The Relevance of QEEG to the Evaluation of Behavioral Disorders and Pharmacological Interventions

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ABSTRACT

It has become apparent that the electrical signals recorded from the scalp of healthy individuals under standardized conditions are predictable, and that patients with a wide variety of brain disorders display activity with unusual features. It also early became apparent that centrally active medications produced striking changes in this activity. The application of computerized signal analysis to EEG recordings collected using standardized procedures has made it possible to obtain quantitative descriptions of brain electrical activity (QEEG) in normal individuals and patients with disorders of brain function or structure, as well as quantitative description of the ways in which centrally active medications alter this activity (Pharmaco-EEG or "PEEG"). With the emergence of three-dimensional EEG source localization techniques, it has recently become possible to visualize the mathematically most probable generators of QEEG abnormalities within the brain as well as the neuroanatomical regions where abnormal activity is most altered by efficacious medication.

As QEEG and PEEG have evolved, a vast body of facts has been accumulated, describing changes in the EEG or event-related potentials (ERPs) observed in a variety of brain disorders or after administration of a variety of medications. With some notable exceptions, these studies have tended to be phenomenological rather than analytic. There has not been a systematic attempt to integrate these phenomena in order to build better understanding of how the abnormal behaviors of a particular psychiatric patient might be related to the specific pattern of the deviant electrical activity, nor just how pharmacological reduction of that deviant activity may have resulted in more normal behavior.

This article is an endeavor to provide a more specific theoretical framework for understanding the relationships between the neuroanatomy and neurochemistry of the homeostatic system underlying the regulation of the QEEG, and the mechanisms revealed by Pharmaco-EEG that aid in correcting these illnesses.

A FUNCTIONAL NEUROANATOMICAL/NEUROCHEMICAL MODEL OF THE EEG HOMEOSTATIC SYSTEM

The following is a preliminary attempt to describe a network of neuroanatomical structures whose interactions, mediated by neurotransmitters, not only generate the EEG and ERP but contribute variously to the generation of behaviors and dimensions of the subjective content of momentary experiences. While this model is certainly incomplete and probably erroneous in some details, it nonetheless outlines the skeleton of a conceptual framework that hopefully might clarify our understanding of why certain modulations of experience arise from phasic or tonic changes in the depicted interactions, and how the problems of selecting and optimizing pharmacological interventions might more analytically be addressed.

The EEG is regulated by a homeostatic system involving dynamic interactions among anatomically dispersed brain structures, mediated by neurotransmitters and dependent upon a stable extracellular environment. This regulation produces a distinctive power spectrum at every position on the scalp. Synchronization and coherence among these regions is also regulated. Age-regression equations that describe the lawful evolution of these spectra and cross-spectra across much of the human life span have been published and confirmed in many different countries, indicating that healthy, normally functioning human individuals of many different ethnic or cultural backgrounds generate EEG activity that is accurately described by these rules. Developmental, psychiatric and neurological disorders produce and are caused by deviations from homeostasis. Numerous papers now confirm that brain electrical activity of patients with such disor-

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ders usually deviates from these normative patterns, and patients with different diagnoses display distinctively deviant patterns. Replicated discriminant functions with acceptable sensitivity and specificity have been reported for a variety of disorders that serve as a useful adjunct to diagnosis, prognosis and treatment selection.[1,2]

As the field of Pharmaco-EEG has evolved, it has become evident that different psychotropic agents produce distinctive profiles of changes in the QEEG arising from identifiable brain regions, and tend to be effective in psychiatric patients with essentially the opposite profiles of QEEG deviance. Correction of QEEG deviations results in normalization of disorders.[3,4] Abundant evidence also exists that within large groups of patients who are diagnostically homogeneous by clinical criteria, heterogeneous subtypes with distinctive QEEG profiles can be identified who respond differentially to pharmacological treatments.[2,5-10] A variety of three-dimensional source localization methods have applied the inverse solution to enable visualization of the most probable neuroanatomical generators of QEEG abnormalities detected from scalp recordings, superimposed upon brain slices from a probabilistic MRI brain atlas (QEEG source localization methods).[11,12] Applications of these methods, now validated in numerous multimodal brain imaging studies, have revealed consistencies in the regional electrophysiological abnormalities associated with particular psychiatric disorders.

The availability of well-replicated reliable normative QEEG data, development of discriminant functions with acceptable sensitivity and specificity, construction of databases with adequate subtyping information, QEEG source localization methods to assess the level of brain activity in brain regions considered to be critically relevant to behavioral disorders before and after medication, together with the availability of compact portable EEG/ERP data acquisition hardware and sophisticated QEEG data analysis and source localization software that can function in a laptop computer, constitute a new neurobiological imaging technique that can be expected to revolutionize treatment of developmental, neurological and psychiatric disorders in the near future. Use of these methods to evaluate the correction of QEEG deviations in serial studies potentially provides a unique and invaluable sensor to aid diagnosis, select treatment, confirm bioavailability of a specific drug, identify appropriate medication and minimize undesirable side-effects.

ORIGINS AND FUNCTIONAL RELEVANCE OF RHYTHMIC EEG OSCILLATIONS

EEG activity has conventionally been described in terms of a set of wide frequency bands, usually defined as delta (1.5 to 3.5 Hz), theta (3.5 to 7.5 Hz), alpha (7.5 to 12.5 Hz), beta (12.5 to 25 Hz) and gamma (25-50 Hz). Factor analysis of the EEG power spectra has found a similar principal component structure, suggesting that relatively independent functional systems produce these rhythms. The observed predictability of the EEG power spectrum arises from regulation by anatomically complex homeostatic systems involving large regions of the brainstem, thalamus, limbic system and cortex and utilizing all neurotransmitters.[13,14]

"Pacemaker neurons" throughout the thalamus interact with the cortex and nucleus reticularis to oscillate synchronously in the alpha frequency range. Efferent projections of these oscillations modulate synchronized neuronal activity also generated by a dipole layer in widely distributed cortical centers, producing the dominant alpha rhythm. Nucleus reticularis can hyperpolarize the cell membranes of thalamic neurons, slowing this rhythm into the theta range, and diminishing sensory throughput to the cortex. Theta activity is also generated in the limbic system by pacemakers in the septal nuclei, which can be inhibited by entorhinal and hippocampal influences.[15] Delta activity is believed to originate in neurons in deep cortical layers and in the thalamus, normally inhibited by input from the ascending reticular activating system (ARAS) and the nucleus basalis of Meynert. Delta activity may reflect hyperpolarization and inhibition of cortical neurons, resulting in dedifferentiation of neural activity. Activity in the beta band reflects cortico-cortical and thalamo-cortical transactions related to specific information processing. Gamma activity reflects cortico-thalamo-cortical and cortical-cortical reverberating circuits engaging inter-neurons and pyramidal neurons, which may play an important role in perception.

Sleep-wake cycles depend upon interactions involving the pontine and mesencephalic reticular formation, locus ceruleus, the raphe nuclei, thalamic nuclei, and the nucleus of Meynert. In essence, the neurons of the thalamus manifest two intrinsic states: When hyperpolarized to a certain level, they enter a bursting mode in which they do not relay information to the cortex and other brain regions, and sleep ensues. When in this state, the EEG manifests large delta waves, perhaps reflecting the release of cortical neurons mentioned above, normally inhibited by the influences of the ARAS. For wakefulness to take place, the thalamocortical neurons must be restored to a state in which throughput of afferent sensory information to the cortex is again possible. A salient role in this state change is played by cholinergic influences of the ARAS and the nucleus of Meynert.

An oversimplified proposal follows for how the initiation of voluntary movement is accomplished and the hypothesized QEEG correlates. A motor plan is formulated by the prefrontal cortex as an adaptive response to the contextual interpretation of current environmental stimulation, indicated by an increase in prefrontal-parietal gamma coherence. Performance of this plan is initiated via the motor cortex to the thalamic motor relays VA and VL, accompanied by an increase in beta and gamma activity in frontal and motor regions. However, movement is blocked because the motor relays are tonically inhibited by the internal globus pallidus (GPi) and the subthalamic nucleus. At the same time, infor-

mation about the multisensory environment is projected from the neocortex to the putamen (accompanied by an increase in posterior beta activity) and about the relevant context from the prefrontal cortex to the caudate in the basal ganglia, via the association nuclei of the thalamus (accompanied by an increase in cortical theta activity). When the GPi is inhibited because the caudate is sufficiently activated by the cortex, and the external globus pallidus (GPe) is excited due to readout via the amygdala from the endogenous system (accompanied by an increase in cortical theta activity), the tonic inhibitions of the motor relay nuclei VA and VL by GPi and the subthalamic nucleus are thereby released, allowing the movement to be implemented by the putamen in concert with the cerebellum. When the caudate is activated by influences from the cortex in the absence of limbic readout, GPe is inhibited, thereby disinhibiting the subthalamic nucleus which then blocks VA and VL and inhibits movements, while cortical alpha persists.

EEG regulation depends upon this extensive neuroanatomical homeostatic system. Structures in that system play an important role in a wide variety of behavioral functions. Thus, behavioral implications are inherent in any detailed evaluation of disturbances from this homeostatic regulation, whether transient as in anesthesia, persistent as in coma, or phasic as in developmental and psychiatric disorders. Major elements of this system, neurotransmitters mediating their interactions and their putative behavioral contributions, are schematized in Figure 1, discussed further by John.[16] Examination of this functional diagram of the homeostatic system makes clear that disruptions of many different local activities might disturb some final common behavioral pathways. Thus, heterogeneous pathophysiological causes may exist for a particular behavioral syndrome that is labeled as a single "disorder."

OPERATIONAL MODES OF THE HOMEOSTAT

A subject who is drowsy will display an EEG dominated by slow waves, perhaps in the theta frequency range, indicating de-differentiation and increased synchrony of cortical neurons disengaged from information processing. This slowing of the alpha rhythm arises from hyperpolarization of the alpha pacemakers, reflecting GABAergic inhibition of thalamic pacemakers by nucleus reticularis (NR), which can be initiated by glutamatergic influences from the cortex or diminished input from the ARAS. Activation of the mesencephalic reticular formation (MRF) by altered environmental stimuli results in inhibition of NR by cholinergic and serotonergic mediation via the ARAS. This inhibition by the ARAS releases the thalamic cells from inhibition by NR, and flow of information through the thalamus to the cortex is facilitated. The dominant activity of the EEG becomes more rapid, with return of alpha and higher frequency beta activity, reflecting differentiation of cortical neurons and resumption of cortical-cortical interactions. However, as an alternative result of cortical influences, dopaminergic striatal projections can inhibit the MRF, enabling differential inhibition of thalamic neurons by NR to occur. These reciprocal interactions between the ARAS, NR, cortex and the thalamocortical relay neurons provide a mechanism whereby the brain dynamically filters and selects permissible stimuli to reach cortical centers. The flux of activity through these pathways constitutes a temporal pattern of synchronized input from the exogenous system to the axosomatic synapses of cortical pyramidal neurons in lower layers of the cortex. In parallel, collateral pathways from MRF enter the limbic system, which is intimately involved in the storage and retrieval of memories and contributes hedonic valence and emotional tone to the momentary brain state. Influences from the limbic system impinge upon the cortex via non-sensory specific pathways, and are the major input from the endogenous system to the apical dendrites of cortical sheet of pyramidal neurons, in upper layers of the cortex. Interactions between the exogenous and endogenous systems are further discussed below in Section 4.

Prior to the initiation of voluntary movement, a motor plan is formulated by the prefrontal cortex as an adaptive response to the contextual interpretation of current environmental stimulation, indicated by an increase in prefrontal-parietal gamma coherence. Performance of this plan is initiated via the motor cortex to the thalamic motor relays VA and VL, accompanied by an increase in beta and gamma activity in frontal and motor regions. However, movement is blocked because the motor relays are tonically inhibited by the internal globus pallidus (GPi) and the subthalamic nucleus. At the same time, information about the multisensory environment is projected from the neocortex to the putamen (accompanied by an increase in posterior beta activity) and about the relevant context from the prefrontal cortex to the caudate in the basal ganglia, via the association nuclei of the thalamus (accompanied by an increase in cortical theta activity). When the GPi is inhibited because the caudate is sufficiently activated by the cortex, and the external globus pallidus (GPe) is excited due to readout via the amygdala from the endogenous system (accompanied by an increase in cortical theta activity), the tonic inhibitions of the motor relay nuclei VA and VL by GPi and the subthalamic nucleus are thereby released, allowing the movement to be implemented by the putamen in concert with the cerebellum. When the caudate is activated by influences from the cortex in the absence of limbic readout, GPe is inhibited, thereby disinhibiting the subthalamic nucleus, which then blocks VA and VL and inhibits movements, while cortical alpha persists.

COINCIDENCE DETECTION BETWEEN EXOGENOUS AND ENDOGENOUS ACTIVITY

Experimental data suggest that coincidence detection between input of information about the environment by an exogenous sensory specific system and readout of relevant memories from an endogenous nonsensory specific

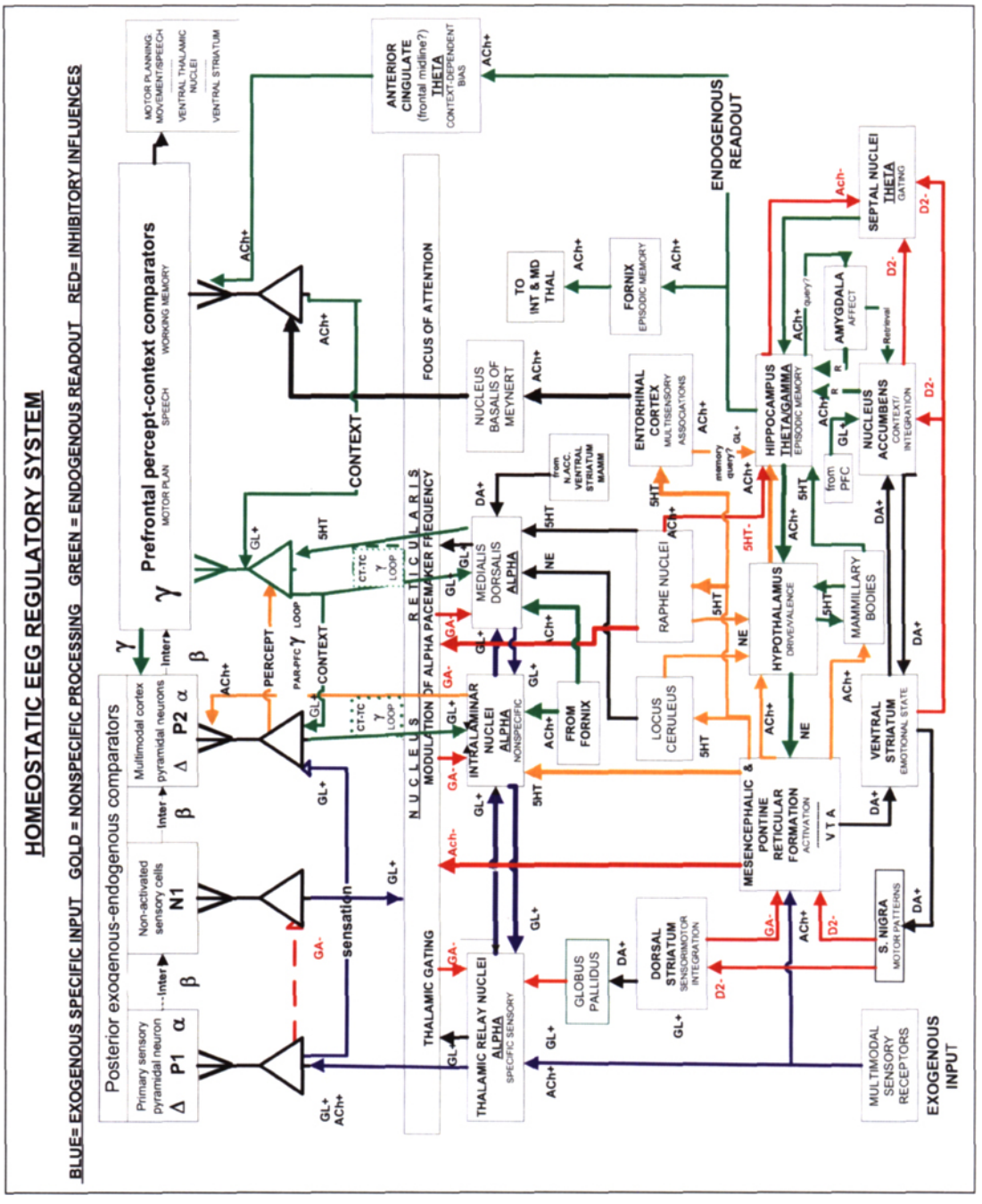

Figure 1.
Oversimplified scheme of the neuroanatomical structures and neurotransmitters comprising the homeostatic system, which regulates the electrical rhythms of the brain. The diagram assigns putative roles in the generation of EEG oscillations in the delta, theta, alpha, beta and gamma frequency ranges and to components of event related potentials. The behavioral functions to which various regions are believed to contribute are tentatively indicated for some of these brain structures (see text for details). Elements of the exogenous system processing sensory specific inputs are encoded as blue, elements performing nonsensory specific processing are encoded as gold, inhibitory influences are encoded as red, and endogenous processing of readout from the memory system is encoded as green. Reprinted from "Progress in Brain Research the Boundaries of Consciousness: Neurobiology and Neuropathology," vol 150. E. Roy John, "From synchronous neuronal discharges to subjective awareness?" 2005: 143-172, with permission from Elsevier.

system, evaluated by a cortical neuronal comparator, is critical for perception and adaptive cognitive behavior. Electrical stimulation of the somatosensory cortex or of the nonsensory specific thalamic nucleus centralis lateralis (CL), appropriately delayed to coincide with arrival of the nonsensory specific component (P200) of the ERP evoked by a mild electrical shock to the wrist, could block subjective awareness of the shock in patients' conscious during brain surgery.[17,18] In comatose patients, absence of P200 reflects severity of traumatic brain injury,[19] and the return of P300 is predictive of recovery from coma.[20]

Exogenous inputs encoding complex environmental stimuli are widely dispersed by sensory specific thalamocortical projections to basal axosomatic synapses in layers 4-5 of sheets of pyramidal neurons throughout the neocortex. Endogenous inputs are dispersed to the apical axodendritic synapses of these cells in layer 1, via the nonsensory specific diffuse projection system of the thalamus. Pyramidal neurons act as comparators, detecting temporal coincidence of inputs to apical and basal synapses.[21] Concurrent stimuli delivered to both apical and basal regions elicited clearly enhanced firing of the neuron, with a back-propagated discharge in the beta (~15-20 Hz) to gamma frequency range (~50 Hz). "Top-down" axodendritic input may modulate the saliency of a "bottom-up" axosomatic signal, changing the neuronal output from a few spikes into a burst.[22] Using voltage sensitive dyes upon brain slices, direct electrical microstimulation of a specific thalamic relay nucleus (VB) caused a visible moderate activation in layer 5 of the corresponding sensory cortex and of a nonsensory specific nucleus (CL) caused moderate activation in cortical layer 1. Coincident electrical simulation of both the exogenous and endogenous systems yielded a burst of cortico-thalamo-cortical gamma oscillations, providing strong feedback to the thalamic regions from which the stimuli had originated.[23]

The dominant contributions to the endogenous system come from an entorhinal-hippocampal-septal circuit, shown in Figure 2, that is involved in the storage and retrieval of episodic memories. Affective valences are attached to these episodic memories by associative linkages with other limbic regions, especially the amygdala and nucleus accumbens. Septal-hippocampal interactions modulate the activity of circuits which generate EEG rhythms in the theta band that are projected to the cortex via nucleus basalis, the cingulate gyrus and the medialis dorsalis nucleus of the thalamus. When this circuit is activated, gamma oscillations arise in the hippocampus, become phase locked to the theta and are projected to the cortex. Thus, cortical theta may reflect either under-activation of the ARAS or activation of affective states, memories or related cognitive processes.

These reciprocal cortical-subcortical interactions can diminish, modulate, or actually block the flow of sensory information to the cortex and, together with the contribution from the limbic system of retrieved memories most relevant to the current environment, play an important role in focusing attention and determining mood. This system can have a decisive influence on selective perception. This continuous interaction between the exogenous and endogenous systems constructs the "remembered present." In view of the dependence of both systems upon the delicate balance and relative abundance of multiple neurotransmitters, the relevance of these interactions to psychiatric disorders becomes self-evident.

The coincidence detection system described above, dispersed throughout the cortex, serves as a comparator between present multimodal exogenous input from the environment and input from the "hedonic system," which integrates endogenous activity reflecting present state, working memory, relevant episodic experience, motivation and idiosyncratic individual values (reviewed by John[16]). The readout from the value system could arise from mechanisms generating experiential associations activated by collateral inputs from the just previous complex sensory stimuli, a process enabling the past to "leap-frog" into the future. These coincidence detectors might act as a filter, segregating random neural "noise" or unimportant elements of the complex stimuli from enhanced neural discharges to extract "signal" of informational value. This synthesis of percepts from the interaction between the past and the present is mediated by a wide variety of neurotransmitters. Adaptive brain functions, often disrupted in psychiatric illnesses, are critically dependent upon the availability of many substances and the integrity of interactions among many regions. Consideration of the systems depicted in Figures 1 and 2 makes it apparent that many sets of similar behavioral symptoms in a group of patients classified diagnostically as homogenous can arise from heterogeneous pathophysiological causes. Subtyping based upon QEEG profiles as well as clinical symptomatology, together with consideration of the underlying neurophysiological interactions and mediating neurotransmitters and the processes that control their synthesis and metabolism, may be of critical utility to better rationalize pharmacotherapy.

CONTRIBUTION TO PERCEPTION OF ENDOGENOUS READOUT FROM MEMORY

It has been proposed that oscillations from this spatially dispersed multimodal comparator converge as synchronous cortico-thalamo-cortical loops, engaging regions of thalamus and cortex in coherent reverberation in the frequency range of the gamma rhythm (25-50 Hz), binding the distributed fragments to play an essential role in perception[23-30] and reflected by induced long-distance synchronization of gamma oscillations.[24,26,31]

Perception is an active process in which a multisensory "exogenous" system encodes the configuration of stimuli in the peripheral environment and transmits this information for central analysis and evaluation. Processing of

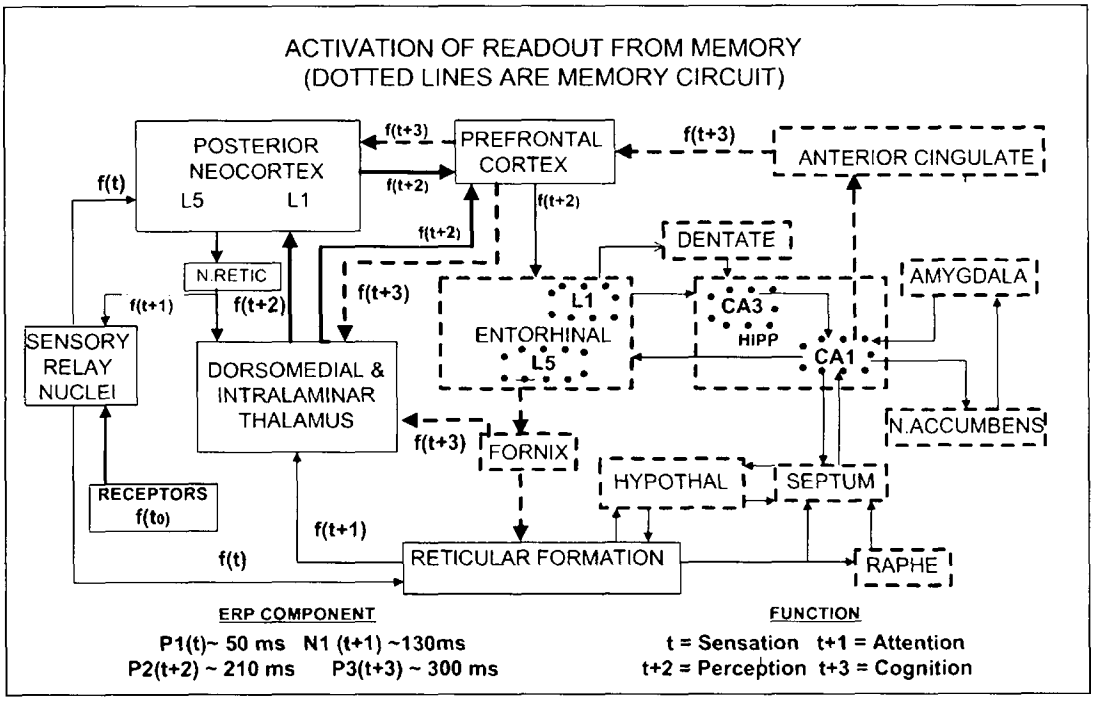

Figure 2.
Simplified scheme of the neurophysiological transactions resulting in the automatic readout of relevant memories from neuroanatomical structures of the endogenous memory storage and retrieval system, and their relation to major components of the event related potentials (see text for details). Reprinted from "Progress in Brain Research the Boundaries of Consciousness: Neurobiology and Neuropathology." vol 150. E. Roy John, "From synchronous neuronal discharges to subjective awareness?" 2005: 143-172, with permission from Elsevier.

this information is modulated strongly by "endogenous" influences representing readout of the relevant recent and episodic past and present state, which place the immediate environmental input into context and enable the individual to generate predictions and expectations about future stimuli. This process is envisaged to occur continuously in parallel multiplexed and multimodal channels, such that the past and the present are inseparably merged in every update of the microstate or perceptual frame. The sequential steps in this process of construction of perception can be derived from our knowledge of "mental chronometry" inferred from psychophysiological ERP research.

While subjective experience appears to be continuous, perception is actually discontinuous, parsed into "perceptual frames."[32] Psychological,[33] electroencephalographic[34] and magnetoencephalographic[35] studies concur in estimating the duration of these frames or "microstates" as about 80-100 milliseconds. An "event-related potential" (ERP) can be conceptualized as an approximation of a sequence of such frames, extracted from one channel by repetitive phase-locked sampling of the continuously ongoing neurophysiological processing of a sensory stimulus configuration. ERP studies provide insights into the events in the brain that take place within one of these sequences and are a potential source of insights into possible remediation of psychiatric disorders by judicious pharmacological interventions. Latencies of ERP components have been correlated with stages of information processing, and successive peaks correspond to a) sensory activation, b) detection of sensation, c) perceptual identification of the information, d) cognitive interpretation of the meaning of the input, e) linguistic encoding of that concept, and f) organization of adaptive reactions.

In Figure 1, the endogenous retrieval system was schematized above by the green arrows indicating interactions between particular brain regions. The exogenous-endogenous interactions comprising the perceptual process are further schematized in Figure 2, conceptualizing evaluation of information hypothetically as sequential stages of registration of sensory input, focusing of attention, perception of the multimodal stimuli and cognitive interpretation of the significance or "meaning" of the input, in the following manner: $\mathbf{f(t_0)}$ Inputs from multimodal sensory receptors activated by a complex environmental scene are encoded as time series, $\mathbf{f(t_0)}$, of nonrandomly synchronized discharges in multiplexed parallel channels of afferent pathways, projecting to sensory specific thalamo-cortical relay (TCR) nuclei of every sensory modality.

f(t) At time **t**, volleys of synchronized outputs from multimodal sensory specific TCR nuclei re-encode **$f(t_0)$** and are propagated as a modified time series, **f(t)**, of non-randomly synchronized exogenous inputs to the lower layers of the sheet of pyramidal neurons dispersed throughout cortical ensembles of feature detectors. Activation of basal synapses of pyramidal neurons in cortical Layer 5 causes the positive ERP component **P1** with latency about 80-100 ms, reflecting initial registration of fragments of sensation. Corresponding synchronized volleys from the TCR nuclei and collateral pathways transmit the modified time series, **f(t)**, to the reticular formation in the brainstem where it is further modulated to reflect the arousal level.

f(t+1) At time **t+1**, efferent volleys from sensory cortical regions instruct nucleus reticularis to modulate the TCR neurons to focus attention by raising the threshold of those pathways that did not significantly contribute to the ascending volley of synchronous activity received at time **t**. These corticofugal volleys cause the ERP component **N1** at about 130 ms. At the same time, the ascending reticular activating system (**ARAS**) sends the time series **f(t+1)** to the nonsensory specific intralaminar and dorsomedial nuclei of the thalamus and to the raphe nucleus and structures of the limbic system.

f(t+2) At time **t+2**, the intralaminar nuclei send the non-randomly synchronized time series **f(t+2)** modified by the ARAS to the apical synapses of cortical Layer 1, enhancing the excitability of pyramidal neurons in which coincidence detection occurs. This coincidence causes the ERP component **P2** at about 210 ms, accompanied by backpropagation of reverberatory cortico-thalamo-cortical gamma activity. The time series **f(t+2)** is rapidly transmitted from posterior cortical regions and converges with **f(t+2)** from the dorsomedial thalamic nucleus upon the prefrontal cortex, which in turn relays **f(t+2)** to Layer 1 of the entorhinal cortex. Activity then propagates from area CA3 to CA1, thence to the amygdala, nucleus accumbens, septum and hypothalamus. Memories stored in the neural networks of this system are activated by associational processes modulated by emotions, valence most relevant to the sensory pattern initially encoded by the exogenous system.

f(t+3) At time **t+3**, the circuit of the time series **f(t+2)** through the memory storage networks of the limbic system is completed. The readout of the activated memory is transmitted as the time series **f(t+3)** via a hippocampus-entorhinal-fornix circuit to the reticular formation and thalamus, and via the anterior cingulate gyrus to the prefrontal cortex, where coincidence detectors compare the time series **f(t+3)** to time series previously received from posterior sensory regions and the thalamus. If the cortical coincidence detection indicates a discrepancy between time series from these two sources, a discharge produces the ERP component **P3** at about 300 ms. The timing of the sequential perceptual frames may be reset whenever a discrepancy is noted.

The process just described must be envisaged as a sliding window of successive microstates, continuously matching the present with representation of the recent past in the prefrontal cortex together with episodic memories retrieved from the limbic system. As subsets of neurons in the coincidence detector network of the prefrontal cortex match the two time series, sustained gamma reverberations link posterior and prefrontal cortex together with cingulate-limbic and thalamus into a resonant field that is proposed to be the physiological basis of subjective experience and consciousness.

OBSESSIVE-COMPULSIVE DISORDER

An example provided by obsessive-compulsive disorder (OCD) illustrates the way in which consideration of the homeostatic system governing generation of the EEG may aid in analyzing the pathophysiology underlying a psychiatric syndrome and in clarifying the basis for efficacy of a pharmacologic treatment in specific subtypes of the disorder. The symptoms of OCD are comprised of two separate but inter-related dysfunctions, namely the recurrence of unwanted thoughts (obsessions) and the performance of ritualistic behaviors (compulsions) that can be viewed as attempts to deal with the apprehensions generated by the obsessive thoughts. We might view this illness as arising from two contributory factors: 1) dysregulation of the endogenous system mediating memory retrieval described above, such that unwanted obsessive ideation arises from hyperactivity of some element of the limbic system. In view of the unpleasant mood and anxiety that characterizes much OCD ideation, hyperactivity of an interaction engaging the amygdala or the anterior cingulate must be considered; 2) dysregulation of the motor system, resulting in uncontrollable compulsive repetition of some movement possibly intended to ward off the danger implicit in the obsessive ideation. In view of the central role played by the globus pallidus in inhibiting as well as enabling movements, as well as their intimate relationship to the amygdala and the caudate, hyperactivity of these structures must also be considered. However, inspection of Figure 1 shows that both the amygdala and globus pallidus are enmeshed in circuits involving both excitatory and inhibitory elements, so that upregulation of their activity might result from a variety of influences. This is suggestive of the existence of subtypes that will display different responses to pharmacotherapy.

CMRgl PET and fMRI studies have revealed that orbitofrontal and caudate regions of OCD patients display hypermetabolism, and the same regions show increased activity when OCD behavior is provoked.[36-39] Using rCMRgl PET methods, reduced metabolism of the caudate, inferior and orbitofrontal regions, dorsolateral prefrontal cortex, and the anterior cingulate has been demonstrated after successful treatment of OCD patients by selective serotonin reuptake inhibitors (SSRIs)[36] or behavioral therapy.[40] However,

neither of these treatment approaches is reliably successful. Inconsistency of these results has been attributed to the presence of possible comorbidity with depression or the heterogeneity of pathophysiology within the OCD population. It has been shown by Prichep and colleagues[6] and replicated by Hansen and colleagues[41] that there exist two clusters of OCD patients with different QEEG profiles. One cluster is characterized by elevated alpha and depressed theta activity at baseline, and responds well to treatment with SSRIs. The second cluster is characterized by increased theta and decreased alpha activity at baseline and does not respond to SSRI treatment. It has been shown by Saletu et al[42] and by Itil et al[43] that SSRIs slow and depress alpha activity and increase theta.

In view of these data, the model proposed in Figure 2 suggests that in one type of OCD patient, correspondence between aspects of the current input from the environment to association cortex and a past experience might cause a persisting episodic memory to be released by a hyperactive prefrontal cortex, leading to an increase in a prefrontal-parietal-striatal oscillation characterized by hypersynchronous excessive *alpha* activity and recurrence of an obsessive thought. Hyperactivity of the caudate nucleus in this type of patient would result in tonic inhibition of the internal globus pallidus, resulting in disinhibition of the thalamic motor relay nuclei and production of compulsive movement repetition, as well as a *deficit of theta* activity. A second type of OCD patient is characterized by an *increase in theta* activity, conversely suggesting an imbalance in the interactions within the limbic system, with increased cholinergic output of obsessive ideation from the endogenous system via the fornix.

Administration of an SSRI to the first type of OCD patient might be expected to down-regulate the caudate nucleus, releasing inhibition of the internal globus pallidus which then inhibits the motor relay nuclei and blocks the compulsive movements. Concomitant release of the substantia nigra would activate the limbic system and increase theta activity in the cortex. The parietal-prefrontal oscillation would be disrupted and alpha hypersynchrony would be replaced by normal amounts of alpha. Treatment of the second subtype with SSRIs might further stimulate excitatory interactions within the limbic system, to cause an increase in obsessive ideation and presumably worsen the condition.

CONCLUSION

A tentative model has been proposed for how the EEG and ERPs are generated and regulated by a homeostatic system, including the hypothetical contribution of particular brain regions to various dimensions of subjective experience and the neurotransmitters probably involved in mediating transactions among these brain regions. Plausible hypotheses for various categories of neurocognitive and psychiatric disorders can be envisaged from this model and multiple disruptions of homeostasis with the same behavioral consequences can be envisaged. QEEG subtyping should aid in constructing a systematic approach to the selection of the most effective pharmaco interventions. Conversely, empirical studies of differential pharmaco-EEG and clinical responses of patients with the same diagnoses to different medications should aid in subtyping heterogeneous psychiatric disorders. An international collaborative effort to establish a comprehensive database, integrating careful baseline standardized psychiatric, QEEG and neuropsychological assessments with systematic follow-up of the effects of pharmacological interventions on all these standardized descriptors, can produce a Psychiatric QEEG-Pharmaco-EEG Atlas to serve as an adjunct to DSM4 for the improved and more analytic selection of treatment.

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