Sleep, Memory Maintenance, and Mental Disorders

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Memory circuits of the brain are activated by self-generated brain waves, primarily during sleep. These activations refresh the efficacies (strengths) of synapses in affected circuits, maintaining the efficacies at the "dedicated" values that support circuit functions. The neural pathologies underlying many mental disorders appear to exert their deleterious influences by inducing abnormalities in brain waves. The abnormal waves, in turn, fail to sustain dedicated synaptic efficacies in memory circuits, leading to mental malfunction. Dreaming is an "unconscious" awareness of circuit reinforcement during sleep, with dream contents being derived from the activated circuits. When synaptic efficacies are degraded, the dreams are illusory.

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It has been said that "in spite of an enormous amount of research, the causes of all major mental disorders are still unknown" (Licinio, p. 198).[1] While this may hold true generally for ultimate causes of mental disorders, that is, for the underlying pathologies, there is reason for optimism regarding proximate causes, that is, the mechanisms by which the underlying pathologies become manifested as mental disorders. A chain of findings, the first link of which dates to over 200 years ago and the most recent to 1999, are helping to bring these mechanisms into focus.

The Scottish royal physician Cullen[2] was the first to analogize illusory dreams (those containing impossible, incongruent, or bizarre content) with delirium. He found that "there are in this state false perceptions, false associations, false judgements, and disproportionate emotions; in short all the circumstances by which I have above defined delirium" (p. 130).

Dream theorists of the 19th century saw dreams "as a form of delirium that at best mimics the conditions of creative thought" (Hunt, p. 10).[3] A most pertinent observation was that of De Manacéïne,[4] who observed, with remarkable prescience, that dreams "have a direct salutory influence insofar as they serve to exercise regions of the brain which in the waking state remain unemployed" (p. 312). Inasmuch as "day residues" oc-

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cur in 47% to 49% of dreams,[5] it is tacit to De Manacéïne's observation that although many brain circuits may be "exercised" during dreams, it is primarily the infrequently employed circuits that are in need of reinforcement.

Another, and until its time the most direct, proposed link between illusory dreams and mental disorders was made by Bleuler[6] and adopted and extended by Kelly.[7] In essence, they suggested that the delusions in schizophrenia have their origin in remembered illusory dreams that masquerade as authentic experiences. This view harmonizes with the findings of Broughton[8] that patients with narcolepsy-cataplexy, with its vivid hypnagogic hallucinations and its characteristic intensification of dreaming, also have difficulty in distinguishing their intense dream experiences from reality.[9]

Cartwright's[10] subjects described their experiences with delirium-producing agents as "like dreaming," while Hunt[3] found that dreaming typically "showed a delirium profile, the sort of diffuse and subtle decrement characteristic of alcohol- and fever-induced states" (p. 71). Most recently, Hobson[11] observed of "our nightly madness" that "dreaming is more like organic delirium than any other pathological condition of the mind. . . . The common features of normal [dreaming, a healthy psychosis] and abnormal delirium are disorientation, inattention, impoverished memory, confabulation, visual hallucinations, and abundant emotions" (p. 121).

In view of these many instances in which very close relations have been inferred between illusory dreams and states of delirium, I undertake here a broadly based analysis of how illusory dreams are generated, for the insights it might give into the genesis of mental disorders. A brief review of the mechanisms of dream genesis precedes a discussion of the role of circuit reinforcement through synaptic efficacy (strength) refreshment and the mechanisms by which it is achieved. When these mechanisms fail in the normal course of events, dreams may become illusory, and illusory awake experiences may occur. Failures of synaptic efficacy refreshment by abnormal brain waves traceable to underlying brain pathologies are then discussed, along with examples of mental malfunction that may result. Last, the electroencephalographic (EEG) abnormalities accompanying mental disorders, influences of psychoactive drugs on EEGs, and therapeutic avenues are considered.

DREAM GENESIS

The most widely accepted view of the genesis of illusory and authentic dreams (the latter being those actually or plausibly within the realm of experience) is supported by the studies of many investigators (see reviews[12,13]). In the views of Hobson and McCarley,[14] Greenberg,[15] and Antrobus,[16,17] dreaming is a by-product of, and tightly linked to, the mental activities that normally occur during sleep. Thus, dreams are thought to accompany the process of activating brain circuits for the purposes of consolidating very recent (labile) memories (the "day residues" of Freud) and reinforcing older, already consolidated (stable) memories. Because synapses are subject continuously to degradative and depletional processes, if they were not periodically refreshed during sleep, many memories would be lost. The contents of the dreams that occur when ensembles of memory circuits are reinforced are thought to be derived from the memories stored in the circuits, some of which may be combined in incongruous or bizarre ways.

"Dedicated" Synaptic Efficacies and Efficacy Refreshment

The efficacy or strength of a synapse refers to the facility with which the presynaptic neuron transmits an impulse or an altered potential to the postsynaptic neuron. The greater the synaptic efficacy, the smaller the frequency or magnitude of the potential required at the presynaptic membrane to produce a given level of change at the postsynaptic membrane. "Dedicated" or functional synaptic efficacies become established initially in memory circuits by a tailoring of their values for specific functions in the course of use of the circuits for those functions (see review[12]). When the functions recur sufficiently frequently, the tailored efficacy values are maintained (refreshed) by virtue of an intrinsic activity-dependent synaptic plasticity—the property of automatic augmentation of synaptic efficacy through use—whereupon the efficacies do not require refreshment during sleep.

Reinforcement During Sleep Is Predominantly by Slow Waves

Further analysis of the connection between illusory dreams and mental disorders requires an inquiry into the precise mechanisms by which circuits underlying dreams are activated. This is another domain in which intensive studies have been carried out. Self-generated electrical potentials (brain waves) are thought to consolidate and reinforce memory circuits during sleep—in both rapid-eye-movement (REM) and non-REM (NREM) states. The potentials are believed to be primarily oscillations (slow waves) at frequencies below about 14 cycles per second (Hz).

Examples of possible reinforcing slow waves are the theta rhythm (4–10 Hz) of REM sleep; irregular sharp spikes (1/50–3 Hz) of NREM sleep; cyclic trains of single spikes or rhythmic spike bursts in thalamocortical

axons resulting from spindle (7–14 Hz) and delta (1–4 Hz) oscillations; continuous synaptic bombardment from the intrinsic neocortical networks that generate the slow sleep rhythm (0.3 Hz) of NREM sleep, and the alpha rhythm (8–12 Hz) of quiet wakefulness. Sawtooth waves (2–3 Hz) and a distinctive delta-wave pattern that occur during REM sleep also may be involved, and reinforcing actions of waves in the beta–gamma range (14–80 Hz) cannot be excluded (see review[12]). It is reasonable to anticipate that mental malfunction probably results when these mechanisms fail in some way, even merely by being withheld.

IlLLUSORY DREAM GENESIS

Several proposals have been advanced to account for illusory dreams. In one view, the absence of external sensory input during REM sleep deprives the brain of its normally coordinating contextual restraints.[18] In another, illusory dreams derive from impaired binding of circuits without real-world feedback.[19] In a third view, such dreams stem from abnormal alignments or participation of the underlying circuits.[20] Although it is not unlikely that such influences play roles, most dreams are ordinary and mundane, with authentic content. These dreams presumably are similar to illusory dreams in circuit binding, alignments, participation, and contextual restraints. Accordingly, additional influences must be at work that underlie the dreams' illusory content. It has been proposed[13] that the principal bases for the differences between illusory and authentic dreams, and also for the occurrence of some mental disorders, lie in the conditions of circuits as they are being activated—"competent" versus "incompetent"—and in the condition of the activating slow waves—normal versus pathologically altered.

The Precise States of Synaptic Efficacies During Refreshment

Preservation of authentic memories in a circuit entails maintenance of the dedicated values of synaptic efficacies for the circuit's specific functions. Two crucial questions, almost completely untreated until very recently,[13] pertain to the precise states of the synaptic efficacies in circuits being reinforced and to the precise conditions that constitute dedicated synaptic efficacies. Specifically, is a dedicated synaptic efficacy value sharply defined, with a slight deviation above or below the value having a deleterious effect on circuit function? Or does the value cover a range over which the synapse operates in the dedicated manner, but outside of which the circuit becomes "incompetent"? Or is a dedicated efficacy value merely a minimum, with the synapse retaining its functional competence at higher values? If the value is sharply defined, as in the first alternative, or covers a range, as in the second, does each synapse retain a "record" of the specific value or of the value-range limits, such that efficacy refreshment ceases upon attainment of the value or of the upper limit? What is the magnitude of the time required for refreshment to achieve dedicated values, and does it occur gradually (incrementally) or abruptly?

There is no definitive answer to any of these questions. However, very recent findings, and other considerations treated below, are providing guidance. For long-term refreshment of the efficacies of CA3–CA1 synapses in the hippocampus, at least, efficacy enhancement appears to occur on an all-or-none basis, with individual synapses having different induction thresholds.[21] Existence of these different induction thresholds supports the view that different synapses in circuits for a specific function can retain individual "records" of singular or minimum and/or maximum dedicated efficacy values for that function.

On the other hand, for synaptic efficacy refreshments that require protein synthesis, synaptic activations lead to a local dendritic accumulation of newly synthesized messenger RNA (mRNA) and proteins[22] and to polyadenylation of certain mRNAs.[23] These findings suggest that the efficacies of these synapses are refreshed by a gradual, rather than an abrupt, process.

"Incompetent" Circuits and Incremental Refreshment

In another very pertinent matter, what would occur if, in the distributed circuitry representing a scene in a dream or memory, efficacies of a small fraction of the synapses—of the many millions to hundreds of millions involved—were altered from their dedicated values for the authentic scene? In answer to this question, one would not expect the scene to be degraded beyond recognition; rather, unpredictable, probably relatively minor alterations might occur—distortions, background or location changes, or altered temporal settings or identities.

Coupling this probable outcome with the knowledge that synaptic efficacies are subject to continuous deleterious influences; that they are refreshed by slow waves during lengthy periods of sleep; and that efficacy alterations by individual activations commonly are additive (as in presynaptic facilitation) leads to two potentially significant implications. First, efficacy refreshment of many synapses may, as suggested above, be a gradual (incremental) process that often requires considerable time and is not necessarily completed in one night. Second, synaptic efficacy refreshment by slow waves often

may act on synapses with partially degraded efficacies.[13]

Circuit Reinforcement Priorities

There evidently is a high priority for consolidation of significant memories of the previous day, perhaps also for others recently acquired, and for reinforcement of all circuits with critical information. Otherwise, we have no information on what determines which portions of the vast memory stores become reinforced on any given night of sleep. Since it is well known that many memories gradually weaken over time, one likely circumstance (taking a cue from the accumulation of mutations in genotypes) is that all very old (childhood) memory circuits become reinforced regularly, but that efficacy errors accumulate in proportion to the age of the circuits.

"Incompetent" Circuitry, Illusory Dreams, and Faulty Recall in Normal Individuals

Consideration of the above points—the existence of decayed synaptic efficacies in incompetent memory circuits; the expected deviations from reality of memories stored in these circuits; and the lengthy periods that may be required to restore dedicated synaptic efficacies in some circuits—leads to the following conclusions. It is a reasonable supposition that, even in normal individuals, the efficacies of some synapses, among the many trillions that exist, are below their dedicated values at any given time; in accord with the above proposal, some synaptic efficacies in circuits for very old memories may be in a weakened state at all times.

Reasoning from these points of view, dreams of authentic content may result from activations of recently consolidated circuits, or of other circuits with fully refreshed synaptic efficacies. Many illusory dreams, on the other hand, may result from the activation of older, incompetent circuits containing synapses with efficacies in various decay states—even with impaired efficacy in only a single synapse. However, a direct effect of impaired efficacies is unlikely to be the only causative influence. Indirect effects probably also play roles in generating illusory dreams, particularly in the combination of circuit outputs. The mechanisms that combine the outputs of complementary circuitry apparently lose their specificity when any of the circuits to be combined are incompetent. Normally addressing the output of a circuit's authentic complement, they instead lead to combinations with the output of uncomplementary circuitry, the result being that the corresponding dream mentation is incoherent or bizarre.

Contents of existing incompetent circuits must be relatively inaccessible or rarely recalled during wakefulness. Otherwise hallucinations and faulty recall would be common in normal, awake individuals. Since most incompetent circuits probably are for very old memories, and a large fraction of adult dreams harken back to childhood experiences,[24] particularly in the aged,[4] a rich substrate for illusory dreams probably exists at all times.

The foregoing proposals also help to elucidate other mental phenomena in healthy individuals. Consider the above conclusion that incompetent circuitry with relatively inaccessible or rarely recalled contents exists. Evidence supporting this conclusion is that hallucinations and bizarre mentation sometimes occur in normal individuals during periods of quiet wakefulness, and they also can be induced in a variety of psychophysiological conditions,[18,25] including sleep deprivation. The hallucinations that sometimes occur after sleep deprivation presumably reflect the accumulation of degraded circuitry during a lengthy absence of the circuit reinforcement normally provided by sleep.

In another context, although one may not take the results of regression hypnosis at face value, the results also accord with the thesis that incompetent circuitry normally exists, particularly for memories of the distant past. Adults taken back in time sometimes claim to remember their first school days, including detailed images of classrooms, teachers, classmates, and even sounds and feelings. However, attempts to verify these reexperiences reveal that they are prone to fantasies, distortion, and inaccuracies.[26,27]

The presence of inauthentic content of reexperiences sometimes is taken to mean that "the psyche smoothly fills up inconvenient gaps in the mental image."[28] However, from the viewpoints presented here, this inauthentic content may instead be faithful recall, but from partially degraded circuitry. Because hypnosis can enhance access to memories that previously were unavailable to consciousness (as is also true of some delirious and febrile states[4]), this interpretation accords well with the finding that hypnotic age regression can "contaminate" later awake memories and the frequent conviction of subjects that their inaccurate memories recovered during hypnosis are, in fact, accurate.[26] If the recall is from degraded circuitry, it would illustrate how faithful recall from incompetent circuitry can masquerade convincingly as authentic recall, even to normal individuals.

ABNORMAL SLOW WAVES AND GENESIS OF MENTAL DISORDERS

Organic Delirium and the Remedial Action of Electroconvulsive Therapy

Assuming that illusory dreams in normal individuals often are the direct or indirect result of activation of in-

competent circuits, and recalling the very close link between illusory dreams and delirium, it becomes likely that organic delirium is produced when incompetent circuitry of pathological origin is activated. To account for the origin of such incompetent circuitry, it has been suggested that the ultimate pathological basis for organic delirium leads to abnormalities in some of the slow waves (deviations from normal frequency, form, magnitude, spiking, or topographical distribution) of sleep that normally provide circuit reinforcement. These abnormal slow waves, in turn, cause deleterious alterations in synaptic efficacies in affected circuits. With loss of dedicated synaptic efficacies in these circuits, activation produces hallucinations, illusory recall, and other hallmarks of delirium.[13]

Adopting this view of the genesis of organic delirium, it seems likely that the efficacious, but temporary, remedial influence of electroconvulsive therapy (ECT) and pharmacoconvulsive therapy on organic delirium[29] hinges on temporary suppression of the abnormal slow-wave regimes, allowing spontaneous resumption of remedial slow waves. These remedial regimes act to restore dedicated synaptic efficacies in incompetent circuitry. On ECT maintenance therapy, the abnormal slow waves remain suppressed, and remedial reinforcement regimes, with their alleviating influences, prevail. But when maintenance therapy ceases, the abnormal slow waves may regain dominance because of the underlying pathology, leading to the return of delirium.[13]

The mechanism proposed for the specific remedial effects of ECT—suppression of abnormal slow waves and resumption of remedial reinforcement of incompetent circuitry during and following seizures, and residually during sleep on immediately following nights—has the potential to resolve some of the classic problems of ECT. One of these problems involves "identifying those changes that were in the therapeutic chain, that changed over time in parallel with the changes in mood and affect, and that persisted with a time course that could be related to the persistence of the behavioral effects" (Fink,[29] p. 74).

Because the brain waves that accomplish circuit reinforcement are believed to be predominantly at low frequencies, it is pertinent to inquire into the nature of the remedial brain waves that are "induced" by ECT. Most of the electroencephalographic energy accompanying and following the seizures is found in delta waves at about 3 Hz, and these are suspected to be crucial to the therapeutic effect.[30] The increase in amplitude and buildup of slow waves are of longer duration when a series of treatments is given, and they tend to be nonspecific, having a therapeutic effect in a variety of neuropathologies.[31]

The above paradigm of alleviation of delirium by ECT helps to account for the equal remedial effectiveness of ECT for severe mania and severe depression, clinically assumed to be opposing neurohumoral pathological processes.[29] The paradigm also is consistent with the need for a period of maturation for ECT effects, and with the exertion of a specific antidelirium effect on underlying pathophysiological mechanisms in some disorders, including delirium tremens, CNS syphilis, typhoid catatonia, and phencyclidine psychosis.[32]

Other Psychoses

Some psychoses other than delirium also may be attributable to a breakdown of normal slow-wave reinforcement regimes, particularly psychoses that benefit from ECT (including even severe depressive syndromes that are unresponsive to antidepressant drug therapy[29]). For these other psychoses, the breakdown of normal slow-wave regimes of reinforcement apparently leads to incompetent states in specific ensembles of neural circuits, among which those that secrete psychoactive substances could be expected to be prominent.

Incompetence, of course, would be most evident in circuits in frequent use, particularly cognitive and sensory circuits. Use of incompetent circuits during wakefulness could be expected to give rise to the same illusory thoughts, hallucinations, and mood alterations that occur in dreams that result from reinforcement of similarly incompetent circuits during sleep.

Hallucinations, Illusions, and Recurring Nightmares Accompanying Spontaneous Epileptic Seizures

Circuit activations (discharges) brought about by abnormal slow waves apparently cause some spontaneous epileptic seizures, which perhaps are triggered when the appropriate stimulus recruits a critical mass of abnormally discharging neurons.[33] Because dreams are thought to accompany normal regimes of circuit reinforcement during sleep, one might expect abnormal activation regimes also to be accompanied by dreamlike mentation. Indeed, nocturnal seizures are thought to be causally linked to dream generation.[9] Psychomotor seizures (fits) that arise primarily from limbic structures of the temporal lobe (and exogenous electrical stimulation of these structures) frequently are accompanied by illusions, hallucinations, recall, and perceptual distortions. These often include visual and auditory components, which are usually more vivid and intrusive than commonplace recollections.[34]

It is most significant that the mentation that accompanies temporal lobe seizures occurs only as the seizures begin.[34] Accordingly, it appears that mentation can be elicited, during a seizure's onset, by the initial regimes

of reinforcement that became altered pathologically to cause the seizures. But beyond a certain point the progression of these brain waves toward becoming epileptiform apparently is too great, and the waves no longer can elicit mentation.

The above progression accords with the observed merging of sleep spindles into epileptiform discharges during the seizures that accompany the abnormal sleep of patients with generalized epilepsies.[35] The initial sleep spindles and accompanying normal slow waves presumably produce dreamlike mentation, but the capability is lost as discharges become epileptiform.[34]

Correlations between mentation and temporal lobe epilepsy extend beyond the above-mentioned early manifestations. Full-blown conscious psychoses of schizophrenic or manic-depressive types also occur in a minority of individuals during the interictal periods. And the epileptic attacks tend to be much diminished at a time when the psychoses are fully developed.[36,37]

From the present point of view, in which the seizures and the psychoses are thought to have their origin in essentially the same phenomenon, namely, circuit activation by pathologically altered slow waves, the correlations appear in a new light. It appears that in time (sometimes only after several years), repeated regimes of the epileptiform discharges that cause the seizures also begin to influence deleteriously the normal postictal slow-wave reinforcement regimes (a phenomenon possibly related to kindling). When these regimes also become pathologically deviant, the conscious psychoses ensue.

To the extent that different episodes of nocturnal seizures are induced by abnormal slow-wave excitations in the same brain region, one would expect the dreams or other induced mentation to be similar to one another across seizures. This follows because authentic or faulty memories encoded in essentially the same brain region would become activated, and in essentially the same manner. The phenomena associated with seizures that lead to recurring nightmares amply support this expectation and also are consonant with other expectations based on the above analysis.

It is relatively well established in clinical neurology that seizure disorders, which commonly occur during NREM sleep, may be associated with recurring nightmares, a link recognized even in antiquity. Recurring nightmares (repeated experience of the same dream or of dreams with a stereotypical theme, sometimes in the form of a hallucinatory aura) usually indicate a discharging lesion in an identical brain region, the right temporal lobe. The perceptual content of these nightmares is consistent with such a focus, typically including smells, affects, and reminiscences. The nightmares sometimes precede the onset of frank epilepsy; at other times they occur simultaneously with the onset of seizures, or they may immediately precede the seizures as dreamy-state aurae.[9]

Accordingly, it appears that each seizure-inducing discharge localized in a particular brain region produces a recurring nightmare (which also can be elicited by surgical stimulation in that region[9]), but the nightmare occurs only initially, presumably before the activating abnormal waveforms become too epileptiform to be accompanied by mentation. Non–seizure-inducing electrical excitation of awake patients at the same point in the temporal lobe also may induce recurring mentation—that is, a series of hallucinatory experiences with a stereotyped theme but different specific details, although the evidence for this is not as strong.[38]

On the assumption that ECT temporarily suppresses seizure-inducing abnormal slow waves, it is of particular interest that ECT also can produce marked remediation of an akinetic-rigid syndrome.[39] This finding suggests that in addition to being able to induce involuntary motor activity (seizures), abnormal slow waves also can suppress voluntary motor activity. (See also the discussion of Parkinson's disease below.)

Sleep Deprivation, Recovery Sleep, and Mood Alterations

Viewing a breakdown in normal regimes of reinforcement of circuitry during sleep as the cause of some psychoses would help to explain some previously puzzling findings: namely, that sleep deprivation has mood-elevating effects in patients with affective disorders, and that mood depression rebounds significantly in such patients after they obtain recovery sleep.[40–42] The responses of some patients are so rigidly fixed that depression is readily "turned off" by sleep deprivation and "turned on again" by sleep.[43]

These effects lend support to the proposal that it is abnormal slow-wave activity that influences mood. Sleep deprivation doubtless is beneficial because it reduces or eliminates the abnormal slow waves that degrade circuits and produce depression; in contrast, the recovery sleep is deleterious because abnormal slow waves resume, leading to further departures of synaptic efficacies from dedicated values.

Parkinson's Disease

Management of idiopathic parkinsonism is of particular interest in connection with the foregoing. ECT is an effective treatment for the majority of patients with Parkinson's disease and psychiatric comorbidity (aside from the usual mild cognitive dysfunction, which is most frequently visuospatial). It temporarily improves both the psychiatric and the motor symptoms.[44] The

psychiatric improvements presumably result from gradual restoration of dedicated synaptic efficacies in degraded circuits by induced remedial slow-wave reinforcement, and the motor improvement presumably hinges on the rapid suppression of the abnormal slow waves that activate motor circuits, just as cardiac fibrillation is suppressed rapidly by a defibrillating shock as discussed below.

In line with this interpretation, one might predict that chronic, appropriate electrical brain stimulation (as opposed to ECT maintenance therapy) localized in appropriate regions might lead to lengthy suppression of the abnormal motor circuit activations that produce the parkinsonian dyskinesias. Indeed, chronic deep brain stimulation (170 Hz, 3.2 V) in the globus pallidus internus or subthalamic nucleus can produce long-lasting motor remediation.[45]

Parallels Between the Actions of ECT and Cardiac Defibrillating Shocks

The remedial action of cardioverter defibrillators on fibrillating and rapidly beating hearts[46] has close parallels with remediation of abnormal slow-wave activity by ECT. Just as the defibrillating shock halts the rapid beating and fibrillations, followed by onset of a normal heartbeat rhythm, the electric shock of ECT suppresses abnormal slow-wave regimes of some circuitry, allowing more nearly normal slow-wave reinforcement regimes to resume; in neither case is the remediation expected to be permanent. Parallels also extend to shock remediation of cardiac arrhythmias that are not responsive to pharmacological therapy.

The parallels with cardiac defibrillation suggest that the normal regimes of reinforcement by slow waves are intrinsic to brain regions—and that once abnormal slow-wave activations are suppressed, more nearly normal regimes resume spontaneously, only gradually to regress under the influence of the underlying pathology. This suggestion accords with the finding that rhythmical electrical activity is an inherent property of isolated cerebral cortex,[47] and even of brain slice preparations (lateral geniculate nucleus) in vitro.[48] Similarly, Niedermeyer[49] has suggested that, assuming a state of nearly total deafferentation in alpha coma (caused by the acute pathological process), intrinsic activities develop in the cortex, with the rhythm of alpha coma simply representing "cortical autorhythmicity."

EEG ABNORMALITIES, PSYCHOACTIVE DRUGS, AND THERAPEUTIC AVENUES

Mental Disorders and Abnormal EEGs

In the light of the foregoing proposals, one would anticipate that EEG abnormalities, particularly in slow-wave activity, would be a hallmark of many mental disorders. (In this connection, the buildup of delta and theta waves after ECT tends to be nonspecific, occurring in patients with a variety of neuropathologies.[31]) This expectation is amply fulfilled, although for some disorders the differences between patients and control subjects are not always highly significant (e.g., for obsessive-compulsive disorder).[50]

The EEG receives special attention in the differential diagnosis of delirium, where the degree of diffuse background slowing in most patients correlates with the degree of cognitive impairment and activity. Slowing of the classic posterior alpha rhythm (8–12 Hz) is found early. Subsequent changes, in order of progression, are generalized delta slowing, a decrease in the EEG level of reactivity, and, finally, loss of alpha and beta (14–30 Hz) activity, concomitantly with the presence of diffuse, very slow delta activity.[51,52]

With very few exceptions, however, such as for delirium tremens and classic petit mal seizures, abnormalities in EEGs accompanying mental disorders are not of unique diagnostic value. In petit mal seizures there is an "extremely impressive EEG correlate" consisting of generalized, synchronous, high-voltage 3-Hz spike and wave discharges, correlated with a decrement in consciousness.[37,51,53] EEG abnormalities provide an irreplaceably unique function-oriented test in epileptology,[37] and they are useful in discriminating between primary and secondary affective disorders.[54]

In patients with schizophrenia, persistent reductions in delta-wave sleep (most prominently at >1–2 Hz) are associated with enduring traits and may reflect thalamocortical dysfunction.[55] Depressed patients, in general, long have been known to have low amounts of slow-wave sleep (usually delta, stages 3 and 4) and reduced REM latency.[56–59] However, the departures are not sufficiently specific to serve as markers for depressive subtypes.[60]

During drowsiness, children suffering from febrile convulsions show generalized slow waves with intermixed spikes and sharp waves.[61] Patients with focal slow waves (frontal, parietal, or at other locations) during waking (70%) or waking and sleep (30%) usually have an underlying destructive lesion, sometimes associated with asymmetrical sleep spindles. Monorhythmic frontal delta activity occurring with hypothalamic, third-ventricle, and posterior fossa masses usually disappears during NREM sleep but reappears upon entering REM sleep; however, slow-wave activity associated with superficial tumors tends to persist during NREM sleep.[62]

Recent studies that correlate fluctuating levels of consciousness (FC) with an attentional choice reaction task

(CRT) and with cortical arousal as measured with EEGs, are of particular interest.[63] The results are consistent with the proposal that abnormal brain waves, mostly slow waves, are the proximate cause of many mental disorders. Parameters for control subjects and patients with Alzheimer's disease (20% generally have FC) and Lewy body dementia (80% to 90% generally have FC) were compared. Significant associations were found between CRT performance, clinical FC scores, and variability in the delta (0–3.8 Hz) power band, and between clinical FC scores and variability in the total average power in the theta (4–7.9 Hz) band.

Performance using the CRT test was found to be a sensitive marker for FC in both Alzheimer's and Lewy body dementia patients. Walker et al.[63] suggest that "the variability pattern of neural activity displayed in the EEG, particularly in the slow delta frequency band, could be key in the genesis of FC." The findings are consistent with the hypothesis that fluctuating consciousness and cognitive abilities, including attention, result from an impaired ascending cholinergic activating system.[63] Presumably the impaired activations cause the EEG fluctuations, which, in turn, lead to the fluctuating levels of consciousness.

Influences of Psychoactive Drugs on EEGs

Once it has been proposed that pathologically altered brain waves are the proximate cause of many mental disorders, it is pertinent to inquire into the influences of efficacious psychoactive drugs on EEGs. Although the basic assumption of pharmaco-EEG studies has been that abnormal EEGs merely are evidence of underlying CNS dysfunctions,[64] the studies serve to elucidate both possible relationships.

A cursory survey of the literature on effects of psychoactive drugs reveals a multiplicity of actions, although only the alpha-rhythm changes often are reported.[53] Various antidepressants administered to normal, healthy individuals may increase slow-wave and fast beta activity, decrease or slow alpha activity, and reduce or suppress REM sleep. In patients with various forms of depressive illness, antidepressants may increase delta wave intensity or stage 4 sleep and redistribute slow-wave sleep, increase beta and alpha waves, suppress REM sleep, and restore normal REM sleep latency. In control subjects, antipsychotics may increase slow-wave or delta, theta, and slow alpha activity while decreasing fast alpha activity. In patients, antipsychotics may increase delta activity, amplitude, and total power, increase theta activity and fast waves, and restore normal REM-sleep latency.

Specific EEG profiles are reported only for chlorpromazine (a tricyclic sedative neuroleptic) and amitriptyline (a tricyclic antidepressant).[64] Chlorpromazine administration generally leads to increases in the delta (1.5–5.5 Hz) and theta (5.5–8.5 Hz) powers, with the relative change in the theta range somewhat greater than that in the delta range, and to decreases in the lower (8.5–10.5 Hz) and upper (10.5–12 Hz) alpha powers and lower (12–18 Hz) and upper (21–30 Hz) beta powers. Some variations are found when the analyses discriminate at the level of topographic maps. For amitriptyline, there is a decrease in the alpha and beta powers and an increase in slow-wave powers, with a relatively greater change in the delta range than in the theta range.

These findings concerning influences of psychoactive drugs on EEGs are broadly consistent with the theses proposed here. The findings do not, of course, distinguish whether abnormal EEGs are the proximate cause of mental malfunctions or are merely symptoms of underlying pathologies. Taken together with the above-described EEG abnormalities that accompany mental disorders, these results suggest that correlations between the two manifestations can be complex. Qualitative, quantitative, and distributional deviations of brain waves from the normal may all make contributions, suggesting the need for in-depth analyses and detailed premorbid and morbid comparisons. Although deviations involving slow waves appear to be at the heart of the pathologies, waves at higher frequencies also may be involved.

Therapeutic Avenues

Aside from psychotherapy, the most promising therapeutic avenues for treating mental disorders appear to be direct surgical intervention, various types of electrical stimulation, and pharmacological intervention. In terms primarily of their influences on brain waves, surgical intervention would seek either to prevent specific deleterious discharges or to restore brain waves to their premorbid condition; electrical stimulation when applied continuously would seek to maintain inhibitory influences on abnormal discharges, or when applied intermittently it would seek to terminate abnormal brain waves for greater or lesser periods, allowing normal brain waves to resume spontaneously; pharmacological approaches would seek to exploit any modification of brain wave patterns and sleep parameters that remediated one or more aspects of mental malfunction. Some few disorders may be susceptible to self-remediation through biofeedback.

SUMMARY

Mentation during sleep states is thought to involve activation of the brain circuits that store and coordinate

the use of inherited and experiential information (memories). All brain circuits are susceptible to spontaneous degradation of the efficacies (strengths) of their synapses because of turnover and other depletion of molecules essential for synaptic function. Synaptic efficacies in circuits employed frequently during waking are reinforced and maintained at their functional levels in the course of waking use by virtue of activity-dependent synaptic plasticity. During sleep, circuit activations induced by spontaneous, self-generated, primarily low-frequency brain waves refresh synaptic efficacies in circuits employed infrequently during waking, also by virtue of activity-dependent synaptic plasticity. This process is accompanied by dreams whose contents are derived from the reinforced circuitry. In the absence of refreshment during sleep, synaptic efficacies in infrequently used circuits would decay and the circuits would become incompetent, their encoded memories degraded or lost.

Maintenance of infrequently used circuitry during sleep is not 100% efficient. Efficacy losses accumulate in the synapses of some circuits, particularly in those for memories of the distant past. When these "incompetent" circuits are activated during sleep, illusory or bizarre dreams are produced. Activation of the circuits during waking can lead to faulty recall, illusions, and hallucinations.

The organic pathologies underlying many mental disorders are believed to cause deviations of the brain's self-generated, circuit-reinforcing waves from their normal parameters (such as frequency, amplitude, and spiking properties) and distribution. When this occurs, the normal efficacy-refreshing actions become compromised to varying degrees and circuits become partially degraded. They remain degraded for as long as the waves remain abnormal and the underlying pathologies persist. Activation of these incompetent circuits during waking and sleep leads directly and indirectly to some of the pathologies that accompany many mental disorders.

Inasmuch as many brain waves appear to be intrinsic to brain regions, when the shock of electroconvulsive therapy brings abnormal brain waves to a halt, more nearly normal brain waves of sleep spontaneously resume and temporarily gain ascendancy. This action is believed to parallel that by which a defibrillating shock halts fibrillations and allows the normal heartbeat rhythm to resume. Examples are given for the remediative influences of ECT on several mental disorders.

Similarly, efficacious psychoactive drugs are thought to bring about remedial modifications of the abnormal brain waves of psychotic patients, leading to more nearly normal refreshment of synaptic efficacies in degraded circuitry. This action is thought to bring about partial to complete, but temporary, restoration of circuit competencies, accompanied by remedial influences on the mental disorders, sleep disorders, seizures, and other dyskinesias.

References

1. Licinio J: Expressing Freudian influences. Science 1998; 282:2197–2198
2. Cullen W: First Lines of the Practice of Physic, vol 4, part 2, book 3. Edinburgh, C Elliot, 1788
3. Hunt HT: The Multiplicity of Dreams. London, Yale University Press, 1989
4. De Manacéïne M: Sleep: Its Physiology, Pathology, Hygiene and Psychology, translated by Jaubert E. London, W Scott, 1899
5. Harlow J, Roll, S: Frequency of day residue in young adults. Percept Mot Skills 1992; 74:832–834
6. Bleuler E: Dementia Praecox or the Group of Schizophrenias (1911), translated by Zinkin J. New York, International Universities Press, 1950
7. Kelly PH: Defective inhibition of dream event memory formation: a hypothesized mechanism in the onset and progression of symptoms of schizophrenia. Brain Res Bull 1998; 46:189–197
8. Broughton RJ: Neurology and dreaming. Psychiatric Journal of the University of Ottawa 1982; 7:101–110
9. Solms M: The Neuropsychology of Dreams: A Clinico-Anatomical Study. Mahwah, NJ, Lawrence Erlbaum, 1997
10. Cartwright RD: Dream and drug-induced fantasy behavior: a comparative study. Arch Gen Psychiatry 1966; 15:7–15
11. Hobson JA: Dreaming as delirium: a mental status analysis of our nightly madness. Semin Neurol 1997; 17:121–128
12. Kavanau JL: Memory, sleep, and the evolution of mechanisms of synaptic efficacy maintenance. Neuroscience 1997; 79:7–44
13. Kavanau JL: Adaptations and pathologies linked to dynamic stabilization of neural circuitry. Neurosci Biobehav Rev 1999; 23:635–648
14. Hobson JA, McCarley RW: The brain as a dream state generator: an activation-synthesis hypothesis of the dream process. Am J Psychiatry 1977; 134:1335–1348
15. Greenberg R: Dreams and REM sleep: an integrative approach, in Sleep, Dreams, and Memory, edited by Fishbein W. New York, SP Medical and Scientific Books, 1981, pp 125–133
16. Antrobus J: Dreaming: cognitive processes during cortical activation and high afferent thresholds. Psychol Rev 1991; 98:96–120
17. Antrobus J: Dreaming: can we do without it? In The Functions of Dreaming, edited by Moffitt A, Kramer M, Hoffman R. Albany, NY, State University of New York Press, 1993, pp 548–558
18. Reinsel R, Antrobus J, Wollman M: Bizarreness in dreams and waking fantasy, in The Neuropsychology of Sleep and Dreaming, edited by Antrobus JS, Bertini M. Hillsdale, NJ, Lawrence Erlbaum, 1992, pp 157–184
19. Kahn D, Pace-Shott EF, Hobson JA: Consciousness in waking and dreaming: the roles of neuronal oscillation and neuromodulation in determining similarities and differences. Neuroscience 1997; 78:13–38
20. Braun AR, Balkin TJ, Wesensten NJ, et al: Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science 1998; 279:91–95

21. Petersen CCH, Malenka RC, Nicoll RA, et al: All-or-none potentiation at CA3–CA1 synapses. Proc Natl Acad Sci USA 1998; 95:4732–4737
22. Steward O, Wallace CS, Lyford GL, et al: Synaptic activation causes the mRNA for the IEG arc to localize selectively near activated postsynaptic sites on dendrites. Neuron 1998; 21:741–751
23. Wu L,Wells D, Tay J, et al: CPEB-mediated cytoplasmic adenylation of the regulation of experience-dependent translation of alpha-CAMKII mRNA at synapses. Neuron 1998; 21:1120–1139
24. Palombo SR: Recovery of early memories associated with reported dream imagery. Am J Psychiatry 1984; 141:1508–1511
25. Mahowald MW, Woods SR, Schenck CH: Sleeping dreams, waking hallucinations, and the central nervous system. Dreaming 1998; 8:89–102
26. Nash MR, Drake SD, Wiley S, et al: Accuracy of recall by hypnotically age-regressed subjects. J Abnorm Psychol 1986; 95:298–300
27. Spiegel D, Frischholz EJ, Spira J: Functional disorders of memory. Rev Psychiatry 1993; 12:747–782
28. Romijn H: About the origin of consciousness: a new multidisciplinary perspective on the relationship between brain and mind. Proceedings of the Koninklijke Nederlanse Akademie van Wetenschappen 1997; 100:181–267
29. Fink M: How does convulsive therapy work? Neuropsychopharmacology 1990; 3:73–82
30. Folkerts H: The ictal electroencephalogram as a marker for the efficacy of electroconvulsive therapy. Eur Arch Psychiatry Clin Neurosci 1995; 246:155–164
31. Weiner RD, Krystal AD: EEG monitoring of ECT seizures. Prog Psychiatry 1993; 38:103–109
32. Fink M: Induced seizures and human behavior: clinical aspects of convulsive therapy, in Psychobiology of Convulsive Therapy, edited by Fink M, Kety S, McGaugh J, et al. New York, Wiley, 1974, pp 117, 271–277
33. Wieser H-G: Seizure induction in reflex seizures and reflex epilepsy. Adv Neurol 1998; 75:69–85
34. Gloor H: Experiential phenomena of temporal lobe epilepsy. Brain 1990; 13:1673–1694
35. Declerck AC: Interaction Epilepsy, Sleep Antiepileptics: A Clinical, Neurophysiological Study. Lisse, The Netherlands, Swets and Zeitlinger, 1983
36. Trimble MR: Psychiatric and psychological aspects of epilepsy, in The Epilepsies, edited by Porter RJ, Morselli PR. London, Butterworth, 1985, pp 322–355
37. Niedermeyer E: The Epilepsies. Baltimore, Urban and Schwarzenberg, 1990
38. Delgado JMR: Physical Control of the Mind. New York, Harper and Row, 1969
39. Lance JW, Hickie I, Wakeford D, et al: An akinetic-rigid syndrome, depression, and stereotypies in a young man. Mov Disord 1998; 13:835–844
40. Gerner RH, Post RM, Gillin JC, et al: Biological and behavioral effects of one night's sleep deprivation in depressed patients and normals. J Affect Disorders 1984; 6:283–286
41. Benca RM: The affective disorders, in Sleep, edited by Cooper R. London, Chapman and Hall Medical, 1994, pp 526–556
42. Wu JC, Bunney WE: The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiatry 1990; 147:14–21
43. Gillin JC, Kripke DF, Janowsky, DS, et al: Effects of brief naps on mood and sleep in sleep-deprived depressed patients. Psychiatry Res 1989; 27:253–265
44. Moellentine C, Rummans T, Ahlskog JE, et al: Effectiveness of ECT in patients with parkinsonism. J Neuropsychiatry Clin Neurosci 1998; 10:187–193
45. Kumar R, Lozano AM, Montgomery E, et al: Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease. Mov Disord 1998; 13(suppl 1):73–82
46. Lüderitz B, Pfeiffer D, Tebbenjohanns J, et al: Nonpharmacologic strategies for treating atrial fibrillation. Am J Cardiology 1996; 77:45A–52A
47. Kristiansen K, Courtois G: Rhythmic electrical activity from isolated cerebral cortex. Electroencephalogr Clin Neurophysiol 1949; 1:265–272
48. von Krosigk M, Bal T, McCormick DA: Cellular mechanisms of a synchronized oscillation in the thalamus. Science 1993; 261:361–364
49. Niedermeyer E: Alpha rhythms as physiological and abnormal phenomena. Int J Psychophysiol 1997; 26:31–49
50. Small JG, Milstein V, Kellams JJ, et al: EEG typography in psychiatric diagnosis and drug treatment. Ann Clin Psychiatry 1989; 1:7–17
51. Schear H: The EEG pattern in delirium tremens. Clinical Encephalography 1985; 16:30–32
52. Slaby AE, Cullen LO: Dementia and delirium, in Principles of Medical Psychiatry, edited by Stoudemire A, Fogel BS. New York, Grune and Stratton, 1987, pp 135–175
53. Hanley J: Electroencephalography in psychiatric disorders, in Psychobiology and Psychopharmacology, edited by Flach F. New York, WW Norton, 1988, pp 190–212
54. Small JG, Milstein V, Medlock CE: Clinical EEG findings in mania. Clinical Electroencephalography 1997; 28:229–235
55. Keshavan MS, Reynolds CF III, Miewald JM, et al: Delta sleep deficit in schizophrenia: evidence from automated analysis of sleep data. Arch Gen Psychiatry 1998; 55:443–448
56. Kupfer DJ, Thase ME: The use of the sleep laboratory in diagnosis of affective disorders. Psychiatr Clin North Am 1983; 6:3–25
57. Armitage R: Microarchitectural findings in sleep EEG in depression: diagnostic implications. Biol Psychiatry 1995; 27:72–84
58. Hubain PP, Souery D, Jonck L, et al: Relationship between the Newcastle scale and sleep polysomnographic variables in major depression: a controlled study. Eur Neuropsychopharmacol 1995; 5:129–134
59. Brunner DP, Kräuchi K, Derk-Jan D, et al: Sleep electroencephalogram in seasonal affective disorder and in control women: effects of midday light treatment and sleep deprivation. Biol Psychiatry 1996; 40:485–496
60. Berger M, Riemann D: REM sleep in depression: an overview. J Sleep Res 1993; 2:211–223
61. Pelliecia A, Ginnotti F, Trasatti G: Rudimentary spike-wave complexes in children during drowsiness. Neurophysiol Clinique 1990; 20:247–252
62. Freemon FR: The practical value of sleep recorded during the clinical electroencephalogram. J Am Acad Psychiatry Neurol 1976; 1:105–108
63. Walker MP, Ayre GA, Ashton CH: A psychophysiological investigation of fluctuating consciousness in neurodegenerative dementias. Human Psychopharmacology 1999; 14:483–489
64. Herrmann WM, Schärer E, Delini-Stula A: Predictive value of pharmaco-electroencephalography in early human-pharmacological evaluations of psychoactive drugs. Pharmacopsychiatry 1991; 24:196–205