negative if sum of terms is negative				

[0053] Table 2 indicates that the CEAD multivariable is calculated from readings collected at four electrode pairs, designated by their names under the International 10/20 system. The electrode pairs are referred to as components 1-4. Z scores are calculated for each electrode pair. The Z scores are normalized using a weighting function,  $C^3$ , as indicated in Table 1. The process of normalization makes it possible to mathematically combine the Z scores. The square is calculated for the sum of each of the components of CEAD. The values are then mapped into a "clinical decision" interval ranging from - 40 to + 40. This mapping creates an integer scale of uniform change for each of the multivariable descriptors. Thus, the weighted Z scores calculated for the electrode pairs within the same brain hemisphere were summed ( $Fp1/Fp2 + F3/F4 = -2.059$ ;  $F7/F8 + C3/C4 = -1.876$ ), squared, ( $-2.059^2 = 4.239$ ;  $-1.876^2 = 3.520$ ), and added together ( $4.239 + 3.520 = 7.760$ ). The sign of the final product was corrected and rounded off to the nearest whole number ( $-7.760 \rightarrow -8$ ).

[0054] Generalizing the process of multivariate classification in an incremental fashion from the example above creates a table of similarly derived measures for an individual patient. A medication-response-specific characterization of brain dysfunction for an individual patient is summarized according to each multivariable in Table 3.

Table 3.1

Multivariables for an Individual Patient			
Multivariable	Value	Multivariable	Value
RMAD	-35	CABL	5
RMPD	-23	CABR	10
RMAT	-40	FMAD	-34
RMPT	-33	FMPD	-30
RMAA	40	FMAT	3
RMPA	27	FMPT	5
RMAB	-30	FMAA	33
RMPB	-21	FMPA	15
CEAD	4	FMAB	-4
CEPD	0	FMPB	10
CEAT	5	AADL	0
CEPT	5	AADR	1
CEAA	-1	AATL	3
CEPA	40	AATR	3
CEAB	10	AAAL	3
CEPB	20	AAAR	3
AEMD	-6	AABL	0
AEMT	-6	AABR	0
AEMA	9	CEBD	2
AEMB	-9	CEBT	2
AEBD	-1	CEBA	26
AEBT	-1	CEBB	3

(continued)

Multivariables for an Individual Patient			
Multivariable	Value	Multivariable	Value
AEBA	-5	RBDL	-13
AEBB	-1	RBDR	-10
CADL	2	RBTL	-18
CADR	1	RBTR	-21
CATL	1	RBAL	21
CATR	1	RBAR	22
CAAL	18	RBBL	-12
CAAR	11	RBBR	-11

[0055] In the example summarized in **Table 3**, the patient has a RMAA value of 40. This value would be expected to occur in the normal population only 3 times in 100,000 observations. A patient with this RMAA value would be judged as having a physiologic brain imbalance of the RMAA type and would be classified accordingly. The information summarized in **Tables 1-3** and the related charts and drawings characterize an individual patient's physiologic brain imbalance as detected by EEG/QEEG and compared to database information collected from individual persons clinically determined to be asymptomatic.

## II. Characterizing and Treating Physiologic Brain Imbalances with Neurometric Information

[0056] In another aspect, the EEG/QEEG analysis of the present invention is designed to identify therapy regimes for changing, or "correcting," from the "abnormal" or symptomatic state to the "normal" or "asymptomatic" state the physiologic brain imbalances detected by EEG/QEEG. These treatment modalities include, but are not limited to drug therapy, electroconvulsive therapy, electromagnetic therapy, neuromodulation therapy, verbal therapy, and other forms of therapy known to, or currently under development in the art. The present invention is thus also directed to a method for making recommendations for the treatment of physiologic brain imbalances using neurophysiologic information such as EEG/QEEG, as depicted in **Figures 1 and 2**.

[0057] According to **Figure 2**, steps *c* and *c*<sub>1</sub>, EEG-based treatment recommendations are not proposed for a patient with a "normal" EEG/QEEG. EEG/QEEG findings for a patient that are found to be "indeterminate" are repeated at a later time (*e.g.*, step *d*). Treatment recommendations are made for patients with "abnormal EEG/QEEGs (*e.g.*, steps *e-f*). Treatment recommendations can involve "monotherapy," or single agent therapy (step *f*<sub>1</sub>) or multiple agent therapy (step *f*<sub>2</sub>).

### IIA. Treating Physiologic Brain Imbalances

[0058] The characterizing steps of the method of the present invention uses an "Outcomes Database" to guide assessment, as well as treatment selection and implementation, for individuals with physiologic brain imbalances. In one aspect, a "psychiatric" Outcomes Database is constructed using EEG/QEEG information from individuals who are behaviorally diagnosed with a range of imbalances and who are undergoing or who have undergone drug therapy for behavioral pathologies (*e.g.*, **Figure 1**, step *k*). The disorders contained in the database include, but are not limited to the following: agitation, attention deficit hyperactivity disorder, abuse, Alzheimer's disease/dementia, anxiety, panic, and phobic disorders, bipolar disorders, borderline personality disorder, behavior control problems, body dysmorphic disorder, cognitive problems, depression, dissociative disorders, eating, appetite, and weight problems, edema, fatigue, hiccups, impulse-control problems, irritability, mood problems, movement problems, obsessive-compulsive disorder, pain, personality disorders, posttraumatic stress disorder, schizophrenia and other psychotic disorders, seasonal affective disorder, sexual disorders, sleep disorders, stuttering, substance abuse, tic disorders/Tourette's Syndrome, traumatic brain injury, Trichotillomania, or violent/self-destructive behaviors.

[0059] In this aspect of the invention, the EEG/QEEG method can be used to guide choices for treating the above-listed psychiatric disorders with various therapeutic regimes, including, but not limited to: drug therapy, electroconvulsive therapy, electromagnetic therapy, neuromodulation therapy, verbal therapy, and other forms of therapy described by the psychiatric and neurologic art.

[0060] Drug therapy guided by these physiological features is possible with minimal modification of the clinicians'

current practices. In one aspect of the invention, a patient's multivariable Z scores are compared directly with the information contained in the "symptomatic" database. However, it is preferable to perform the treatment in two steps. That is, the patient's pretreatment multivariable EEG/QEEG information is obtained and compared firstly with EEG/QEEG information contained in the "asymptomatic" database, and secondly with information contained in the "symptomatic" database. The "symptomatic" database contains information for patients with known medication responsivity profiles (e.g., **Figure 1**, *step k*). Next, the robustness of the statistical association of the current patient's EEG/QEEG information with the database of previously treated individuals is determined. The degree of statistical robustness can provide a physiological basis for the selection of medication.

**[0061]** In the drug therapy aspect of the present invention, EEG/QEEG information from a patient, who has a physiologic brain imbalance, is compared to multivariate outcome measures in the Outcomes Database. By comparing the patient EEG/QEEG information to the Outcomes Database EEG/QEEG multivariate measurements, it is possible to identify drug treatments that are likely to correct EEG/QEEG abnormalities. For example, the patient, whose information was previously presented, with an RMAA of 40 (*cf.*, **Table 3**), belongs to a group of individuals who have responded positively to the antidepressant class of drugs, or more particularly to a group of agents which normalize RMAA. A clinician can use this measure to guide therapeutic choices.

**[0062]** At least two types of analysis are possible according to the method of the present invention—*Type One and Type Two Analysis*. *Type One Analysis* provides that patients are drug and medication free. *Type Two Analysis*, discussed below, provides for patients who will not or cannot be medication free. Medication status must preferably duplicate that of the referential control population as well as fulfill the definition of a baseline measurement (less than 1 per cent residual medication). Patients are preferably free of medication for at least seven half-lives of their prior medication and its metabolites. The *Type One* patient's baseline EEG/QEEG is then matched with similar EEG/QEEG's and their correlated medication outcomes in the Outcomes Database. As indicated, the Outcomes Database is the "symptomatic" database containing the multivariate Z scores of patients with psychiatric and/or neurologic imbalances and the treatment modalities that convert the abnormal multivariate Z scores of these patients to normal. Next, a neuroactive medication candidate is identified in the Outcomes Database according to its physiological effects on brain function. Each medication is classified by its influence on EEG/QEEG information. This procedure furnishes the physician with a physiological link between the agents and their effect on brain function across diverse symptomatic behavioral expressions.

**[0063]** The probability that a patient will respond to different types of pharmacologic agents is then determined. These pharmacologic agents, classes of agents, or combination of agents or classes of agents include antidepressants, anti-anxiety agents, side effect control agents, treatments for alcohol abuse, mood stabilizers, anti-ADD agents, antipsychotics and hypnotic agents.

**[0064]** The procedure for determining the response probability classifies the untreated patient into one of the diverse subtypes of medication response profile that occur within and across DSM imbalances. The procedure compares the patient's Z score profile with the Outcomes Database described above. The Outcomes Database of the present method is designed to track responsivity profiles based on EEG/QEEG information for a number of drugs, known by their generic names such as, for example: alprazolam, amantadine, amitriptyline, atenolol, bethanechol, bupropion, buspirone, carbamazepine, chlorpromazine, chlordiazepoxide, citalopram, clomipramine, clonidine, clonazepam, clozapine, cyproheptadine, divalproex, deprenyl, desipramine, dextroamphetamine, diazepam, disulfiram, divalproex, doxepin, ethchlorvynol, fluoxetine, fluvoxamine, felbamate, fluphenazine, gabapentin, haloperidol, imipramine, isocarboxazid, lamotrigine, levothyroxine, liothyronine, lithium carbonate, lithium citrate, lorazepam, loxapine, maprotiline, meprobamate, mesoridazine, methamphetamine, midazolam, meprobamate, mirtazepine, molindone, moclobemide, naltrexone, phenelzine, nefazodone, nortriptyline, olanzapine, oxazepam, paroxetine, pemoline, perphenazine, phenelzine, pimozide, pindolol, prazepam, propranolol, protriptyline, quetiapine, reboxetine, risperidone, selegiline, sertraline, sertindole, trifluoperazine, trimipramine, temazepam, thioridazine, topiramate, tranlycypromine, trazodone, triazolam, trihexyphenidyl, trimipramine, valproic acid or venlafaxine.

**[0065]** Responsivity profiles based on EEG/QEEG information is possible for medicinal agents having the following trademarks, for example, Adapin, Altruline, Antabuse, Anafranil, Aropax, Aroxat, Artane, Ativan, Aurorix, Aventyl, Buspar, Catapres, Celexa, Centrax, Cibalith-S, Cipramil, Clozaril, Cylert, Cytomel, Decadron, Depakene, Depakote, Deprax, Desoxyn, Desyrel, Dexedrine, Dextroamphetamine, Dobupal, Dormicum, Dutonin, Edronax, Elavil, Effexor, Eskalith, Eufor, Fevarin, Felbatol, Haldol, Helix, Inderal, Klonopin, Lamictal, Librium, Lithonate, Lithotabs, Loxitane, Ludiomil, Lustral, Luvox, Manerex, Marplan, Miltown, Moban, Nalorex, Nardil, Nefadar, Neurontin, Norpramin, Nortrilen, Orap, Pamelor, Parnate, Paxil, Periactin, Placidyl, Prisdal, Prolixin, Prozac, Psiquial, Ravotril, Remeron, ReVia, Risperdal, Ritalin, Saroten, Sarotex, Serax, Sercerin, Serlect, Seroquel, Seropram, Seroxat, Serzone, Symmetrel, Stelazine, Surmontil, Synthroid, Tegretol, Tenormin, Thorazine, Tofranil, Tolrest, Topamax, Tranxene, Trilafon, Typtanol, Tryptizol, Urecholine, Valium, Verotina, Vestal, Vivactil, Wellbutrin, Xanax, Zoloft, or Zyprexa. The generic descriptions of these trademarked agents and their source are available from the Physicians Desk Reference (New York: Medical Economics Company, 2000).

**[0066]** Because the EEG/QEEG information of the present invention link medications to their effects on brain function,

a new pharmaceutical nomenclature in which agents are identified by their electrotherapeutic profile is appropriate. **Table 4** contains selected drug agents in the database of the present invention, electrotherapeutically classified by 72 discriminating features.

5 **[0067]** According to **Table 4.1**, a drug response prediction can be made based on the magnitude of observed EEG/QEEG parameters. For example, an absolute power average greater than 300 microvolts squared (e.g., **QEEG Parameter 1**) predicts a response to the antidepressant class or alpha-2 agonist class of drugs; or in the nomenclature of the present invention, to drugs in electrotherapeutic classes 1.11-1.23. As **Table 4.1** suggests, a particular QEEG parameter reading may predict a response to single or multiple drug classes. To that end, a ratio of frontal to posterior alpha indices  
10 less than 4 (e.g., **QEEG Parameter 1**) predicts a response to multiple electrotherapeutic drug classes. Similar results are reflected in Tables **4.2-4.6**. **Table 4.7** lists in alphabetical order the names of the drugs or drug classes appearing in **Tables 4.1-4.6**

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Table 4.1  
QEEG PARAMETERS & INDICES 1-12

	1	2	3	4	5	6	7	8	9	10	11	12
<b>QEEG PARAMETERS &amp; INDICES 1-12</b>	QEEG ABSOLUTE POWER AVERAGE = >300 MICROVOLTS SQUARED	QEEG ABSOLUTE POWER AVERAGE = <300 & >50 MICROVOLTS SQ.	QEEG ABSOLUTE POWER AVERAGE = <50 MICROVOLTS SQUARED	FRONTAL MIDLINE PROGRESSION ON INDEX (ALPHA BAND) = >2.5	FRONTAL MIDLINE PROGRESSION ON INDEX (ALPHA BAND) = <2.5	POSTERIOR MIDLINE PROGRESSION ON INDEX (ALPHA BAND) = > 1	POSTERIOR MIDLINE PROGRESSION INDEX (ALPHA BAND) = < 1	RATIO OF FRONTAL / POSTERIOR ALPHA INDICES = >4	RATIO OF FRONTAL / POSTERIOR ALPHA INDICES = <4	AVERAGE MIDLINE (FPZ, FZ, CZ) THETA / BETA RATIO = >2.5	AVERAGE MIDLINE (FPZ, FZ, CZ) THETA / BETA RATIO = <2.5 & >1.5	AVERAGE MIDLINE (FPZ, FZ, CZ) THETA / BETA RATIO = <1.5
PREDICTS RESPONSE TO 1.11 - 2.3 AGENTS: (ANTIDEPRESSANTS / ALPHA-2 AGONIST)	SSRI SNRI TCA CLONIDINE	SSRI SNRI TCA BUPROPRN MAOI CLONIDINE	BUPROPRION MAOI	SSRI SNRI TCA: (1.11-1.23)	SSRI SNRI TCA: (1.22-1.31) + STIMULANT	SSRI SNRI TCA: (1.11-1.31)	BUPROPRION, MAOI +/- STIMULANT	SSRI SNRI TCA: (1.11-1.3)	SNRI BUPROPRION MAOI	SNRI TCA: (1.31) BUPROPRION MAOI	SNRI SSRI TCA: (1.31) BUPROPRION N CLONIDINE	SSRI TCA: (1.11-1.23) CLONIDINE
PREDICTS RESPONSE TO 2.4 - 2.8 AGENTS: (STIMULANTS)	STIMULANT	STIMULANT	STIMULANT MAOI				STIMULANT +/- BUPROPRION MAOI		STIMULANT	STIMULANT MAOI		
PREDICTS RESPONSE TO 3.0 - 3.9 AGENTS: LITHIUM / ANTI-CONVULSANTS / BENZO-DIAZEPINES / BETA BLOCKERS *			VALPROATE BENZODIAZ BETA BLKR				VALPROATE BENZODIAZ BETA BLKR		VALPROATE BENZODIAZ BETA BLKR	VALPROATE BENZODIAZ BETA BLKR	CRMAZPN	



Table 4.3  
QEEG PARAMETERS & INDICES 25-36

	25	26	27	28	29	30	31	32	33	34	35	36
QEEG PARAMETERS & INDICES 25-36	CEAA =>10 +/- CEPA =>10	CEAA =<10 +/- CEPA =<10	CEAB =>10 +/- CEPB = >10	CEAB =<10 +/- CEPB = <10	FMAD =>10 +/- FMPD =>10	FMAD = <10 +/- FMPD =<10	FMAT =>10 +/- FMPT = >10	FMAT = <10 +/- FMPT = <10	FMAA =>10 +/- FMPA = >10	FMAA =<10 +/- FMPA =<10	FMAB =>10 +/- FMPB = >10	FMAB =<10 +/- FMPB = <10
PREDICTS RESPONSE TO 1.11 - 2.3 AGENTS: (ANTIDEPRESS- ANTS / ALPHA-2 AGONIST)	SSRI SNRI TCA		SSRI SNRI TCA		SSRI SNRI TCA (1.31)	SSRI SNRI TCA: (1.11-1.23)	BUFRPN SNRI TCA: (1.31) CLONIDINE	SSRI TCA: (1.11-1.23) CLONIDINE	SSRI TCA: (1.1-1.23) CLONIDINE	BUFRPN SNRI MAOI	SSRI: (1.41- 1.43; 1.51)	SNRI SSRI: (1.41-1.43; 1.51)
PREDICTS RESPONSE TO 2.4 - 2.8 AGENTS: (STIMULANTS)					STIMULANT MAOI		STIMULANT MAOI			STIMULANT MAOI		STIMULANT MAOI
PREDICTS RESPONSE TO 3.0 - 3.9 AGENTS: LITHIUM / ANTICONVUL- SANTS / BENZODIAZEPINES / BETA BLOCKERS *	LITHIUM CRBMZEPN BETA BLKR		LITHIUM VALPROATE CRBMZEPN BETA BLKR		BENZODIAZ		BENZODIAZ		BETA BLKR CRBMZEPN LITHIUM	BENZODIAZ VALPROATE	BETA BLKR CRBMZEPN LITHIUM	BENZODIAZ VALPRO- ATE

Table 4.4  
QEEG PARAMETERS & INDICES 37-48

	37	38	39	40	41	42	43	44	45	46	47	48
QEEG PARAMETERS & INDICES 37-48	AADL => 10, OR AADR => 10	AADL =< 10, OR AADR =< 10	AATL => 10, OR AATR => 10	AATL =< 10, OR AATR =< 10	AAAL => 10, OR AAAR => 10	AAAL =< 10, OR AAAR =< 10	AABL => 10, OR AABR => 10	AABL =< 10, OR AABR =< 10	AED => 10, AND/OR AET > 10	AET =< 10, AND/OR AET =< 10	AEA => 10, AND/OR AEA =< 10	AEB => 10, AND/OR AEB =< 10
PREDICTS RESPONSE TO 1.11-2.3 AGENTS: (ANTIDEPRESSANTS / ALPHA-2 AGONIST)		SSRI SNRI TCA: (1.22-1.31)		SSRI SNRI TCA: (1.22-1.31)	SSRI SNRI TCA: (1.22-1.31)		SSRI SNRI TCA: (1.11-1.21)					
PREDICTS RESPONSE TO 2.4-2.8 AGENTS: (STIMULANTS)	STIMULANT MAOI	STIMULANT MAOI	STIMULANT MAOI			STIMULANT MAOI						
PREDICTS RESPONSE TO 3.0-3.9 AGENTS: LITHIUM / ANTICONVULSANTS / BENZODIAZEPINES / BETA BLOCKERS *									LITHIUM / ANTI-CONVULSANT BENZO (3-X AGENT)	LITHIUM / ANTI-CONVULSANT BENZO (3-X AGENT)	LITHIUM / ANTI-CONVULSANT BENZO (3-X AGENT)	LITHIUM / ANTI-CONVULSANT BENZO (3-X AGENT)

Table 4.5  
QEEG PARAMETERS & INDICES 49-60

	49	50	51	52	53	54	55	56	57	58	59	60
QEEG PARAMETERS & INDICES 49-60	AEBD => 10 AND/OR AEBD =< 10	AEBT => 10 AND/OR AEBT =< 10	AEBA => 10 AND/OR AEBA =< 10	AEBB => 10 AND/OR AEBB =< 10	CADL => 10, OR =< 10	CADR => 10, OR =< 10	CATL => 10, OR =< 10	CATR => 10, OR =< 10	CAAL => 10, OR =< 10	CAAR => 10, OR =< 10	CABL => 10, OR =< 10	CABR => 10, OR =< 10
PREDICTS RESPONSE TO 1.11 - 2.3 AGENTS: (ANTIDEPRESSANT S / ALPHA-2 AGONIST)												
PREDICTS RESPONSE TO 2.4 - 2.8 AGENTS: (STIMULANTS)												
PREDICTS RESPONSE TO 3.0 - 3.9 AGENTS: LITHIUM / ANTICONVULSANT S / BENZODIAZEPINES / BETA BLOCKERS *	LITHIUM / ANTI- CONVUL- SANT/BENZ O (3.X AGENT)	LITHIUM / ANTI- CONVUL- SANT/BENZ O (3.X AGENT)	LITHIUM / ANTI- CONVUL- SANT/BENZO (3.X AGENT)	LITHIUM / ANTI- CONVUL- SANT / BENZO (3.X AGENT)	VALPRO- ATE BENZO- DIAZ	VALPRO- ATE BENZODIAZ	VALPROATE BENZODIAZ	VALPRO- ATE BENZODIA Z	CRBMZEPN BETA BLKR	CRBMZEPN BETA BLKR	VALPRO- ATE BETA BLKR	VALPRO- ATE BETA BLKER

Table 4.6  
QEEG PARAMETERS & INDICES 61-72

	61	62	63	64	65	66	67	68	69	70	71	72
QEEG PARAMETERS & INDICES 61-72	CEBD => 10, OR =< 10	CEBT => 10, OR =< 10	CEBA => 10, OR =< 10	CEBB => 10, OR =< 10	RBDL => 10, AND/OR RBDR => 10	RBDL =< 10, AND/OR RBDR =< 10	RBTL => 10, AND/OR RBTR => 10	RBTL =< 10, AND/OR RBTR =< 10	RBAL => 10, AND/OR RBAR => 10	RBAL =< 10, AND/OR RBAR =< 10	RBBL => 10, AND/OR RBBR => 10	RBBL =< 10, AND/OR RBBR =< 10
PREDICTS RESPONSE TO 1.11 - 2.3 AGENTS: (ANTIDEPRESSANTS / ALPHA-2 AGONIST)						SSRI SNRI TCA: (1.22-1.31) CLONIDINE		SSRI SNRI TCA: (1.11-1.31) CLONIDINE	SSRI SNRI TCA: (1.22-1.31) CLONIDINE		SSRI SNRI TCA: (1.11-1.23) CLONIDINE	
PREDICTS RESPONSE TO 2.4 - 2.8 AGENTS: (STIMULANTS)					STIMULANT MAOI	STIMULANT MAOI	BPROPRN STIMULANT MAOI			STIMULANT MAOI		
PREDICTS RESPONSE TO 3.0 - 3.9 AGENTS: LITHIUM / ANTI CONVULSANTS / BENZODIAZEPINES / BETA BLOCKERS *	VALPROATE BENZODIAZ	VALPROATE BENZODIAZ	CRBMZEPN BETA BLKR	CRBMZEPN VALPROATE BETA BLKR							LITHIUM	

Table 4.7

Abbreviation Key for Tables 4.1-4.6	
Abbreviation	Name
Benzo	Benzodiazepine
Benzodiaz	Benzodiazepine
Beta Blkr	Beta Blocker
Bupoprpn	Bupropion
CRBMAZPN	Carbamazepine
MAOI	Monoamine Oxidase Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
SNRI	Seretonin Norepinephrine Reuptake Inhibitor
TCA	Tricyclic Antidepressant

**[0068]** According to the *Type Two Analysis* procedure, individuals who cannot be tested according to Type One Analysis can be tested under conditions where ongoing medications are allowed. Type Two Analysis reports the impact of medication on the EEG/QEEG information. Follow-up EEG recordings are used to track changes produced by the administration of medications. When Type Two Analysis has been preceded by Type One Analysis, it is possible to observe the absolute changes attributable to medication and appreciate the spectrum of actions on the EEG/QEEG 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 information for the current patient and the reference group within the Outcomes Database are substantially similar, this comparison further validates the characteristics of the medication and helps to refine the electrotherapeutic class of the medication. In the absence of such confirmation the patient's information are not allowed into the Outcomes Database. This provides a quantitative quality assurance standard and segregates those individuals requiring further study.

**[0069]** For patients analyzed according to Type Two Analysis without a preceding Type One Analysis, therapeutic guidance is derived from treating the information as if it were derived from Type One Analysis and adjusting medication using both the electrotherapeutic agent recommendation and the current medication information. After the steady state has been reached for the new medications, a follow-up Type Two Analysis can be treated in a manner similar to the patient who had an initial Type One Analysis. No one can be added to the Outcomes Database without an initial Type One Analysis.

**[0070]** In follow-up studies, the patient is examined by the treating physician and receives a Clinical Global Improvement (CGI) score. The CGI score is used to gauge the behavioral success of a given therapy regime for improving or correcting the patient's disturbance. Typically a treating physician will assign a CGI score of -1 to 3 to a patient based on observed behavioral indicia. In the context of the drug therapy embodiment, a CGI score of negative one (-1) indicates an adverse medication effect. A CGI score of zero (0) indicates no improvement. A CGI score of one (1) indicates minimal or mild improvement. A CGI score of two (2) indicates moderate improvement. Finally, a CGI score of three (3) indicates marked improvement, including complete absence of symptoms.

**[0071]** The EEG Report Use Algorithm and associated flow charts (*cf. Figures 3-7*) summarize several embodiments or examples of the clinical procedure developed according to the treatment method of the present invention. These examples are useful for the optimization of treatment regimes for individual patients with physiologic brain imbalances. Although subject to revision as new agents and more information are added to the database, these algorithms offer a guide for improving the treatment outcomes of refractory patients.

**[0072]** To that end, **Figure 3.1** summarizes a typical embodiment of the process of single drug therapy based on the preferred EEG/QEEG method of the present invention. In the first step of the depicted example of a therapy process (*step a*), clinicians establish baseline parameters to measure various physiologic and behavioral changes. In *step b*, the medication of choice is administered to the patient in a single low dose. Dosage is increased as needed and indicated by repeat QEEG analysis and CGI scores.

**[0073]** **Figure 3.2** summarizes a typical embodiment of the process of multi-agent drug therapy based on the preferred EEG/QEEG method of the present invention. Treatment recommendations are organized according to the drug electrotherapeutic classes described earlier. A typical embodiment of a treatment recommendation involving agents in electrotherapeutic classes 1 or 2, are further summarized in **Figure 5**. According to **Figure 5**, *step b*, therapy is initiated

according to the monotherapy regime (*c.f.*, **Figure 3.1**) using a class 1 electrotherapeutic agent. After at least five half lives of treatment with the class 1 agent, treatment with the class 2 agent is initiated (*step d*). A follow-up QEEG is administered after at least five half lives of treatment with the class 2 agent (*Step e*). Based on the results of follow-up QEEGs and CGI scores, treatment is modified or discontinued. **Figures 5-7** replicate similar treatment algorithms.

**[0074]** The method of the present invention is not a substitute for obtaining the clinical history, psychiatric assessment, medical examination and requisite laboratory studies. It augments, rather than replaces established diagnostic and treatment regimes. Medication correlations with the medication Outcomes Database of the present invention are a useful adjunct to clinical management. Determining the suitability of EEG/QEEG correlations, medication dosage, time(s) of administration, and recording of clinical outcome by symptom and behavioral rating scales remain the responsibility of the attending physician.

#### **IV. Method for Remote Diagnosis and Treatment Using EEG/QEEG**

**[0075]** The present invention also relates to a method for the remote diagnosis and treatment of physiologic brain imbalances using quantified neurophysiologic information, preferably EEG/QEEG. In the method, an electronic link is typically established between a medically underserved area and a center of neurophysiologic expertise, preferably EEG/QEEG expertise, using special communications software, designed to insure patient confidentiality and assist in maintaining a portion of an electronic medical record. In the context of diagnosing and treating physiologic brain imbalances, the electronic link is between a physician with digital neurophysiologic collection capabilities or a neurophysiologic recording facility and neurophysiologic information analysis center. In short, in the remote diagnosis and treatment method, a patient's neurophysiologic information is transmitted electronically without loss of resolution to a neurophysiologic information analysis center as previously presented in the diagram entitled Neurophysiologic Data Acquisition and Analysis, as depicted in **Figure 1**, *steps d-g, step m*). The neurophysiologic information is then evaluated as described below to devise diagnosis and treatment strategies.

**[0076]** According to **Figure 1**, the first step of the process is as described earlier for assessing and treating physiologic brain imbalances, and involves collecting neurophysiologic information from a patient and occurs at a neurophysiologic recording facility. In *step f*, the digitized neurophysiologic information along with additional patient identifying information is packaged using the special communications software. Packaging means the neurophysiologic information computer file(s) is/are compressed and encrypted so that it cannot be opened or examined by unauthorized personnel. The information is encrypted at the recording facility with a key known only to the neurophysiologic analysis center. The information is rigorously secured to protect the confidentiality of patient records. Patient identifying information may include the patient's name; date of birth; referring physician; handedness; height; weight; date of test; and patient social security number. This patient identifying information is algorithmically transformed as part of the encryption process. The compressed information package is then protected with an additional password.

**[0077]** In the *step f*, the compressed information files are electronically transmitted to a secure analysis site. Transmission of patient information is routinely scheduled for the early morning hours using standard file transfer protocols (FTP) via the Internet. However, "high priority" files can be immediately transferred to an analysis center for priority processing by the Site Commander software. The transmitted neurophysiologic information files are logged as they are sent, processed, and returned. All date and time log entries are Y2K compliant and are calibrated in Greenwich Mean Time (GMT). In the fourth step, the transmitted neurophysiologic information files are decompressed and decrypted at the neurophysiologic information center. The information is then analyzed according to the methods described previously.

**[0078]** When neurophysiologic analysis is complete, a formal report of findings is generated for the referring physician (*steps l-m*). The report is returned in portable document format (PDF) using commercially available software from Adobe, Inc., or the equivalent, to a neurophysiologic information transfer site. PDF files are opened and displayed using an interface to Adobe Acrobat Reader™ software or the equivalent. Reports can be printed using any operating system compatible printer but are password protected so that they cannot be modified once they leave the neurophysiologic information center.

**[0079]** The report includes a range of information elements, including: a professional medical interpretation of the individual patient's neurophysiologic profile; a presentation of selected features extracted by quantitative neurophysiologic analysis; a presentation of deviations from the "asymptomatic" and "symptomatic" databases; and a statement of the likelihood of favorable pharmacotherapeutic outcomes based on comparison with the Outcomes Database of patients having similar QEEG/EEG features. The formal report is designed to guide treatment strategies. However, the treating physician is ultimately responsible for medication selection, dosage titration, and side effect monitoring.

#### **EXAMPLES**

**[0080]** The present invention is more particularly described in the following examples which are intended for illustration purposes only, since numerous modifications and variations will be apparent to those skilled in the art.

## Protocol

### Collecting EEG/QEEG Information

5 [0081] An EEG is administered to a patient using a commercially available EEG instrument. Current suppliers of EEG instrumentation include but are not limited to Caldwell, Laboratories, Bio-Logic Systems, Inc., Nicolet Biomedical and Oxford Instruments. Electrodes are placed on the patient's scalp using the International 10/20 System convention for determining the appropriate location of the electrodes. The raw EEG information is then stored in a digital format for subsequent FFT processing.

10 [0082] The following patient criteria are operative for Type One Analyses. The patient must be between the ages of 6 and 90. In addition, for Type One Analysis the patient must not be undergoing drug therapy. This is because all medications may influence EEG information, giving rise to "false" outcomes. "Medications" include prescription drugs, over the counter sleeping pills, pain medication, nutritional health supplements, and megavitamins. If the patient is undergoing drug therapy, the therapy must be discontinued or avoided for seven half lives prior to the EEG test. However, 15 the patient may be undergoing hormone replacement therapy for insulin, thyroid, progesterone, and estrogen, as well as for other hormonal deficiencies.

[0083] A variety of patients are not suitable for Type One Analysis. These include individuals who have under gone intramuscular depo-neuroleptic therapy within the proceeding twelve months. Individuals who have a history of craniotomy with or without metal prosthesis or have current unstable of seizure disorder, dementia, and metal retardation are also 20 not candidates for Type One Analyses. Individuals who are currently using marijuana, cocaine, hallucinogens, or other illicit psychotropic compounds are not candidates for Type One Analyses. Individuals with a significant metabolic abnormality e.g. CBC, chemistry or thyroid difficulties are not candidates for Type One Analyses until these systemic processes have been normalized.

[0084] The EEG information collected from the individuals is then digitized, subjected to FFT processing, and analyzed. 25 The first stage of analysis involves extracting a standard set of quantitative univariate measures from the FFT processed digitized EEG information. These quantitative measures include power and relative power. Power is the square of the signal amplitude, measured in microvolts squared ( $\mu V^2$ ). Relative power measures the proportion of power in a given frequency band detected at a given electrode compared to the total band power detected at that electrode. As indicated earlier there are four EEG frequency bands of interest: delta (0.5-3.5 H); theta (3.5-7.5 H); alpha (7.5-12.5 H); and beta 30 (12.5-35 H). The total EEG spectrum therefore runs from 0.5 to 35 H. The method of the current invention is not limited to these frequency bands and can be applied to any frequency banding.

[0085] Another standard measure extracted in the first stage of analysis is coherence. Coherence measures the similarity of activity for two scalp electrodes for all interhemispheric and intrahemispheric electrode pairs, for each of the defined frequency bands. Peak frequency measures are also computed within each frequency band. Finally, power and 35 coherence combination measures are computed for defined sets of scalp electrodes.

### Example 1

#### Guiding Drug Treatment of Patients with Manic Depressive Imbalance Using EEG/QEEG

40 [0086] Patients with chronic Major Depressive Imbalance (MDD), determined by two senior faculty members, who had been non-responsive to at least two previous medication regimens of adequate dosage(s) and duration were accepted in the study from consecutive evaluations of outpatients at the Veterans Administration Medical Center, Sepulveda. Their lack of response to repeated previous clinical efforts provided a clear baseline from which to note any increase 45 in treatment efficacy with EEG/QEEG information. Human Subjects Committee approval of the protocol was obtained (*c.f.* **Figure 8**). Informed consent was obtained from all study participants.

[0087] Patients were consecutively assigned to control and experimental treatment groups. Every other patient who met study criteria was treated solely on the joint decision of the treating psychiatric resident and a supervising faculty psychopharmacologist. No concurrent report of these choices was given to the staff of this study nor did the staff of this 50 study have any part in the selection of these patients' medication. This group was called DSM DIRECTED.

[0088] A psychiatric resident and their supervising faculty psychopharmacologist, who had agreed to follow medication recommendations based on EEG/QEEG correlation, treated patients not assigned to the DSM DIRECTED group. This group was called DSM + EEG DIRECTED.

[0089] Before acceptance into the study, patients were evaluated to exclude concurrent illness. This included a physical 55 examination with laboratory studies consisting of a hemogram, chemistry panel, thyroid stimulating hormone, urine drug screen,  $\beta$ -HCG (in females) and an EKG. The treating physician then interviewed patients. Hamilton-D (HAM-D) and Beck Depression (BECK) Scale scores were obtained during this interview.

[0090] After these assessments, an experienced clinician that was not and would not be involved in the treatment of

## EP 1 253 853 B1

the patient evaluated the patient. This initial process provided a basis for future assessment of treatment response by this clinician. This evaluating physician played no role in medication selection, had no other contact with the patient until assessing outcome of treatment, had no knowledge of which experimental group the patient belonged, nor any information on the EEG/QEEG findings. All clinical ratings present are the ratings of this clinician.

**[0091]** Patients taking medications other than antihypertensive or hormone replacement agents were disqualified because the control groups were selected using these criteria. Also excluded were subjects with a present or past primary psychotic diagnosis, history of intramuscular neuroleptic therapy, documented closed head injury with loss of consciousness, history of craniotomy, history of cerebrovascular accident, current diagnosis of seizure imbalance, current diagnosis of dementia, presence of mental retardation or active substance abuse.

**[0092]** All patients were required to be medication-free (at least seven half-lives of the longest lived medication) and illicit substance free (ascertained by a urine screen for drugs on the day of the EEG).

### Patient Population

**[0093]** The gender and age compositions of the DSM DIRECTED group (N=6) were 4 males to 2 females, with an average age of 45. This was similar to the DSM + EEG DIRECTED group (N=7) with 5 males to 2 females and an average age of 41. **Table 5** summarizes the patient population of the present study.

**Table 5**

Patient Population and Results		
DSM DIRECTED	Number of Patients	Mean/24h in mg
Clonazepam	1	1
Lithium	2	1200
Fluoxetine	2	40
Nefazodone	1	300
Carbamazepine	1	400
Buspirone	1	30
Med/Pt Average	1.3 3	
DSM + EEG DIRECTED	Number of Patients	Mean/24h in mg
Valproic acid	3	500
Lithium	2	600
Paroxetine	1	30
Fluoxetine	3	30
Methylphenidate	2	27.5
Carbamazepine	2	850
Sertraline	1	100
Med/Pt Average	2	

### Psychotherapy

**[0094]** Prior to the study, all patients were in similar types and frequency of psychotherapy, which was maintained for the duration of the study.

**EEG/QEEG Information Acquisition and Analysis Procedure**

[0095] Each patient had a conventional digital EEG according to the protocol given above. Twenty-one electrodes were applied according to the International 10/20 System. Then, 10 to 20 minutes of eyes-closed, awake, resting EEG was recorded on a Spectrum 32 (Cadwell Laboratories, Kennewick, WA), referenced to linked ears.

[0096] The conventional EEG was reviewed to exclude paroxysmal events, spikes, sharp waves, focal disturbances and other abnormalities apparent by visual inspection. Artifact-free epochs of conventional EEG, selected by a technician, were based on the rule that all artifact-free segments were to be included in the sample until at least 32 epochs of 2.5 seconds were obtained. These procedures were performed with no knowledge of which treatment group the patient had been assigned. No attempt was made to remove artifact from the EEG record using statistical techniques. During the technician's collection of EEG for quantitative analysis, when an artifact-containing portion of the record was encountered, that interval was excluded from the sample considered for quantitation. All intervals that were subjected to quantitative analysis according to the method of the invention were reviewed by the electroencephalographer/ physician prior to analysis. EEG recordings were considered *a priori* unsuitable for quantitative analysis, due to unfavorable signal to noise ratio [less than or equal to 3:1], if average frontal power was less than  $9 \mu V_2$ . No pretreatment prediction was made for these patients.

[0097] To accomplish the quantitative analysis, the sample of digitized waveforms was fast Fourier transformed into the standard EEG frequency bands of delta activity (0.5-3.5 H), theta activity (3.5-7.5 H), alpha activity (7.5-12.5 H) and beta activity (12.5-35 H). The signal features obtained for each electrode site (monopolar derivations), or across electrode pairs (bipolar derivations) included absolute power, relative power, coherence, frequency, and symmetry. EEG information was log transformed to obtain Gaussianity, age-regressed and transformed according to the multivariate Z score profiling method of the invention. This produced measures of each study patient's EEG deviation from a database of age-matched referential EEG's collected from asymptomatic individuals from 6 to 90 years of age. A differential eye channel was used for the detection of eye movement. All impedances were less than 5,000 ohms. The EEG amplifiers had a band pass from 0.5 to 70 H (3dB roll off per octave). A 60 H notch filter was used during the collection process.

**Method of Classifying EEG/QEEG Medication Response**

[0098] A database of medication-free patients containing EEG/QEEG findings and subsequent medication outcomes compiled in our laboratory over the past eight years was used for deriving the medication response predictions. A rule-based classifier using the current patient's neurophysiologic information profile as described above and the database from the inventor's patient population was used to review pretreatment EEG/QEEG information from each study patient. An EEG/QEEG specific medication outcome prediction, containing the correlated medication responses of antidepressant, anticonvulsant and stimulant classes was reported to the patient control officer. This information was distributed only to the treating physician of the individual DSM + EEG DIRECTED patient, as described above. Medication outcome predictions for all other patients were sealed until the end of the study.

[0099] An antidepressant responsive spectrum identified in previous studies was incorporated in the rule-based classifier used to predict antidepressant responsivity for all patients in the present study. **Figure 9** depicts the average relative power spectrum of sixty patients with affective and attentional imbalances that were antidepressant responsive. This spectrum demonstrates global delta frequency deficit from -2.5 to -1.8 mean-units extending posteriorly, a diffuse theta deficit trend of -0.8 to -1.0 mean-units sparing the temporal regions, a +2.3 mean -units alpha maximum in the frontal polar region and a second alpha maximum of + 2.1 mean-units in the posterior frontal region. These maxima are accompanied by a relative alpha minimum of +1.2 mean-units in the temporal region and sustained posterior alpha excess.

[0100] A stimulant responsive spectrum identified in previous studies was incorporated in the rule-based classifier used to predict stimulant responsivity for all study patients. **Figure 10** depicts the average relative power spectrum of twenty-one patients with affective and attentional imbalances that were stimulant responsive. This spectrum exhibited a frontal polar delta frequency deficit from -2.0 to -2.3 mean-units. There were two frontal maxima in the theta band at +2.6 and +2.5 mean-units. The theta frequency showed +1.7 mean-units excess in the temporal region, gradually diminishing posteriorly toward +0.9 mean-units. The alpha and beta bands of this spectrum were distributed about a mean-score of zero.

[0101] An anticonvulsant/lithium responsive spectrum identified in previous work was incorporated in the rule-based classifier used to predict anticonvulsant/lithium responsivity for all study patients. **Figure 11** depicts the average inter-hemispheric coherence spectra of twenty-six patients with affective and attentional imbalances indicated anticonvulsant and or lithium responsivity. The spectra exhibited posterior delta hypocoherecence (up to -1.7 mean-units), posterior theta hypocoherecence (up to -1.4 mean-units), frontal alpha hypercoherence (up to +2.9 mean-units), and frontal beta hypercoherence (up to +1.7 mean-units).

## Clinical Monitoring

[0102] The treating physician and their faculty supervisor for both experimental groups monitored treatment in weekly follow-up sessions. The mean follow-up for the study groups was 25 weeks. After six weeks on medication(s) at maximal tolerated dosage, treatment efficacy was assessed by the independent evaluating physician, blind to patient status [DSM DIRECTED or DSM + EEG DIRECTED] and medication regimen, who had assessed the patient prior to treatment. This physician's prior knowledge of the patient permitted the use of Clinical Global Improvement (CGI) ratings. A CGI score of zero indicated no improvement, 1 indicated mild improvement, 2 indicated moderate improvement and 3 indicated marked improvement or no residual symptoms. A CGI rating equal to, or greater than 2 levels was required to qualify as improved.

## Results

### Neurometric Spectral Features

[0103] Two patients, one each in the DSM DIRECTED and DSM + EEG DIRECTED groups, had EEG records that exhibited an average frontal power of less than  $9 \mu V^2$ . No EEG/QEEG medication prediction was made for these patients.

[0104] The remaining eleven patients were classified into EEG/QEEG sets based on objective spectral features. EEG/QEEG sets included relative theta frequency excess (the percentage of total power contributed by the theta frequency band in excess of that expected from the age-matched reference population previously noted), relative alpha frequency excess (the percentage of total power contributed by the alpha frequency band in excess of that expected) and inter-hemispheric hypercoherence and hypo-coherence (synchronization of electrical activity in homologous brain regions, separately for each frequency band and for the entire spectrum).

[0105] The average relative power spectra of antidepressant responders in both the DSM DIRECTED (N=4) and DSM + EEG DIRECTED (N=3) treatment groups were compared. The spectra included global delta frequency deficits of -2.2/-2.4 mean-units to -2.1/-2.0 mean-units extending posteriorly. There were fronto-central theta deficits of -2.1/-1.6 mean-units with temporal sparing and sustained posterior theta deficits of up to -1.7/-2.4 mean-units. In the alpha band these spectra show frontal polar maxima's of +2.1/+1.7 mean -units.

[0106] The average relative power spectra of stimulant responders in both the DSM DIRECTED (N=2) and DSM + EEG DIRECTED (N=2) treatment groups were compared. These spectra included irregular frontal delta frequency deficits up to -1.4/-0.9 mean-units. Theta excess in the frontal region was +2.2/+2.2 mean-units. Theta excesses attenuate posteriorly. Alpha and beta relative powers are distributed about a mean-score of zero.

[0107] The average coherence spectra of anticonvulsant or lithium responders in both the DSM DIRECTED (N=3) and DSM + EEG DIRECTED (N=4) treatment groups were compared. The spectra exhibited frontal delta frequency hypercoherence of +1.7/+1.3 mean-units, posterior delta frequency hypo-coherence of up to -2.0/-0.8 mean-units, frontal theta hypercoherence of +2.2/+1.9 mean-units, frontal alpha hypercoherence of +2.3/+2.1 mean-units, and frontal beta hypercoherence of +1.8/+2.1 mean-units.

### Main Outcome Measures

#### Medication Regimens

[0108] Table 5 shows the medications were prescribed in recommended doses and plasma medication monitoring was conducted and maintained within therapeutic range for valproate, carbamazepine and lithium.

#### HAM-D and BECK Behavioral Outcome Sets

[0109] The HAM-D for the DSM DIRECTED group showed a mean pretreatment score of 24 compared to a mean treatment score of 18. The BECK Scale showed a mean pretreatment score of 22 compared to a mean treatment score of 20. The HAM-D for the DSM + EEG DIRECTED group showed a mean pretreatment score of 23 compared to a mean treatment score of 9. The BECK Scale showed a mean pretreatment score of 26 compared to a mean treatment score of 13. These changes in test scores between the two treatment groups are highly significant (Friedman ANOVA  $\chi^2$  (N=13; df=3)  $p < 0.009$ ).

#### Clinical Global Improvement Ratings

[0110] In the DSM + EEG DIRECTED group 6 of 7 patients had a CGI change of 2 or more; additionally 4 of 7 of these patients achieved a CGI of 3 indicating no evidence of illness. In the DSM DIRECTED group 1 of 6 patients had

a CGI change of 2 or more and 5 of 6 patients had a CGI change of 0 indicating no improvement ( $p = 0.02$ ; Fisher's exact).

### EEG Outcome Sets

5 [0111] All but one patient (low power) in the DSM DIRECTED group had medication outcome predicted from pretreatment EEG/QEEG information, but this information was not reported to the treating physicians. When the study finished, the prediction was examined with respect to the patient's clinical response.

10 [0112] All patients in the DSM DIRECTED group were predicted from their EEG/QEEG study to be nonresponsive to the physicians' medication selections. DSM + EEG DIRECTED patients were treated with the agents that were predicted by EEG/QEEG information to produce a favorable clinical outcome. Six of seven patients in this group responded as predicted *a priori* by EEG/QEEG information. When the positive and the negative *a priori* predictions are combined, ten out of eleven predictions were correct ( $p = 0.015$ ; Fisher's exact). These information are associated with an 86 per cent likelihood of positive patient outcome with each prediction and Youdin Index of 0.8 (Youden WJ. Index for rating diagnostic test. Cancer 1950;3: 32-35).

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### Discussion

20 [0113] Patients treated in the DSM DIRECTED group had an inferior response to pharmacotherapy. Only one of six patients demonstrated improved behavioral and clinical outcome measurements by HAM-D, BECK and CGI ratings. In comparison, six of seven patients in the DSM + EEG DIRECTED group responded with significantly improved HAM-D, BECK and CGI ratings. Furthermore, remission of symptoms or a CGI rating of 3 was achieved by four of seven patients in the DSM + EEG DIRECTED group. These therapeutic improvements would be unanticipated given the chronic and refractory nature of the imbalance in this select population

25 [0114] Pharmacotherapeutic choices in the DSM + EEG DIRECTED paradigm differed substantially from the control group by demonstrating initial combination pharmacotherapy with anticonvulsant/anticyclic agents and stimulants. With behavioral based treatment algorithms, these medication classes are recommended for pharmacotherapy of MDD only after failures of antidepressant class agents has labeled a patient refractory. Differences in selection of type of agent and number of agents used in initial treatment by the two groups are striking. Selection of monotherapy in the absence of objective EEG/QEEG information reveals a clear bias of the clinicians. A sequential strategy was supported and encouraged by numerous current reports (See Sharan SP, Saxena S. Treatment-resistant depression: clinical significance, concept and management. Natl. Med J India 1998 Mar-Apr;11(2):69-79; Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. J Clin Psychiatry 1997, 58 Suppl 13:23-9; Nelson JC. Treatment of antidepressant nonresponders: augmentation or switch? J Clin Psychiatry 1998, 59 Suppl 15:35-41). Augmentative strategies are also supported but only as a secondary approach (Shelton RC, Treatment options for refractory depression. J Clin Psychiatry 1999, 60 Suppl 4:57-61; discussion 62-3; Thase ME, Howland RH, Friedman ES. Treating antidepressant nonresponders with augmentation strategies: an overview. J Clin Psychiatry 1998, 59 Suppl 5:5-12; Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. J Clin Psychiatry 1998, 59 Suppl 6:28-33; Nierenberg AA, Dougherty D, Rosenbaum JF. Dopaminergic agents and stimulants as antidepressant augmentation strategies. J Clin Psychiatry 1998, 59 Suppl 5:60-3; Dougherty D, Rosenbaum JF, Joffe RT. Refractory depression: treatment strategies, with particular reference to the thyroid axis. J Psychiatry Neurosci 1997 Nov 22(5):327-31). The diagnoses of the clinicians treating the DSM DIRECTED patients and lacking electrophysiological information was consistent with current recommended treatment pathways.

30 [0115] Outcome prediction from EEG/QEEG information correlated with symptomatic behavioral assessments - CGI ratings, HAM-D and BECK scores. *A priori* identification of both non-response and response to particular pharmacotherapies suggests that EEG/QEEG information can reduce iatrogenic morbidity by correlating medication selection with the distribution of physiological response in MDD. Such an understanding adds clarity to the definition of "treatment non-responsive" and "treatment resistant", namely unsuccessful matching of medication to a particular pathophysiology.

35 [0116] This study shows that medication response in refractory MDD patients can be predicted by EEG/QEEG information. The prognostic ability of pretreatment EEG/QEEG information with respect to pharmacotherapeutic outcome in this population is consistent with previously reported retrospective associations of EEG/QEEG measurements and psychiatric medication response. Also demonstrated is the ability of psychiatric physicians to incorporate EEG/QEEG information with medication correlation as a laboratory test in clinical practice. The DSM + EEG paradigm allows physicians to select medications which were associated with improved patient outcomes.

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**Example 2****Method for Assessing Physiologic Brain Imbalances and Predicting Pharmacoresponsivity Using EEG/QEEG**

5 [0117] Patients with DSM-III-R diagnoses of 296.xx, 311.00, and 314.xx were prospectively enrolled in a study from consecutive evaluations of a largely (> 90%) Caucasian, suburban, population seeking care in a fee for service environment. Patients were evaluated as given below, and treated according to current clinical practice. Retrospective analyses of the relationships between clinical responsivity and neurophysiologic features were performed in order to identify those neurophysiologic features associated with unsuccessful and successful outcomes of pharmacotherapy.

10 [0118] Two samples of medication-free (no medicine for seven half-lives of the longest half-life agent) patients: those with affective imbalance diagnoses (296.xx or 311.00) and those with attentional imbalance diagnoses (314.xx) were identified by historic and clinical examination. These diagnoses were then confirmed in review by a second experienced clinician. One hundred and three (103) consecutive individuals were included in the study from those patients who were considered appropriate for the testing procedure. Subsequent to the Neurometric testing, patients were excluded from the study if laboratory results (Chem. 24, CBC, TSH, UDS, and HCG) were not available or there was not follow-up for at least six months after the initiation of pharmacotherapy. These criteria eliminated 2 patients with attentional imbalances and 1 patient with affective imbalance.

15 [0119] The attentional disordered sample consisted of 46 patients, 34 males and 12 females, with a mean age of 12.4 years. The affectively disordered population consisted of 54 patients, 20 males and 34 females, with a mean age 13.5 years in the adolescent population and a mean age of 40.4 years in the adult population.

20 [0120] Fifty per cent of the attentionally disordered population had not been previously diagnosed or treated for their attentional problems, despite chronic complaints and long-standing behavioral aberrations. The other half of this population was previously diagnosed and classified as treatment refractory by the referring clinician. In the affective disordered population there was a four-fold excess of unipolar patients by DSM-III-R criteria. Only one adolescent received the diagnosis of Bipolar Imbalance.

**EEG Information Acquisition and Analysis**

30 [0121] Using the international 10/20 system of electrode placement, twenty-one paste-on electrodes were applied to the scalp. Eyes closed resting EEG was recorded on a Cadwell Spectrum 32, referenced to linked ears, allowing for retrospective montage analysis of all information.

35 [0122] After examining the EEG record, a minimum of thirty-two 2.5 second epochs of artifact-free EEG were selected and subjected to quantitative analysis according to the method of the present invention including absolute power, relative power, power asymmetry, mean frequency, and coherence for the delta (1.5 - 3.5 H), theta (3.5 - 7.5 H), alpha (7.5 - 12.5 H), and beta (12.5 - 35 H) frequency bands. These measurements were logarithmically transformed to obtain Gaussianity, age-regressed, and transformed relative to population norms. A differential eye channel was used for the detection of eye movement. All electrode impedances were less than 5,000 ohms. The EEG amplifiers had a band pass from 0.5 to 70 H (3 dB points), with a 60 H notch filter.

**40 Clinical Monitoring**

[0123] Treatment was monitored in weekly, bimonthly, or monthly follow-up sessions using Clinical Global Improvement (CGI) ratings. CGI's taken from the patient's baseline presentation were generated using information gathered from parent and teacher Conner's scales, patient and parent interviews, contact with teachers, and the treating clinician's assessment for the attentionally disordered population. CGI's were rated on a 4 point scale, with 0 = no improvement, 1 = minimal improvement, 2 = moderate improvement, and 3 = marked improvement or no evidence of illness. A similar process was used in rating the affectively disordered population, but without the consideration of Conner's scales in deriving the CGI ratings.

**50 Treatment Selection**

[0124] The protocols were as follows. The attentional deficit population was initially treated with a stimulant medication, principally methylphenidate at a dose not exceeding 1.0 mg/kg body weight per day. If the patient did not achieve a Clinical Global Improvement score of 2 (moderate global improvement) or 3 (marked global improvement) after one month of medication, the stimulant was discontinued and secondary treatment with an antidepressant medication was initiated. If the patient did not achieve a Clinical Global Improvement score of 2 or 3 after six weeks of medication, the antidepressant was augmented with tertiary treatment consisting of an anticonvulsant (carbamazepine, valproic acid) or stimulant.

[0125] Affectively disordered patients without a history of mania were initially treated with a heterocyclic antidepressant (up to 3.0 mg/kg/day) or a serotonin reuptake inhibitor antidepressant. If by six weeks the patient did not achieve a Clinical Global Improvement score of 2 or 3, they received secondary treatment with anticonvulsant (carbamazepine, valproic acid) or lithium. Failure to improve after three weeks at therapeutic plasma levels caused tertiary measures to be instituted, most frequently a stimulant challenge with methylphenidate. If the challenge demonstrated stimulant responsiveness a therapeutic trial of stimulant was added to the patient's regimen.

**Results**

**Neurometric Spectral Features**

[0126] The population was heuristically divided into four groups based on objective spectral features. These groups included those who exhibited, respectively, relative alpha frequency excess, relative theta frequency excess, inter-hemispheric hypercoherence, or patients whose neurophysiologic spectra did not demonstrate one of the preceding profiles. These Neurometric profiles could be identified within both attentionally disordered and affectively disordered patients, as can be seen in **Figures 12 and 13**, where the theta excess and alpha excess groups with each diagnostic category were easily distinguished. In addition, the striking electrophysiologic similarity of the under and over eighteen year old affectively disordered groups shown in **Figure 14** demonstrated a robustness of these findings across ages. It was further noted that all these groups share the feature of delta frequency relative power deficit.

[0127] In **Figure 12**, the theta excess subgroup of attentional disordered patients demonstrated a spectrum with global delta frequency deficit, a +2.7 mean-units theta maxima in the frontal polar region, and a smaller but significant theta excess of +2.3 mean-units in the posterior frontal region. These maxima accompanied a relative theta minima in the central region, and a theta relative power decrease posteriorly. In contrast, the alpha excess subgroup of attentional disordered patients demonstrated a spectrum with global delta frequency deficit, a +2.1 mean-units alpha maxima in the frontal polar region and a second alpha maxima of +2.0 mean-units in the posterior frontal region. These maxima were then accompanied by a relative alpha minima in the temporal region, and an alpha relative power increase posteriorly. Twenty-five per cent (25%) of the attentional disordered patients demonstrated inter-hemispheric hypercoherence primarily in the frontal region.

[0128] **Figure 13** indicates that the theta excess subgroup of affectively disordered patients demonstrated a spectrum with global delta frequency deficit, a theta maxima of +2.2 mean-units in the frontal polar region, a second theta maxima of +2.4 mean-units in the posterior frontal region, and a decrease of relative theta power posteriorly. The alpha excess subgroup of affectively disordered patients demonstrated a spectrum with global delta frequency deficit, alpha maxima of +2.2 mean-units in the frontal polar region, a broad frontal alpha plateau of approximately +2.0 mean-units, and a second smaller alpha relative power plateau posteriorly of +1.0 mean-unit. Interhemispheric hypercoherence was seen in thirty-six per cent (36%) of the affectively disordered adolescent and fifty-seven per cent (57%) of the adult groups, mainly between the frontal regions.

[0129] **Figure 14** depicts the examination of the relative power spectrum as a function of age in affectively disordered patients who also exhibited inter-hemispheric hypercoherence found similar delta frequency power deficits in the two age groups. The under eighteen year-old group deficit was minimally 1 unit larger than the adult population. In the alpha frequency region of **Figure 14**, the under eighteen year-old group exhibited maximal relative power in the frontal polar region where it reached a mean of +2.6 mean-units. This maxima was followed by an alpha plateau of approximately +2.2 mean-units in the remaining portions of the frontal region. The adult affectively disordered spectrum showed qualitatively similar distributions with an alpha plateau of +1.8 mean-units in the frontal region.

[0130] The relative frequency of each of these electrophysiologic subgroups differs across these DSM-III-R diagnostic categories and by age, as can be seen in **Table 6**. These Neurometric subgroup frequency distributions are statistically significant for both imbalances and both age groups of the affectively disordered patients ( $X^2$  df= 2,  $p < 0.01$ ). It was noted that for both DSM-III-R diagnoses the largest percentage of the groups share a neurophysiologic alpha excess profile.

**Table 6**

<b>Neurometric Subgroups in Attentionally and Affectively Disordered Patients</b>			
<b>DSM-III-R Diagnostic Categories</b>	<b>FRONTAL ALPHA EXCESS</b>	<b>OTHER</b>	<b>FRONTAL THETA EXCESS</b>
<b>Attentionally Disordered</b>	25 [54%]	7 [15%]	14 [31%]
<b>Affectively Disordered under 18 Years Old</b>	18 [72%]	4 [16%]	3 [12%]

(continued)

Neurometric Subgroups in Attentionally and Affectively Disordered Patients			
DSM-III-R Diagnostic Categories	FRONTAL ALPHA EXCESS	OTHER	FRONTAL THETA EXCESS
Affectively Disordered 18 Years and Older	17 [58%]	8 [29%]	4 [13%]

### Outcome Sets

[0131] At six months after the initiation of treatment CGI ratings for the frontal alpha and theta excess subgroups were divided into treatment responsive and treatment refractory as shown in **Tables 7** and **8**.

**Table 7**

Clinical Response of DSM-III-R Affective Disorders by Neurometric Subgroup		
	FRONTAL ALPHA EXCESS	FRONTAL THETA EXCESS
RESPONSIVE	30 [86%]	2 [29%]
NON RESPONSIVE	5 [14%]	5 [71%]

[0132] The affective disordered population of **Table 7** with frontal alpha excess was responsive 86% of the time to the treatment paradigm ( $X^2$  df = 1,  $p < 0.001$ ) while the affective disordered population with frontal theta excess was responsive 29 % of the time ( $X^2$  df = 1,  $p = 0.26$ ), not a significant difference.

[0133] Similarly the attentionally disordered population of **Table 8** with frontal alpha excess was responsive 80% of the time to the treatment paradigm ( $X^2$ , df=1,  $p < 0.003$ ) while the attentional disordered population with frontal theta excess was responsive 71% of the time ( $X^2$ , df=1,  $p = 0.1$ ), not a significant difference. The non-responsive category also contained three affectively disordered patients and two attentionally disordered patients who were not compliant with pharmacotherapy. The treatment responsive category consisted of those patients with CGI's of 2 (26 patients - 42%) or 3 (36 patients - 58%).

**Table 8**

Clinical Response of DSM-III-R Attentional Disorders by Neurometric Subgroup		
	FRONTAL ALPHA EXCESS	FRONTAL THETA EXCESS
RESPONSIVE	20 [80%]	10 [71%]
NON RESPONSIVE	5 [20%]	4 [29%]

[0134] Clinical response was analyzed as a function of neurophysiologic spectral findings and class(es) of pharmacotherapeutic agent(s) for the normocoherent groups as shown in **Table 9**. The frontal alpha excess/normocoherent subgroup was 87% or more responsive to antidepressants without regard to the patient's clinical presentation with attentional or affective symptoms. The frontal theta excess/normocoherent subgroup appeared only in the attentionally disordered clinical population. In that population it was 100% responsive to stimulants.

**Table 9**

Pharmacoresponsivity of Normocoherent Clinical Populations		
	FRONTAL ALPHA EXCESS RESPONSIVE TO ANTIDEPRESSANTS	FRONTAL THETA EXCESS RESPONSIVE TO STIMULANTS
AFFECTIVELY DISORDERED	9/10 [90%]	0 [0%]
ATTENTIONALLY DISORDERED	13/15 [87%]	7/7 [100%]

[0135] Clinical response as a function of neurophysiologic spectral findings and class(es) of pharmacotherapeutic

agent(s) for the hypercoherent populations as shown in **Table 10**. Here, the frontal alpha excess/hypercoherent subgroup was 85% or more responsive to anticonvulsants/lithium without regard to the patient's clinical presentation with attentional or affective symptoms. The frontal theta excess/hypercoherent subgroup represented only a total of 5 patients, 4 of whom (80%) were responsive to anticonvulsants.

Table 10

Pharmacoresponsivity of Hypercoherent Clinical Populations		
	FRONTAL ALPHA EXCESS RESPONSIVE TO ANTICONVULSANTS/Li	FRONTAL THETA EXCESS RESPONSIVE TO ANTICONVULSANTS
AFFECTIVELY DISORDERED	17/20 [85%]	2/2 [100%]
ATTENTIONALLY DISORDERED	5/5 [100%]	2/3 [67%]

## Discussion

**[0136]** As the findings demonstrate, the patient samples in each of the DSM-III-R diagnostic categories studied were not neurometrically homogeneous. Neurometrically distinguishable subgroups were present within each category; moreover, the Neurometric subgroups were qualitatively similar across the DSM-III-R diagnostic categories. The relative frequency of the subgroups differed between the categories examined as well as between age groups within the affectively disordered population. It is important to note that the Neurometric subgroups in the affectively disordered patients were qualitatively similar independent of the patient's age, demonstrating the existence of electrophysiologic similarities between childhood and adult affective imbalances.

**[0137]** Retrospective analyses of clinical outcomes as a function of Neurometric subgroup membership demonstrate differential responsiveness to selected classes of pharmacologic agents. The design of the clinical treatment paradigm for these different DSM-III-R categories might be expected to prejudice the findings because they should produce groups of affectively disordered patients with a high frequency of response to antidepressants and an attentionally disordered population with a high frequency of response to stimulants; however, the outcomes show that subgroups with similar neurophysiologic features responded to the same class of psychopharmacological agent despite the impact of the clinical treatment paradigm and the DSM-III-R classification of the patient's presenting problems. That is, the presence of the excess frontal alpha Neurometric pattern was associated with responsiveness to antidepressant class pharmacotherapy whether it appeared in a patient with DSM-III-R behavioral features consistent with depressive imbalances or in a patient with DSM-III-R behavioral features consistent with attentional imbalances. Other quantitative electrophysiologic studies have shown that the serotonin reuptake inhibitors decrease alpha abundance (Saletu B, Grunberger J. Classification and Determination of Cerebral Bioavailability of Fluoxetine: Pharmacology-EEG, and Psychometric Analyses. *Clinical Psychiatry* 1985; 46:45-52; Itil T, Itil K, Mukherjee S, Dayican G, Shaw G. A Dose-Finding Study with Sertraline, a New 5-HT Reuptake Blocking Antidepressant Using Quantitative Pharmacology-EEG and Dynamic Brain Mapping. *Journal of Integrative Psychiatry* 1989; 7:29-39). This finding is consistent with our finding that the excess frontal alpha/normo-coherent patient subgroup was highly responsive to the antidepressant class of medications.

**[0138]** In this study, it was also found that patients with hypercoherent Neurometric patterns responded to anticonvulsant/lithium class agents without regard to DSM-III-R diagnosis. These findings demonstrate the clinical utility of the Neurometric method of QEEG with its ability to define alpha frequency and coherence abnormalities not appreciated in qualitative electroencephalography.

**[0139]** Our information suggests that this population was made responsive by the addition of anticonvulsants or lithium. The recognition of a physiologic feature common to this subgroup of treatment resistant schizophrenic, affective, and attentionally disordered patients, which appears to specify the need for augmented pharmacotherapy, has clinical impact in the reduction of morbidity. This technology may obviate sequential agent trials toward justifying combined pharmacotherapies by indicating combined pharmacotherapy at the onset of treatment.

**[0140]** The theta excess population could be divided into two subtypes: a frontal theta excess group and a global theta excess group. The frontal theta excess group responded to stimulants. The global theta excess group responded to anticonvulsant agents. The findings are consistent with the common clinical experience of heterogeneous responses to classes of pharmacologic agents in DSM-III-R diagnostic categories.

## Claims

1. A method for recommending therapy for a patient having a behaviourally diagnosed psychiatric condition, wherein a plurality of monopolar or bipolar EEG signals are obtained from the patient, and a plurality of patient univariate measures are extracted from the patient EEG signals, each univariate measure representing a quantitated deviation from a plurality of monopolar or bipolar EEG signals from an asymptomatic normal population, wherein the method comprises:
  - using an outcomes database that includes symptomatic profiles for symptomatic individuals who exhibit clinical manifestations of psychiatric imbalances with known therapy outcomes, the symptomatic profiles being derived from selected combinations of two or more univariate measures extracted from each symptomatic individual's EEG signals, the outcomes database including symptomatic profiles comprising pre-therapy profiles and post-therapy profiles for the symptomatic individuals;
  - deriving one or more patient multivariate EEG descriptors from selected combinations of two or more patient univariate measures to form a patient profile;
  - comparing the patient profile to the symptomatic pre-therapy profiles in the outcomes database to identify one or more individuals who have a symptomatic profile similar to the patient profile, and
  - recommending at least one therapy for the patient from among those therapies with known outcomes for the individuals of the symptomatic population who have a symptomatic profile similar to the patient profile, wherein the recommended therapies are selected from the symptomatic post-therapy profiles that deviate less from the asymptomatic normal population than the pre-therapy profiles corresponding to the symptomatic post-therapy profiles.
2. The method of Claim 1, wherein the asymptomatic normal population EEG signals comprise one or more of the absolute power, relative power, coherence, asymmetry, or ratios thereof, of EEG signals from selected anatomic brain regions.
3. The method of Claim 1, wherein the patient or the symptomatic univariate measures are selected so that the patient or the symptomatic multivariate descriptors comprise representations of the absolute power, relative power, coherence, asymmetry, or ratios thereof, of EEG signals from selected anatomic brain regions.
4. The method of Claim 3, wherein the multivariate descriptors further comprise representations of the EEG information in one or more selected frequency bands.
5. The method of Claim 4, wherein the frequency bands comprise one or more of the delta, theta, alpha, or beta bands.
6. The method of Claim 3, wherein the selected anatomic regions comprise one or more of the anterior, posterior, left side, right side, or the entire brain.
7. The method of Claim 1, wherein the patient profile and symptomatic profile are similar if the association of their values is statistically robust.
8. The method of Claim 1, wherein the recommended therapy comprises one or more of electroconvulsive therapy, electromagnetic therapy, pharmacologic therapy, neuromodulation therapy, or verbal therapy.
9. The method of Claim 1, wherein the known outcome comprises normalizing the EEG signals or of normalizing the behaviorally-diagnosed psychiatric condition in one or more individuals in the symptomatic population.
10. The method of Claim 1, wherein a plurality of asymptomatic multivariate descriptors are derived from the asymptomatic normal population EEG signals.
11. The method of Claim 1, wherein the patient multivariate descriptors comprise patient quantified functional information, wherein the quantified functional information reflects physiologic brain functioning in a plurality of anatomic regions of the brain.
12. The method of Claim 11, wherein the patient quantified functional information is compared with quantified functional information from at least one reference population comprising individuals exhibiting similar symptomatic responsivity profiles thereby identifying quantitated deviations of the patient quantified functional information from the at least

one reference population.

- 5
13. The method of Claim 11, wherein a plurality of patient multivariate descriptors are derived from the quantitated deviations, wherein each multivariate descriptor is responsive to a plurality of the quantitative deviations, and wherein multivariate descriptors together form a profile for the patient representing the patient's physiologic brain functioning.
14. The method of Claim 11, wherein the quantified functional information reflects an eyes-closed, background state.
- 10
15. The method of Claim 1, wherein the profiles are compared by performing rule-based classification of profile similarity.
16. The method of Claim 1 wherein the profiles are compared by performing a statistical assessment of the robustness of profile similarity.
- 15
17. The method of Claim 1, wherein the therapies are recommended for the patient profile that is similar to the pre-therapy profile of the symptomatic individual, wherein the symptomatic individual's post-therapy profile deviates less from normal than their corresponding pre-therapy profile.
18. The method of Claim 1, wherein the univariate measures are generated using a Fast Fourier Transformation of the EEG information.
- 20
19. The method of Claim 1, wherein the quantified deviations responsive to only a single univariate measure are expressed as a Z score.
- 25
20. A method according to Claim 12, wherein the reference population is the asymptomatic normal reference population comprising individuals who are asymptomatic for behaviorally-diagnosed psychiatric conditions.
21. The method of Claim 12, wherein the reference population is the symptomatic population and the patient quantified functional information is compared with quantified functional information from the symptomatic population to produce a group of similarities for the patient.
- 30
22. The method of Claim 21, wherein the group of similarities are organized by multivariate descriptors to provide a similarities profile.
23. The method of Claim 1, wherein the symptomatic individuals in the symptomatic population exhibit behavioral indicia of physiologic brain imbalances.
- 35
24. The method of Claim 1, wherein the behaviorally-diagnosed psychiatric condition comprises a brain pathology.
25. The method of Claim 1, wherein the therapy is selected from the group consisting of drug therapy, electroconvulsive therapy, electromagnetic therapy, neuro-modulation therapy, verbal therapy, and combinations thereof.
- 40
26. The method of Claim 25, wherein the therapy is drug therapy and the drug is selected from the group consisting of a psychotropic agent, a neurotropic agent, multiple of psychotropic agents or neurotropic agents, and any combination thereof.
- 45
27. The method of Claim 26, wherein the drug has a direct or indirect effect on the CNS system of the patient.
28. The method of Claim 27, wherein the behaviorally-diagnosed psychiatric condition comprises a panic disorder, and the drug therapy comprises a drug selected from the group consisting of valproic acid, clonazepam, carbamazepine, methylphenidate and dextroamphetamine.
- 50
29. The method of Claim 27, wherein the behaviorally-diagnosed psychiatric condition comprises an eating disorder, and the drug therapy comprises a drug selected from the group consisting of methylphenidate and dextroamphetamine.
- 55
30. The method of Claim 27, wherein the behaviorally-diagnosed psychiatric condition comprises a learning disorder, and the drug therapy comprises a drug selected from the group consisting of amantadine, valproic acid, clonazepam and carbamazepine.

31. The method of Claim 1, wherein after one or more of the recommended therapies are administered to the patient a plurality of follow-up multivariate descriptors are derived from quantified deviations from the reference population of follow-up quantified functional information and a plurality of follow-up multivariate descriptors are derived from the patient when in the selected physiologic brain state.

32. The method of Claim 31, wherein the recommended therapy is changed depending on the patient's follow-up multivariate descriptors.

## Patentansprüche

1. Verfahren zur Therapieempfehlung für einen Patienten mit verhaltensdiagnostisch ermitteltem psychiatrischem Leiden, wobei eine Vielzahl von monopolaren oder bipolaren EEG-Signalen von dem Patienten aufgenommen werden und eine Vielzahl von eindimensionalen Maßen aus den EEG-Signalen des Patienten extrahiert werden, wobei jedes eindimensionale Maß eine quantitativ bestimmte Abweichung von einer Vielzahl monopolarer oder bipolarer EEG-Signalen aus einer asymptotischen normalen Population darstellt, wobei das Verfahren aufweist:

Verwendung einer Ergebnisdatenbank, die Symptomprofile für symptomatische Personen enthält, die klinische Manifestationen psychiatrischer Ungleichgewichte mit bekannten Therapieergebnissen aufweisen, wobei die Symptomprofile von ausgewählten Kombinationen von zwei oder mehreren eindimensionalen Maßen abgeleitet sind, die aus den EEG-Signalen jeder symptomatischen Person extrahiert werden, wobei die Ergebnisdatenbank Symptomprofile enthält, die prätherapeutische Profile und posttherapeutische Profile für die symptomatischen Personen aufweisen;

Ableitung eines oder mehrerer mehrdimensionaler Patienten-EEG-Deskriptoren aus gewählten Kombinationen von zwei oder mehreren eindimensionalen Patientenmaßen, um ein Patientenprofil zu bilden;

Vergleich des Patientenprofils mit den prätherapeutischen Symptomprofilen in der Ergebnisdatenbank, um eine oder mehrere Personen zu ermitteln, die ein dem Patientenprofil ähnliches Symptomprofil aufweisen, und

Empfehlen mindestens einer Therapie für den Patienten unter den Therapien mit bekannten Ergebnissen für die Personen der symptomatischen Population, die ein dem Patientenprofil ähnliches Symptomprofil aufweisen, wobei die empfohlenen Therapien unter den symptomatischen posttherapeutischen Profilen ausgewählt sind, die weniger von der asymptotischen normalen Population abweichen als die prätherapeutischen Profile, die den symptomatischen posttherapeutischen Profilen entsprechen.

2. Verfahren nach Anspruch 1, wobei die EEG-Signale der asymptotischen normalen Population einer oder mehrere der Größen absolute Leistung, relative Leistung, Kohärenz, Asymmetrie oder deren Verhältnisse von EEG-Signalen von ausgewählten anatomischen Gehirnregionen aufweisen.

3. Verfahren nach Anspruch 1, wobei der Patient oder die symptomatischen eindimensionalen Maße so ausgewählt werden, daß der Patient oder die symptomatischen mehrdimensionalen Maße Darstellungen der absoluten Leistung, relativen Leistung, Kohärenz, Asymmetrie oder von deren Verhältnissen von EEG-Signalen von ausgewählten anatomischen Gehirnregionen aufweisen.

4. Verfahren nach Anspruch 3, wobei die mehrdimensionalen Deskriptoren ferner Darstellungen der EEG-Informationen in einem oder mehreren Frequenzbändern aufweisen.

5. Verfahren nach Anspruch 4, wobei die Frequenzbänder ein oder mehrere von den  $\delta$ -,  $\theta$ -,  $\alpha$ - oder  $\beta$ -Bändern aufweisen.

6. Verfahren nach Anspruch 3, wobei die ausgewählten anatomischen Regionen eine oder mehrere von der vorderen, hinteren, linken, rechten Seite oder das gesamte Gehirn aufweisen.

7. Verfahren nach Anspruch 1, wobei das Patientenprofil und das symptomatische Profil ähnlich sind, wenn die Zuordnung ihrer Werte statistisch robust ist.

8. Verfahren nach Anspruch 1, wobei die empfohlene Therapie eine oder mehrere der folgenden aufweist: Etektrokrampftherapie, elektromagnetische Therapie, pharmakologische Therapie, Neuromodulationstherapie oder verbale Therapie.

## EP 1 253 853 B1

9. Verfahren nach Anspruch 1, wobei das bekannte Ergebnis die Normalisierung der EEG-Signale oder die Normalisierung des verhaltendiagnostisch ermittelten psychiatrischen Leidens bei einer oder mehreren Personen in der symptomatischen Population aufweist.
- 5 10. Verfahren nach Anspruch 1, wobei die Vielzahl asymptomatischer mehrdimensionaler Deskriptoren aus den EEG-Signalen der asymptomatischen normalen Population abgeleitet werden.
11. Verfahren nach Anspruch 1, wobei die mehrdimensionalen Patientendeskriptoren quantitativ bestimmte funktionale Patienteninformationen aufweisen, wobei die quantitativ bestimmten funktionalen Informationen die physiologische Gehirnfunktion in mehreren anatomischen Regionen des Gehirns widerspiegeln.
- 10 12. Verfahren nach Anspruch 11, wobei die quantitativ bestimmten funktionalen Patienteninformationen mit quantitativ bestimmten funktionalen Informationen von mindestens einer Vergleichspopulation verglichen werden, die Personen mit ähnlichen symptomatische Empfindlichkeitsprofilen aufweist, wodurch quantitativ bestimmte Abweichungen der quantitativ bestimmten funktionalen Patienteninformationen von der mindestens einen Vergleichspopulation ermittelt werden.
- 15 13. Verfahren nach Anspruch 11, wobei die Vielzahl von mehrdimensionalen Patientendeskriptoren aus den quantitativ bestimmten Abweichungen abgeleitet werden, wobei jeder mehrdimensionale Deskriptor auf eine Vielzahl der quantitativen Abweichungen anspricht, und wobei mehrdimensionale Deskriptoren zusammen ein Profil für den Patienten bilden, das die physiologische Gehirnfunktion des Patienten darstellt.
- 20 14. Verfahren nach Anspruch 11, wobei die quantitativ bestimmten funktionalen Informationen einen Hintergrundzustand bei geschlossenen Augen widerspiegeln.
- 25 15. Verfahren nach Anspruch 1, wobei die Profile durch Ausführen einer regelbasierten Klassifikation der Profilähnlichkeit verglichen werden.
16. Verfahren nach Anspruch 1, wobei die Profile durch Ausführen einer statistischen Bewertung der Robustheit der Profilähnlichkeit verglichen werden.
- 30 17. Verfahren nach Anspruch 1, wobei die Therapien für das Patientenprofil empfohlen werden, das ähnlich dem prätherapeutischen Profil der symptomatischen Person ist, wobei das posttherapeutische Profil der symptomatischen Person weniger vom Normalprofil abweicht als ihr entsprechendes prätherapeutisches Profil.
- 35 18. Verfahren nach Anspruch 1, wobei die eindimensionalen Maße unter Anwendung einer schnellen Fouriertransformation der EEG-Informationen erzeugt werden.
19. Verfahren nach Anspruch 1, wobei die quantitativ bestimmten Abweichungen, die nur auf ein einziges einclintensionales Maß ansprechen, als eine Z-Maßzahl ausgerückt werden.
- 40 20. Verfahren nach Anspruch 12, wobei die Vergleichspopulation die symptomatische normale Vergleichspopulation mit Personen ist, die für verhaltendiagnostisch ermittelte psychiatrische Leiden asymptomatisch sind.
- 45 21. Verfahren nach Anspruch 12, wobei die Vergleichspopulation die symptomatische Population ist und die quantitativ bestimmten funktionalen Patienteninformationen mit den quantitativ bestimmten funktionalen Informationen von der symptomatischen Population verglichen werden, um eine Gruppe von Ähnlichkeiten für den Patienten zu erzeugen.
22. Verfahren nach Anspruch 21, wobei die Gruppe von Ähnlichkeiten durch mehrdimensionale Deskriptoren organisiert wird, um ein Ähnlichkeitenprofil bereitzustellen.
- 50 23. Verfahren nach Anspruch 1, wobei die symptomatischen Personen in der symptomatischen Population Verhaltensanzeichen von physiologischen Gehirnungleichgewichten aufweisen.
- 55 24. Verfahren nach Anspruch 1, wobei das verhaltendiagnostisch ermittelte psychiatrische Leiden einen pathologischen Gehirnbefund aufweist.
25. Verfahren nach Anspruch 1, wobei die Therapie aus der Gruppe ausgewählt ist, die aus medikamentöser Therapie,

## EP 1 253 853 B1

Elektrokrampftherapie, elektromagnetischer Therapie, Neuromodulationstherapie, verbaler Therapie und Kombinationen davon besteht.

- 5 26. Verfahren nach Anspruch 25, wobei die Therapie eine medikamentöse Therapie ist und das Medikament aus der Gruppe ausgewählt ist, die aus einem Psychopharmakon, einem neurotrophen Mittel, mehreren Psychopharmaka oder neurotrophen Mitteln und irgendeiner Kombination davon besteht.
- 10 27. Verfahren nach Anspruch 26, wobei das Medikament eine direkte oder indirekte Wirkung auf das Zentralnervensystem des Patienten hat.
- 15 28. Verfahren nach Anspruch 27, wobei das verhaltensdiagnostisch ermittelte psychiatrische Leiden eine Panikstörung aufweist und die medikamentöse Therapie ein Medikament aufweist, das aus der Gruppe ausgewählt ist, die aus Valproinsäure, Clonazepam, Carbamazepin, Methylphenidat und Dextroamphetamin besteht.
- 20 29. Verfahren nach Anspruch 27, wobei das verhaltensdiagnostisch ermittelte psychiatrische Leiden eine Essstörung aufweist und die medikamentöse Therapie ein Medikament aufweist, das aus der Gruppe ausgewählt ist, die aus Methylphenidat und Dextroamphetamin besteht.
- 25 30. Verfahren nach Anspruch 27, wobei das verhaltensdiagnostisch ermittelte psychiatrische Leiden eine Lernstörung aufweist und die medikamentöse Therapie ein Medikament aufweist, das aus der Gruppe ausgewählt ist, die aus Amantadin, Valproinsäure, Clonazepam und Carbamazepine besteht.
- 30 31. Verfahren nach Anspruch 1, wobei nach Anwendung einer oder mehrerer der empfohlenen Therapien auf den Patienten mehrere mehrdimensionale Nachsorgedeskriptoren aus quantitativ bestimmten Abweichungen von der Vergleichspopulation von quantitativ bestimmten funktionalen Nachsorge-Informationen abgeleitet werden und mehrere mehrdimensionale Nachsorgedeskriptoren von dem Patienten abgeleitet werden, wenn er sich in dem gewählten physiologischen Gehirnzustand befindet.
- 35 32. Verfahren nach Anspruch 31, wobei die empfohlene Therapie in Abhängigkeit von den mehrdimensionalen Nachsorgedeskriptoren des Patienten verändert wird.

### Revendications

- 35 1. Procédé de recommandation d'une thérapie pour un patient ayant un état psychiatrique diagnostiqué comme trouble comportemental, dans lequel une pluralité de signaux d'EEG unipolaires ou bipolaires sont obtenus du patient, et une pluralité de mesures à variable unique sont extraites des signaux d'EEG du patient, chaque mesure à variable unique représentant un écart quantifié à partir d'une pluralité de signaux d'EEG monopolaires ou bipolaires parmi un population asymptomatique normale, dans lequel le procédé comprend:
- 40 l'utilisation d'une base de données de résultats qui incluent des profils symptomatiques pour des individus symptomatiques qui font preuve de manifestations cliniques de déséquilibres psychiatriques avec des résultats de thérapie connus, les profils symptomatiques étant dérivés de combinaisons choisies de deux ou plusieurs mesures à variable unique extraites de chacun des signaux d'EEG symptomatiques de l'individu, la base de données de résultats incluant des profils symptomatiques comprenant des profils pré-thérapie et des profils post-thérapie provenant d'individus symptomatiques ;
- 45 le fait de faire dériver un ou plusieurs descripteur(s) d'EEG à variables multiples de patient de combinaisons choisies de deux ou plusieurs mesures à variable unique de patient afin de former un profil de patient ;
- 50 la comparaison du profil du patient à des profils pré-thérapie symptomatiques dans la base de données de résultats afin d'identifier un ou plusieurs individu(s) qui a (ont) un profil symptomatique similaire au profil du patient, et
- 55 la recommandation d'au moins une thérapie pour le patient parmi ces thérapies présentant des résultats connus pour les individus de la population symptomatique qui ont un profil symptomatique similaire au profil du patient, dans laquelle les thérapies recommandées sont choisies parmi les profils post-thérapie symptomatiques qui s'écartent moins de la population asymptomatique normale que les profils pré-thérapie correspondant aux profils post-thérapie symptomatiques.
2. Procédé selon la revendication 1, dans lequel les signaux d'EEG de la population asymptomatique normale com-

## EP 1 253 853 B1

prennent un ou plusieurs des signaux d'EEG de puissance absolue, puissance relative, cohérence, asymétrie, ou rapports de ceux-ci, provenant de régions anatomiques choisies du cerveau.

- 5 3. Procédé selon la revendication 1, dans lequel le patient ou les mesures symptomatiques à variable unique sont choisies de sorte que le patient ou les descripteurs symptomatiques à variables multiples comprennent des représentations de signaux d'EEG de puissance absolue, puissance relative, cohérence, asymétrie ou rapports de ceux-ci, provenant de régions anatomiques choisies du cerveau.
- 10 4. Procédé selon la revendication 3, dans lequel les descripteurs à variables multiples comprennent en outre des représentations de l'information d'EEG sur une ou plusieurs bande(s) de fréquence choisie(s).
- 15 5. Procédé selon la revendication 4, dans lequel les bandes de fréquence comprennent une ou plusieurs des bandes delta, thêta, alpha ou bêta.
- 20 6. Procédé selon la revendication 3, dans lequel les régions anatomiques choisies comprennent une ou plusieurs des parties antérieure, postérieure, gauche, droite, ou le cerveau entier.
- 25 7. Procédé selon la revendication 1, dans lequel le profil du patient et le profil symptomatique sont similaires si l'association de leurs valeurs est statistiquement solide.
- 30 8. Procédé selon la revendication 1, dans lequel la thérapie recommandée comprend l'une ou plusieurs parmi l'électroconvulsothérapie, la thérapie électromagnétique, la thérapie pharmacologique, la thérapie de neuromodulation, ou la thérapie verbale.
- 35 9. Procédé selon la revendication 1, dans lequel le résultat connu comprend la normalisation des signaux d'EEG ou la normalisation de l'état psychiatrique diagnostiqué comme trouble du comportement chez un ou plusieurs individu(s) dans la population symptomatique.
- 40 10. Procédé selon la revendication 1, dans lequel une pluralité de descripteurs asymptomatiques à variables multiples sont dérivés des signaux d'EEG de la population asymptomatique normale.
- 45 11. Procédé selon la revendication 1, dans lequel les descripteurs à variables multiples du patient comprennent de l'information fonctionnelle quantifiée du patient, dans lequel l'information fonctionnelle quantifiée reflète le fonctionnement physiologique du cerveau au niveau d'une pluralité de régions anatomiques du cerveau.
- 50 12. Procédé selon la revendication 11, dans lequel l'information fonctionnelle quantifiée du patient est comparée à de l'information fonctionnelle quantifiée provenant d'au moins une population de référence comprenant des individus faisant preuve de profils de réponse symptomatique similaires identifiant de là des écarts quantifiés de l'information fonctionnelle quantifiée du patient par rapport à la au moins une population de référence.
- 55 13. Procédé selon la revendication 11, dans lequel une pluralité de descripteurs à variables multiples de patient sont dérivés des écarts quantifiés, dans lequel chaque descripteur à variables multiples répond à une pluralité d'écarts quantitatifs, et dans lequel les descripteurs à variables multiples forment conjointement un profil pour le patient représentant le fonctionnement physiologique du cerveau du patient.
14. Procédé selon la revendication 11, dans lequel l'information fonctionnelle quantifiée reflète un état d'éveil calme, yeux fermés.
15. Procédé selon la revendication 1, dans lequel les profils sont comparés en effectuant une classification basée sur des règles de similitude de profils.
16. Procédé selon la revendication 1, dans lequel les profils sont comparés en effectuant une évaluation statistique de la robustesse de la similitude des profils.
17. Procédé selon la revendication 1, dans lequel les thérapies sont recommandées pour le profil du patient qui est similaire au profil pré-thérapie de l'individu symptomatique, dans lequel le profil post-thérapie de l'individu symptomatique s'écarte moins de la normale que son profil pré-thérapie correspondant.

## EP 1 253 853 B1

18. Procédé selon la revendication 1, dans lequel les mesures à variable unique sont générées utilisant une transformation de Fourier accélérée de l'information EEG.
- 5 19. Procédé selon la revendication 1, dans lequel les écarts quantifiés qui répondent seulement à une mesure à variable unique individuelle sont exprimés sous la forme d'une note Z.
- 10 20. Procédé selon la revendication 12, dans lequel la population de référence est la population de référence asymptotique normale comprenant les individus qui sont asymptotiques pour les états psychiatriques diagnostiqués comme troubles du comportement.
- 15 21. Procédé selon la revendication 12, dans lequel la population de référence est la population symptomatique et l'information fonctionnelle quantifiée du patient est comparée à l'information fonctionnelle quantifiée provenant de la population symptomatique afin de produire un groupe de similitudes pour le patient.
- 20 22. Procédé selon la revendication 21, dans lequel le groupe de similitudes est organisé par descripteurs à variables multiples afin de fournir un profil de similitudes.
- 25 23. Procédé selon la revendication 1, dans lequel les individus symptomatiques dans la population symptomatique font preuve d'indices de comportement de déséquilibres physiologiques du cerveau.
- 30 24. Procédé selon la revendication 1, dans lequel l'état psychiatrique diagnostiqué comme trouble du comportement comprend une pathologie du cerveau.
- 35 25. Procédé selon la revendication 1, dans lequel la thérapie est choisie parmi le groupe constitué de la thérapie médicamenteuse, de l'électroconvulsivothérapie, de la thérapie électromagnétique, de la thérapie de neuromodulation, de la thérapie verbale, et des combinaisons de celles-ci.
- 40 26. Procédé selon la revendication 25, dans lequel la thérapie est la thérapie médicamenteuse et le médicament est choisi parmi le groupe constitué d'un agent psychotrope, d'un agent neurotrope, de multiples agents psychotropes ou agents neurotropes, et de n'importe quelle combinaison de ceux-ci.
- 45 27. Procédé selon la revendication 26, dans lequel le médicament a un effet direct ou indirect sur le SNC du patient.
- 50 28. Procédé selon la revendication 27, dans lequel l'état psychiatrique diagnostiqué comme trouble du comportement comprend un trouble panique, et la thérapie médicamenteuse comprend un médicament choisi parmi le groupe constitué de l'acide valproïque, du clonazépam, de la carbamazépine, du méthylphénidate et de la dextroamphétamine.
- 55 29. Procédé selon la revendication 27, dans lequel l'état psychiatrique diagnostiqué comme trouble du comportement comprend un trouble de l'alimentation, et la thérapie médicamenteuse comprend un médicament choisi dans le groupe constitué du méthylphénidate et de la dextroamphétamine.
30. Procédé selon la revendication 27, dans lequel l'état psychiatrique diagnostiqué comme trouble du comportement comprend un trouble d'apprentissage, et la thérapie médicamenteuse comprend un médicament choisi parmi le groupe constitué de l'amantadine, de l'acide valproïque, du clonazépam et de la carbamazépine,
31. Procédé selon la revendication 1, dans lequel après que l'une ou plusieurs des thérapies recommandées soi(en)t administrée(s) au patient, une pluralité de descripteurs de suivi à variables multiples sont dérivés des écarts quantifiés provenant de la population de référence de l'information fonctionnelle quantifiée de suivi et une pluralité de descripteurs de suivi à variables multiples sont dérivés du patient lorsqu'il se trouve dans l'état physiologique choisi du cerveau.
32. Procédé selon la revendication 31, dans lequel la thérapie recommandée est modifiée en fonction des descripteurs de suivi à variables multiples du patient.

FIGURE 1  
DATA ACQUISITION  
AND  
ANALYSIS

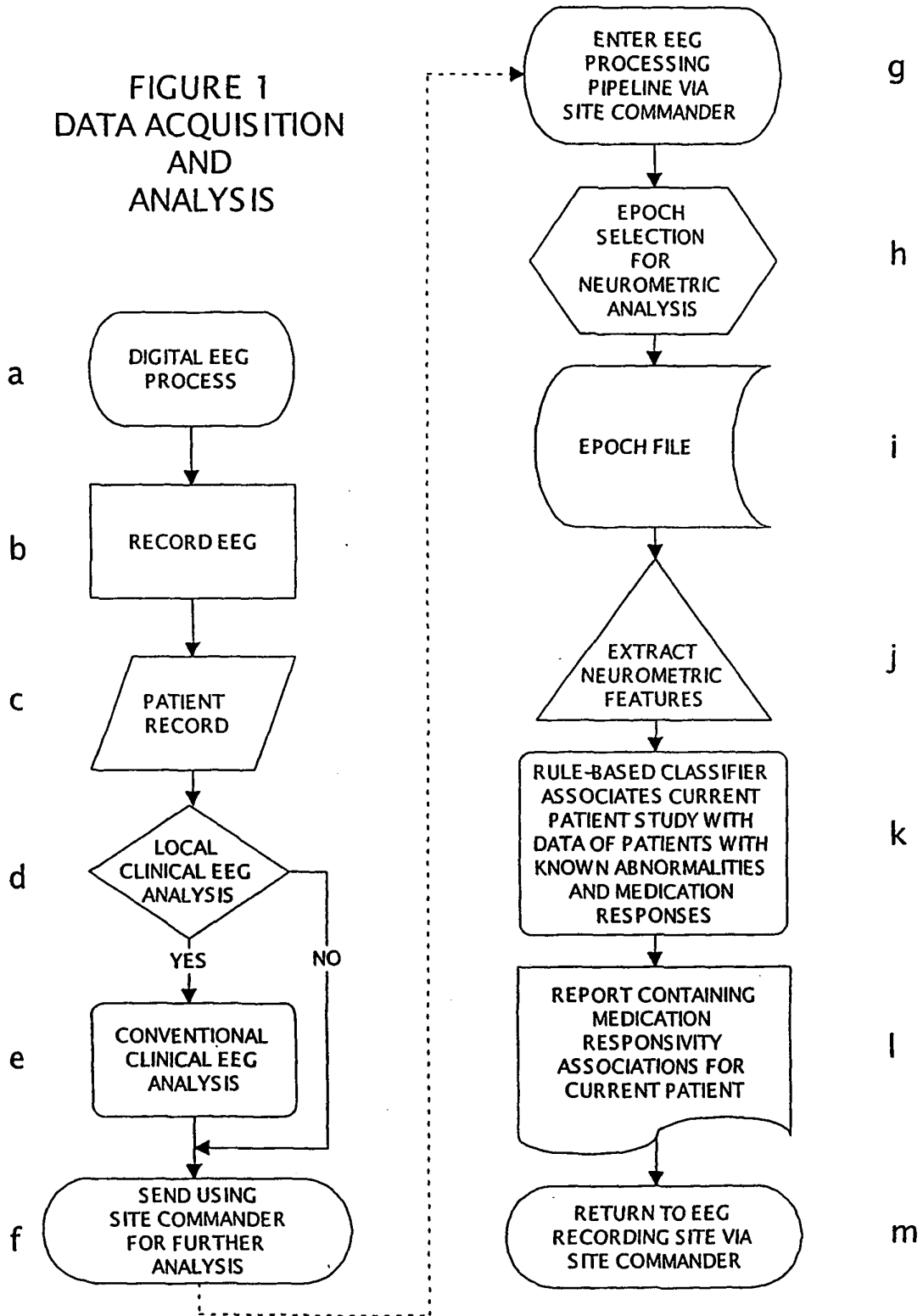


FIGURE 2

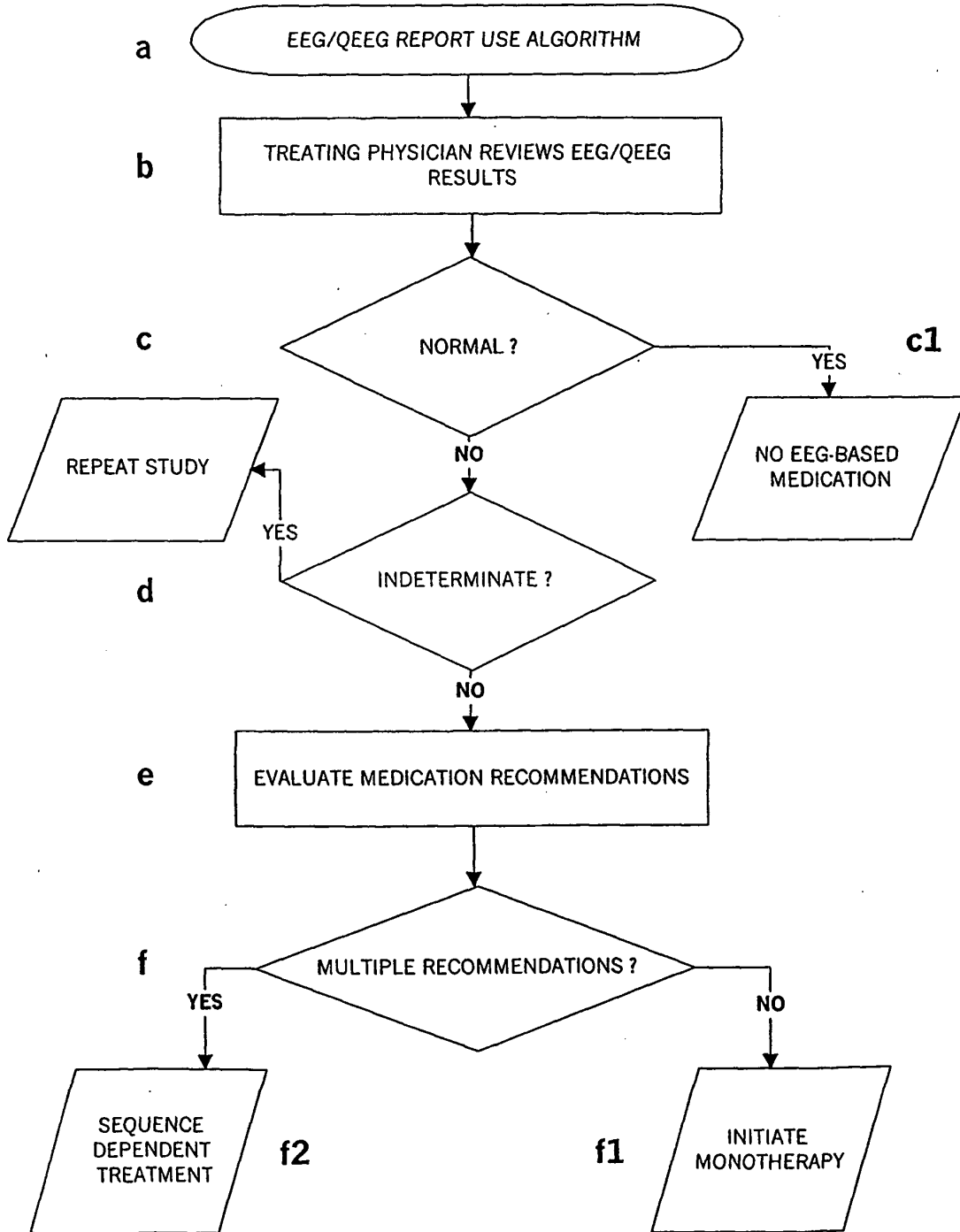


FIGURE 3.1

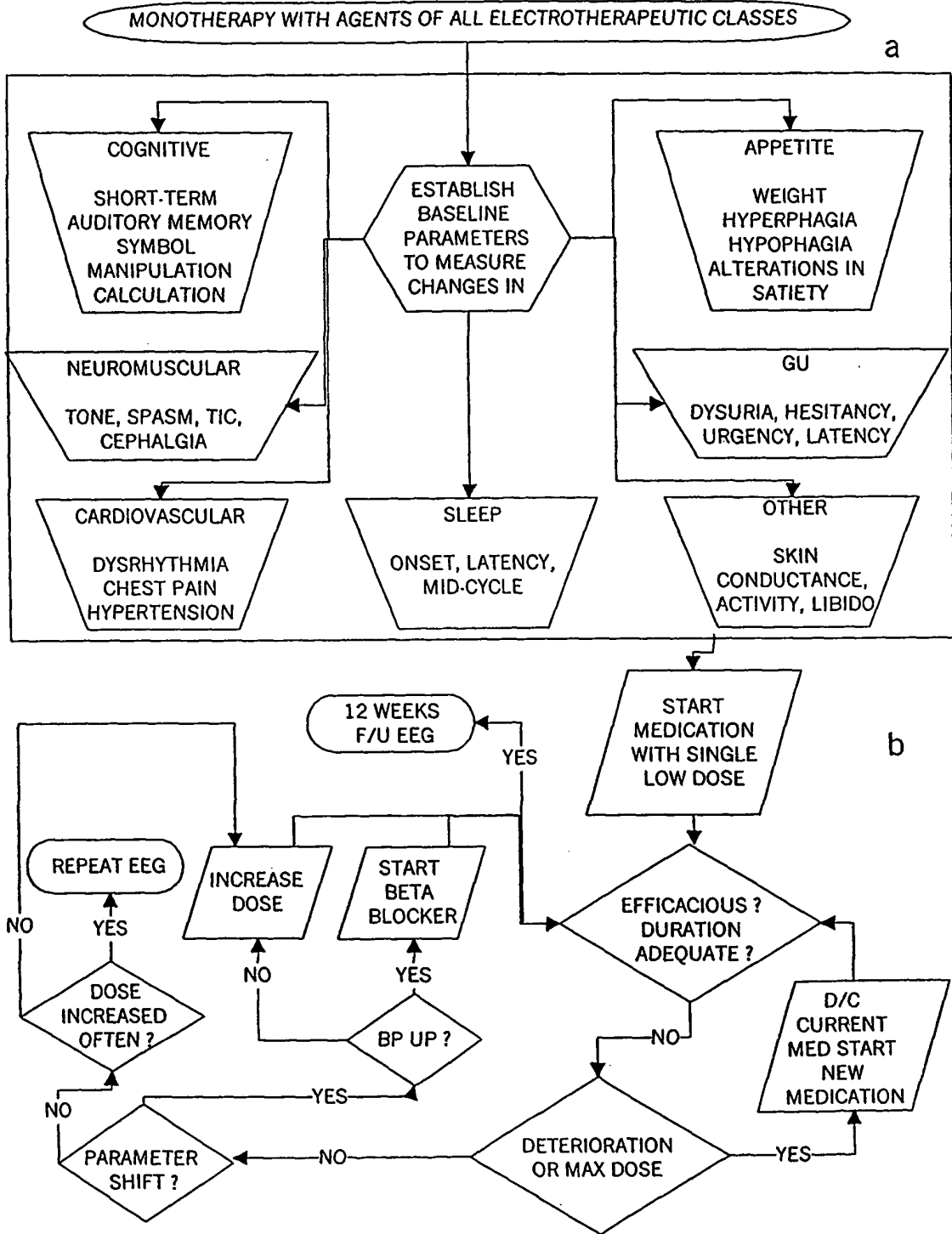


FIGURE 3.2

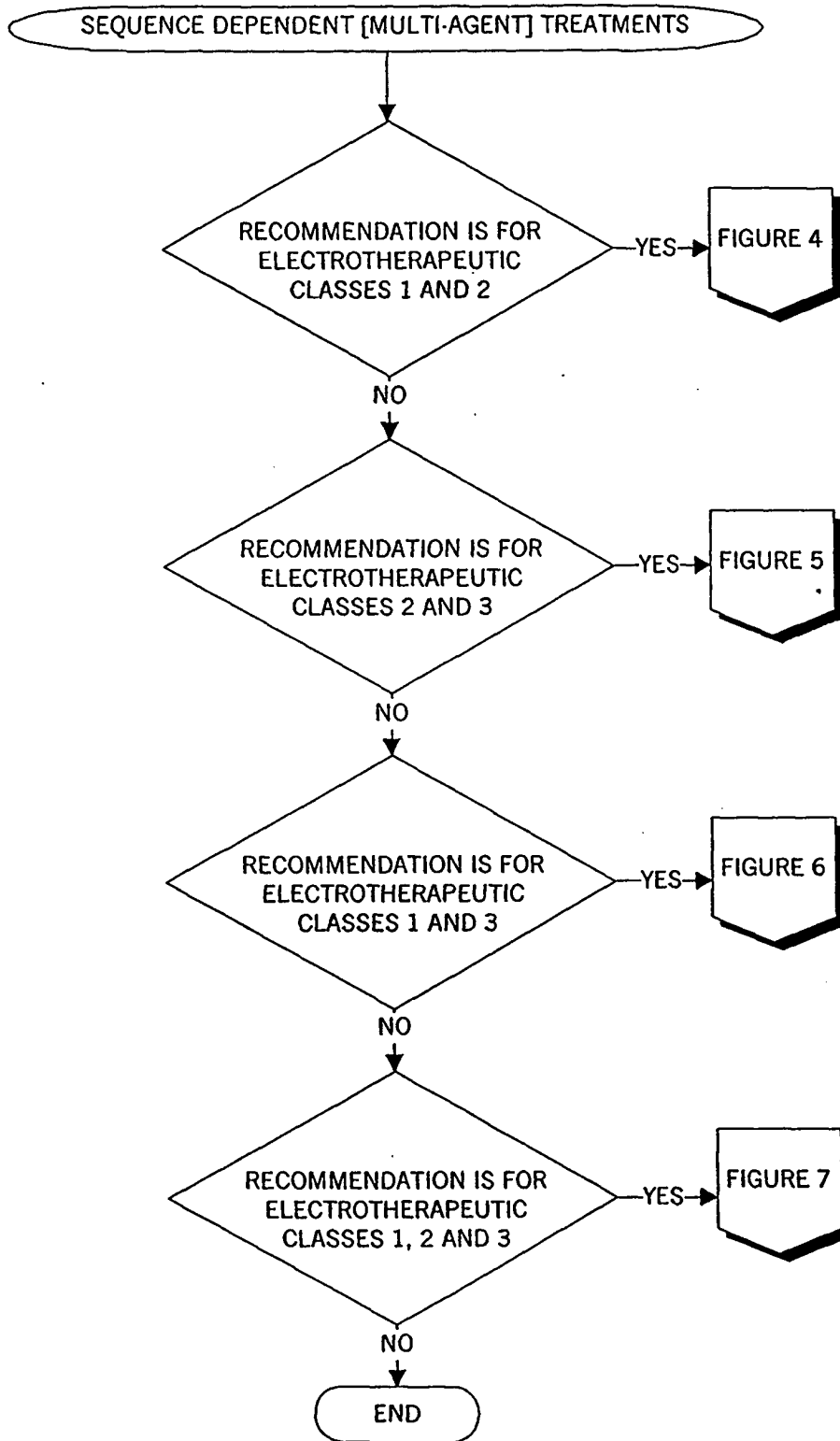
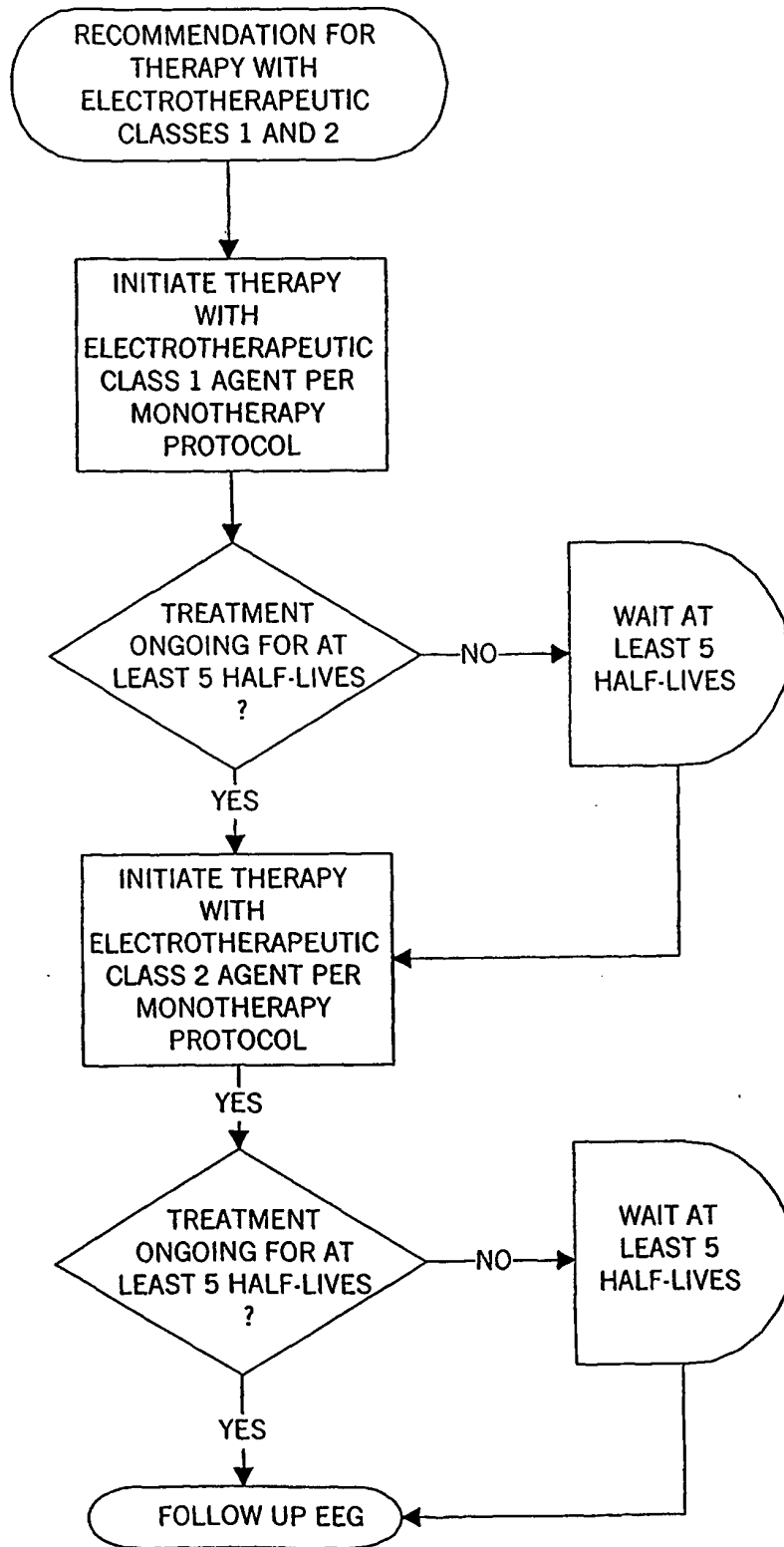


FIGURE 4



**FIGURE 5**

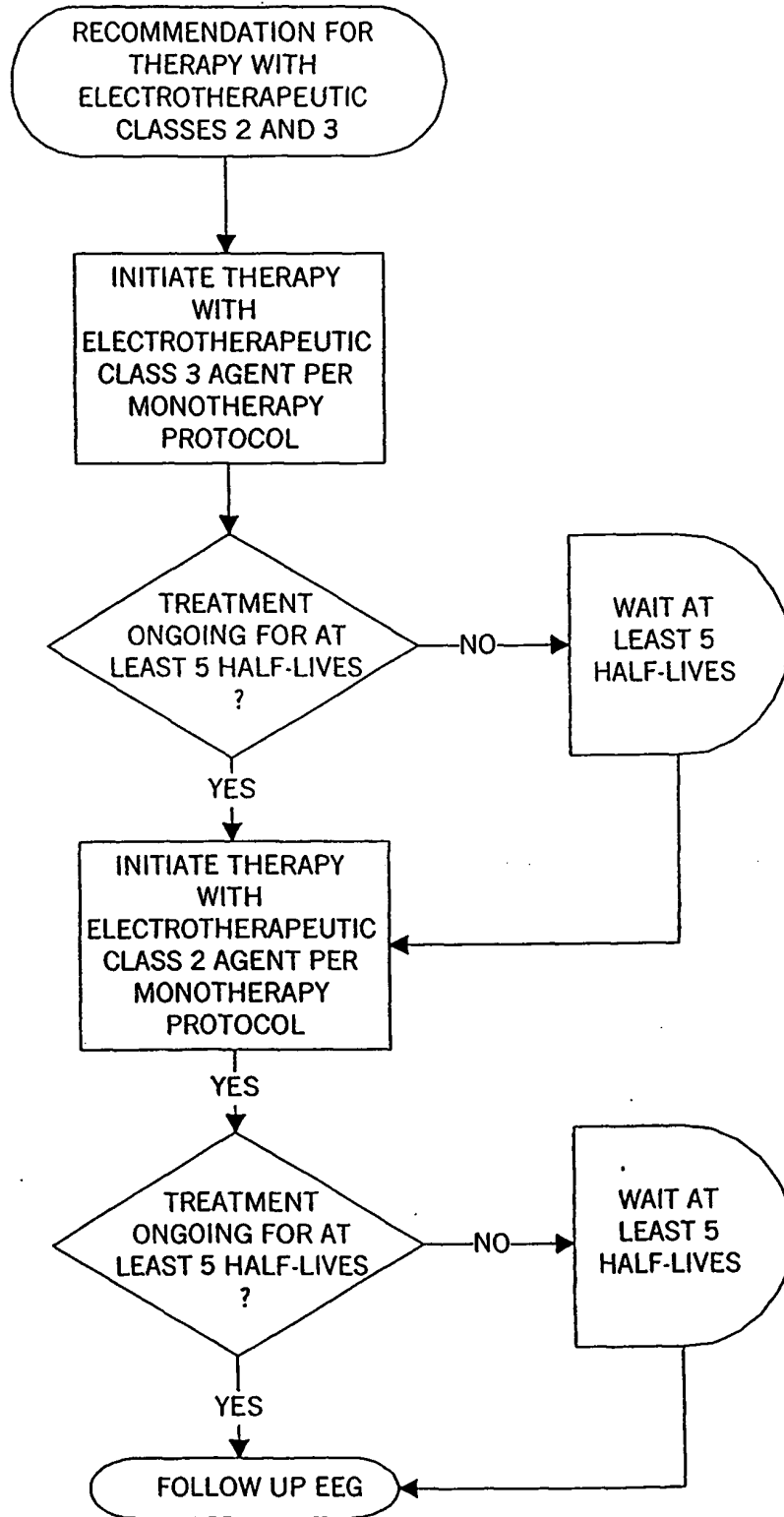


FIGURE 6

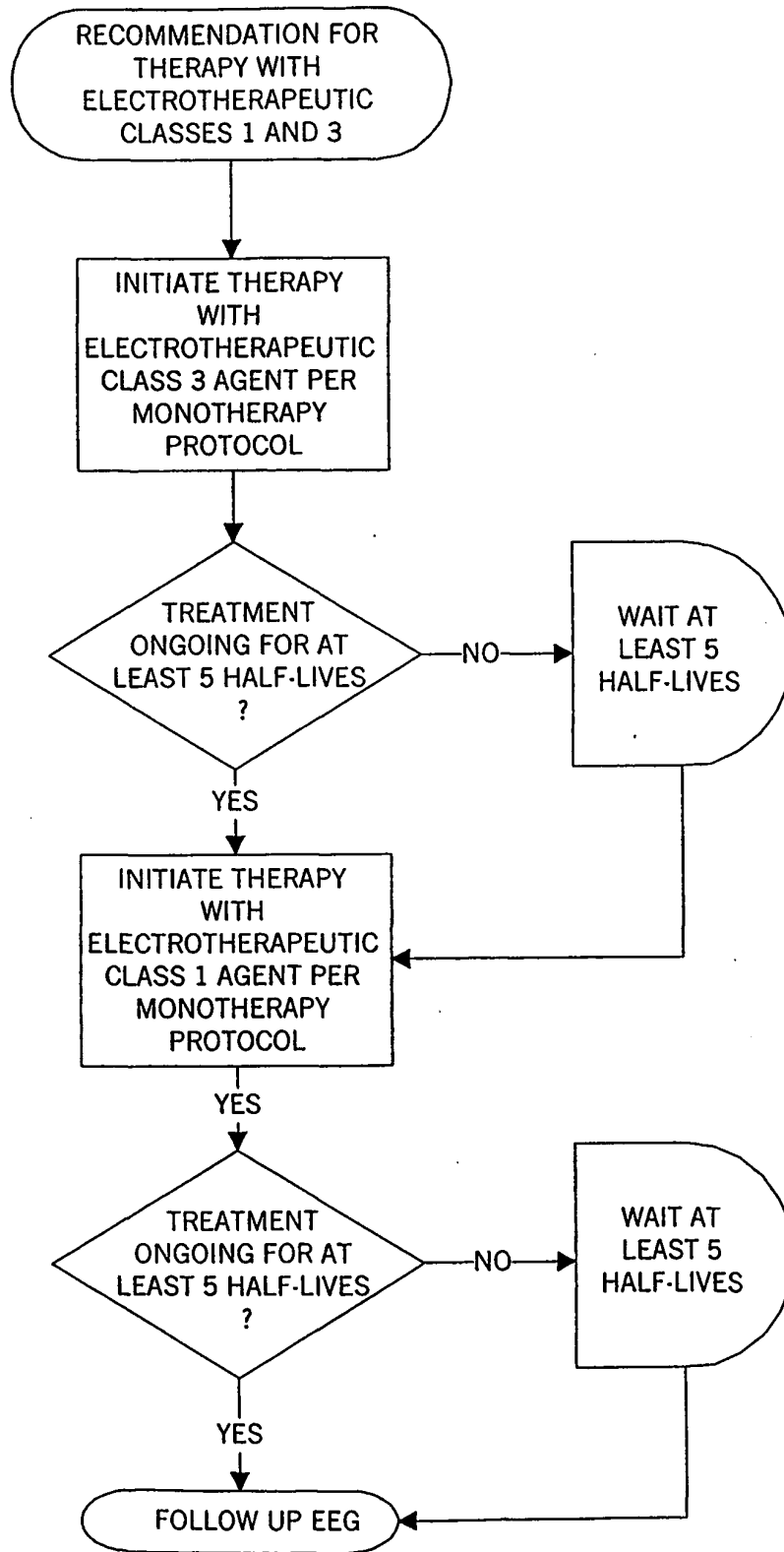


FIGURE 7

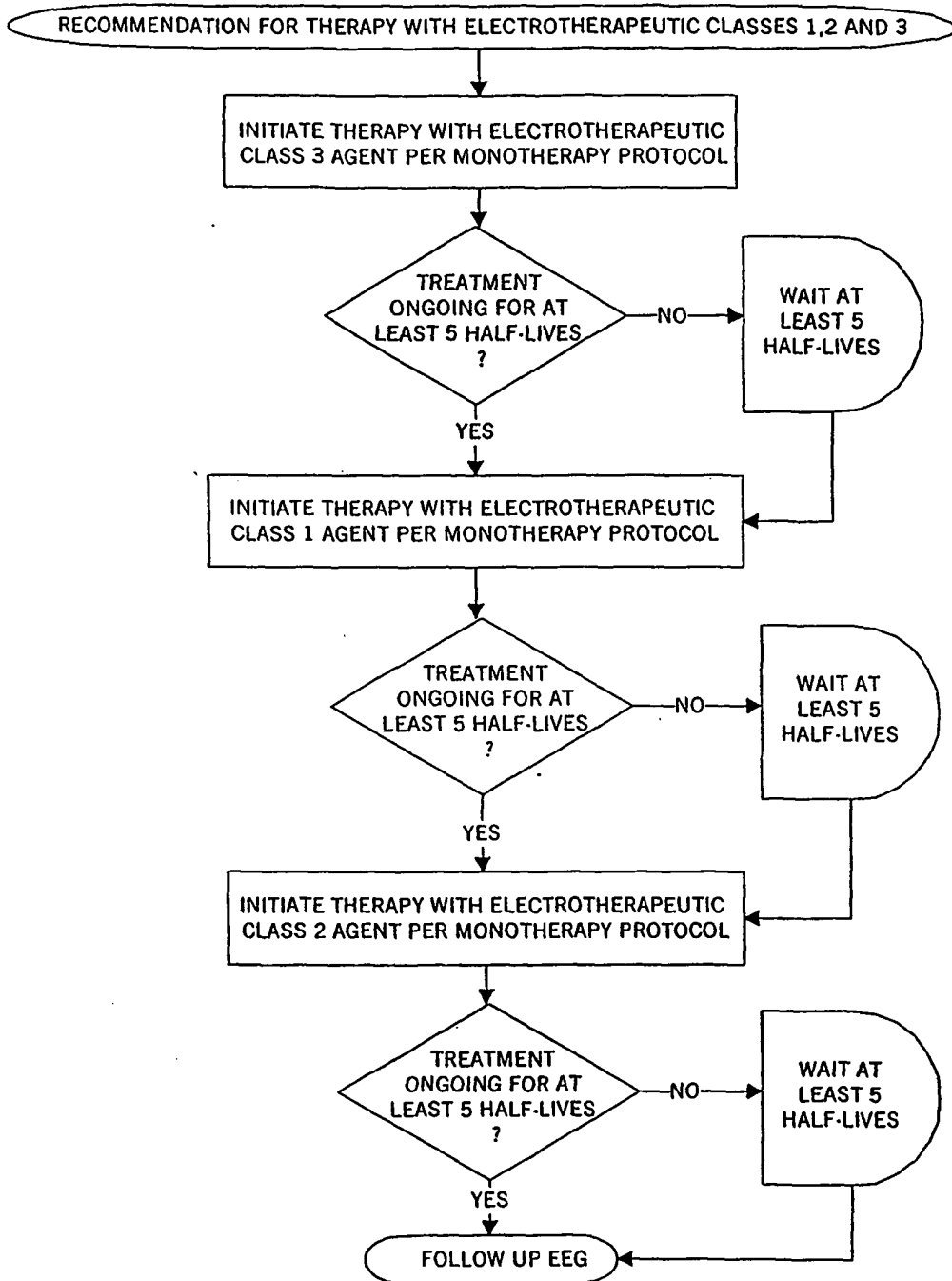


Figure 8  
EEG Medication Prediction Pathway

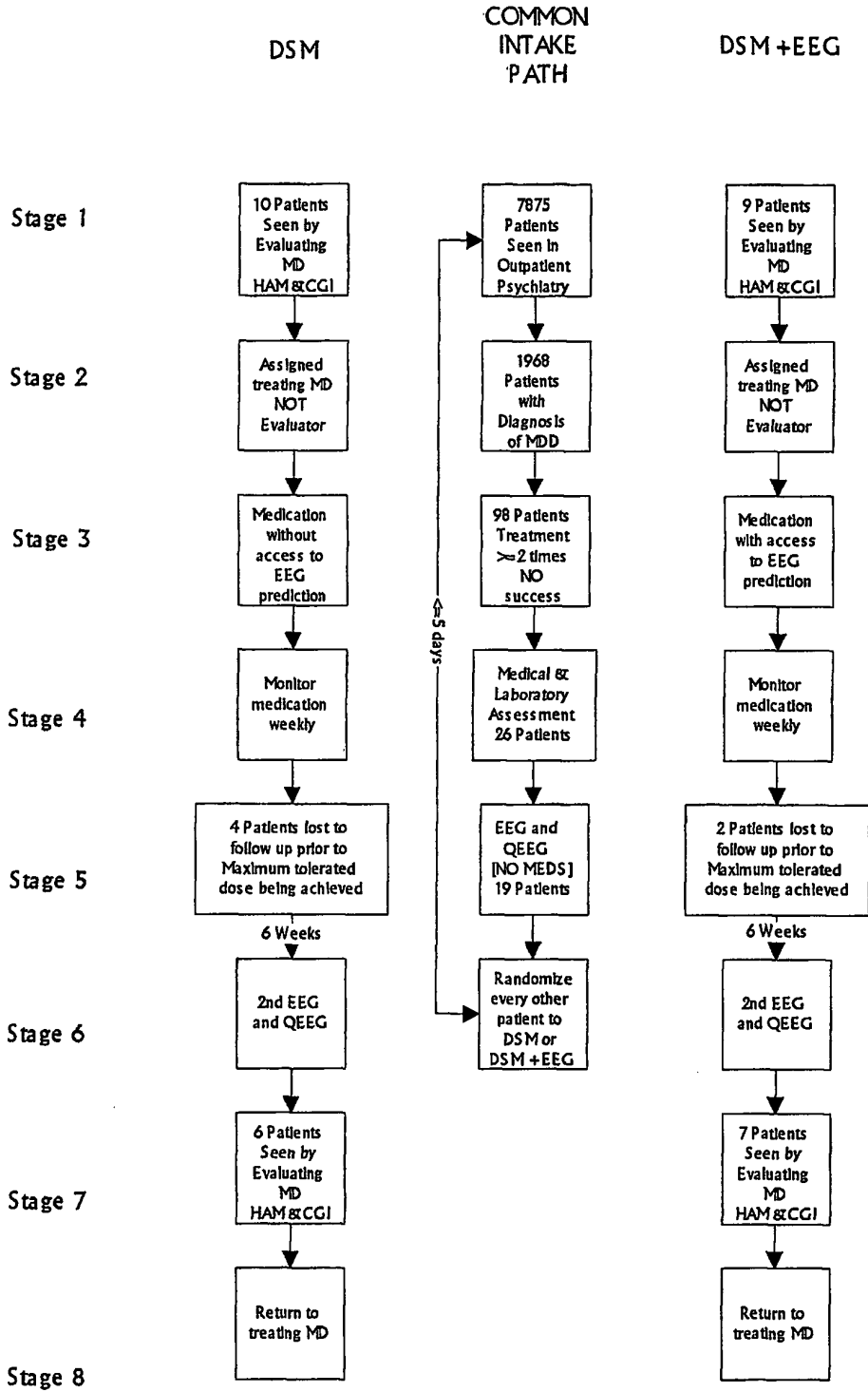


FIGURE 9

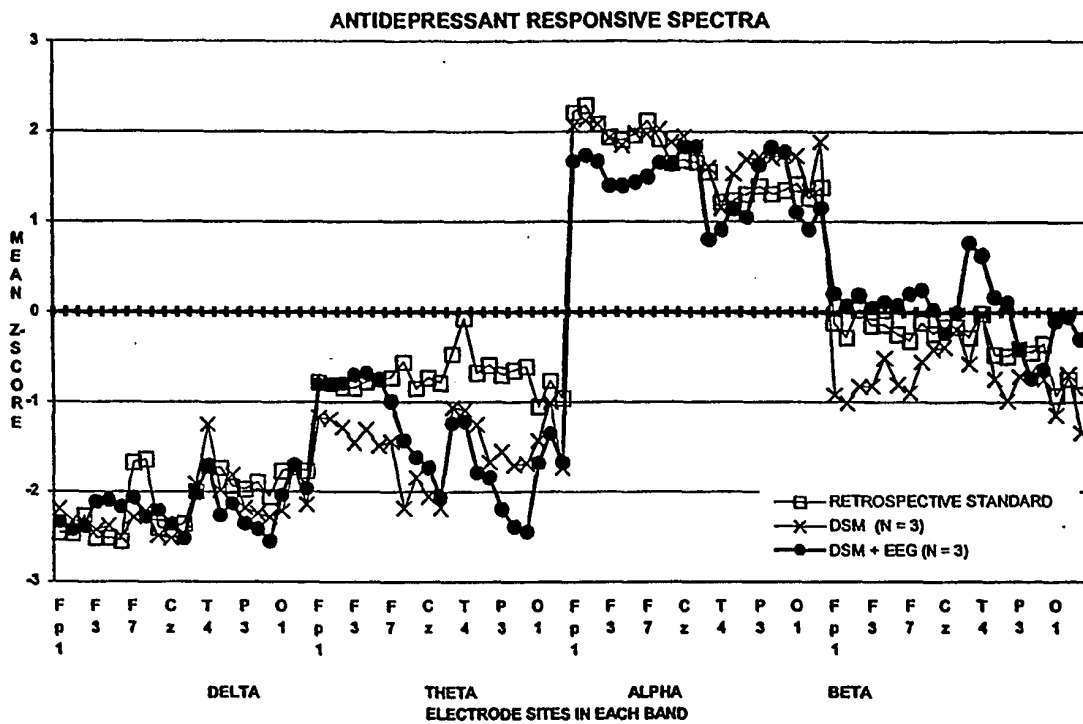


FIGURE 10

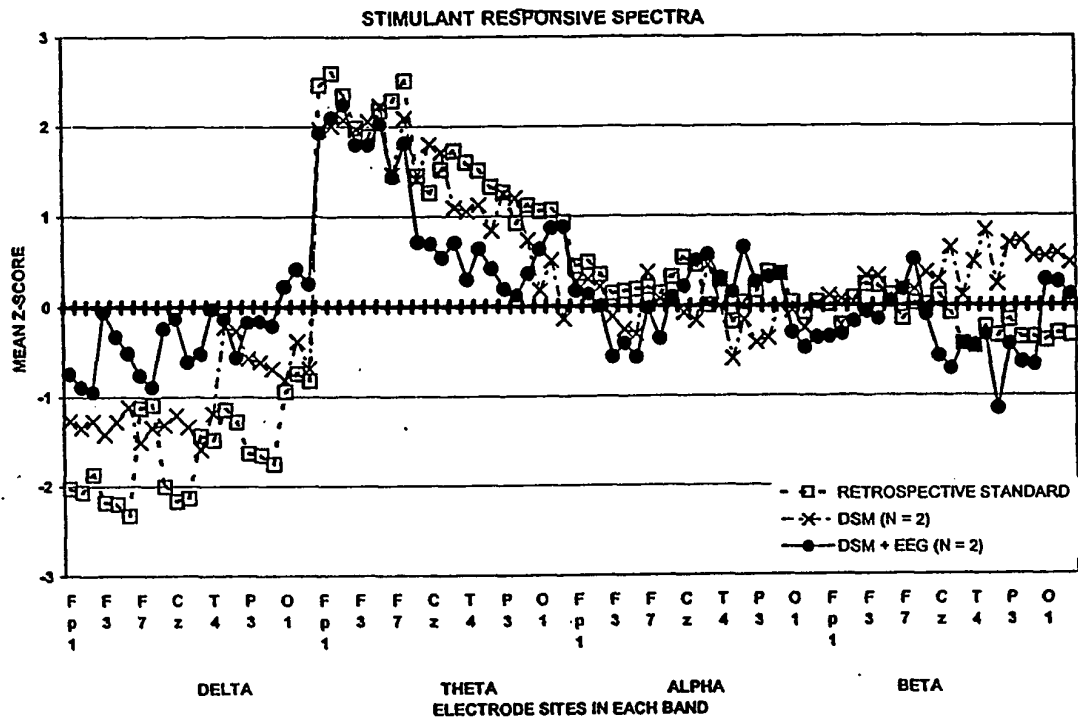


FIGURE 11

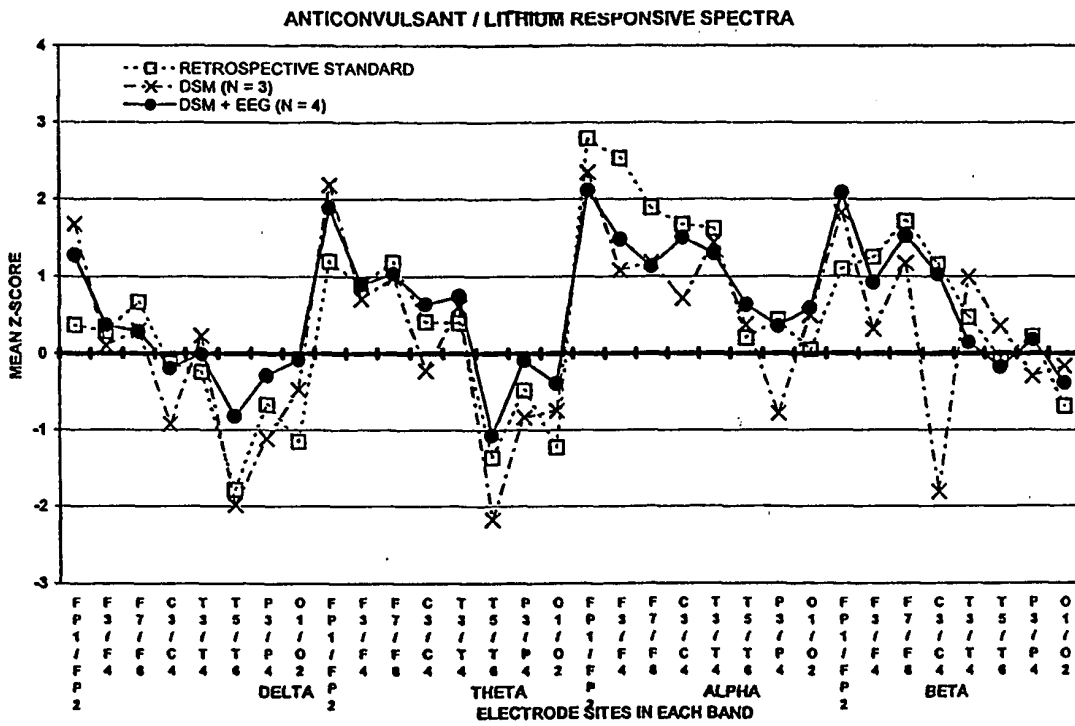


FIGURE 12

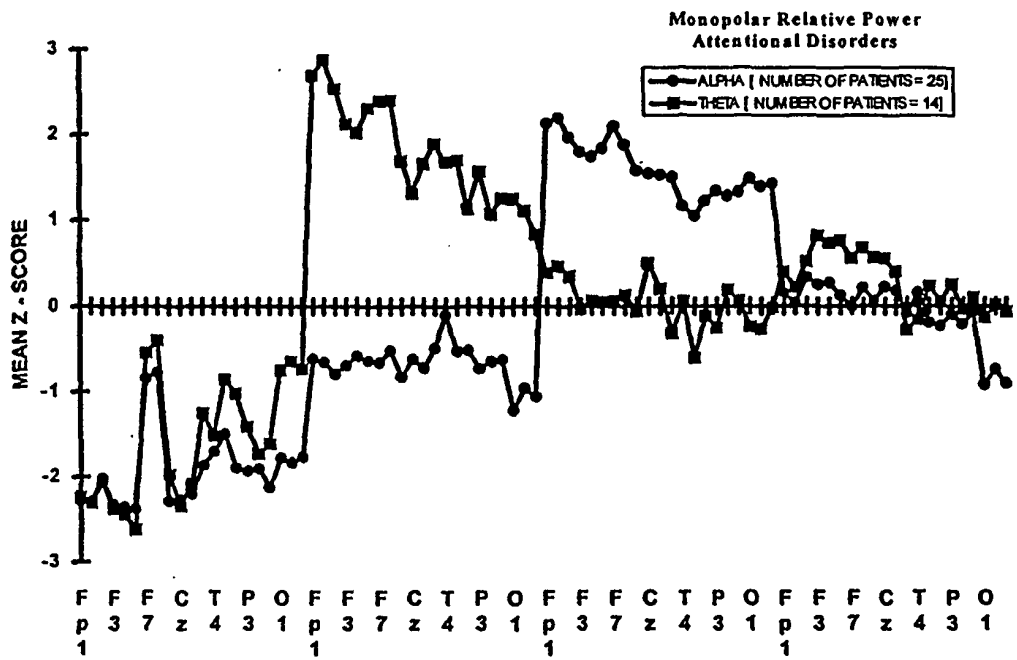


FIGURE 13

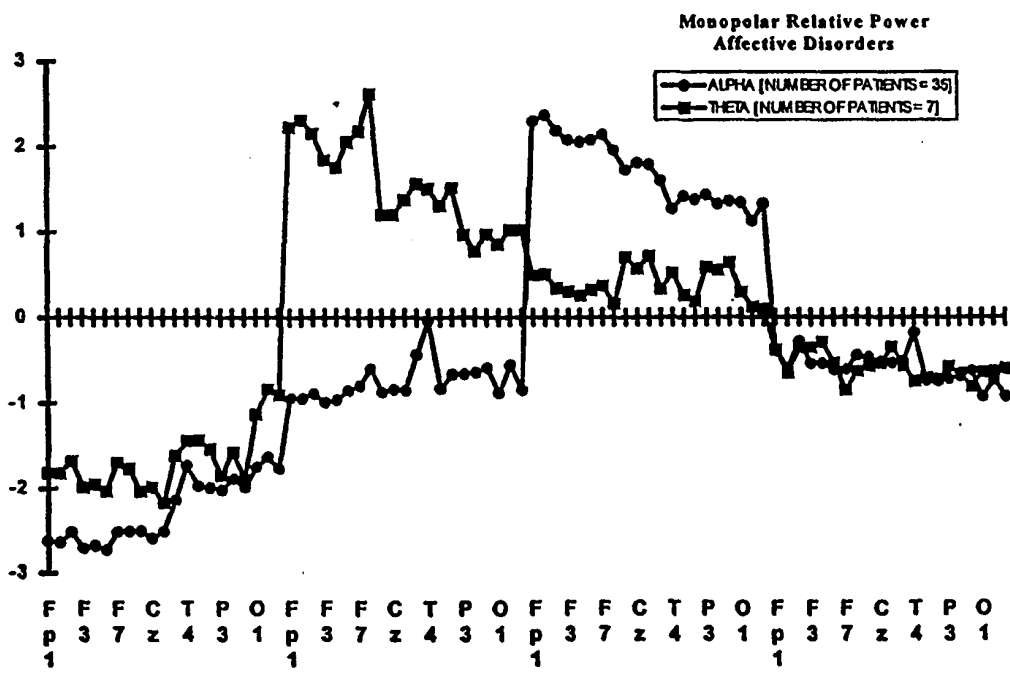
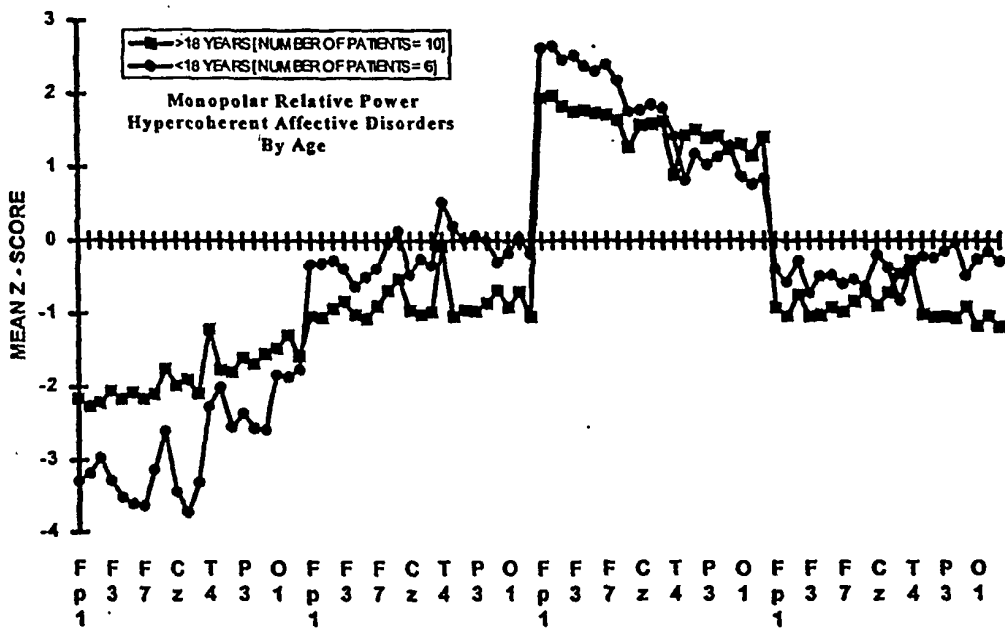


FIGURE 14



## REFERENCES CITED IN THE DESCRIPTION

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专利名称(译)	使用定量eeg分类生理性脑失衡的方法		
公开(公告)号	<a href="#">EP1253853B1</a>	公开(公告)日	2009-06-03
申请号	EP2001908996	申请日	2001-02-09
[标]申请(专利权)人(译)	CNS RESPONSE		
申请(专利权)人(译)	中枢神经系统反应公司		
当前申请(专利权)人(译)	中枢神经系统反应公司		
[标]发明人	SUFFIN STEPHEN		
发明人	SUFFIN, STEPHEN		
IPC分类号	G06F19/00 A61B5/0476 A61B5/048 A61B5/04 A61B5/00 A61B5/0484 A61B5/055 A61B5/11 A61B19/00 A61K31/135 A61K31/19 A61K31/4458 A61K31/55 A61K31/5513 A61K45/00 A61P25/00 A61P25/18 A61P25/28		
CPC分类号	A61B5/0006 A61B5/0476 A61B5/048 A61B5/0484 A61B5/1104 A61B5/16 A61B5/165 A61B5/4833 A61B5/7257 A61B5/7264 A61B5/7275 A61P25/00 A61P25/12 A61P25/18 A61P25/28 G06F19/3456 G06F19/3481 G16H10/60 G16H15/00		
代理机构(译)	MACDOUGALL , DONALD CARMICHAEL		
优先权	09/501149 2000-02-09 US		
其他公开文献	EP1253853A4 EP1253853A1		
外部链接	<a href="#">Espacenet</a>		

摘要(译)

定量脑电图 ( QEEG ) 等神经生理学信息可用于分类, 诊断和治疗生理性脑不平衡的方法, 神经生理学信息还可用于指导心理药物候选药物的临床测试样本选择, 最后, 神经生理学信息可用于 远程评估和治疗具有生理性脑不平衡的患者。

$$12/10 \sum_{10}^1 RMA?1..RMA?n .$$