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Adaptations and pathologies linked to dynamic stabilization of neural circuitry

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Abstract

Brain circuits for infrequently employed memories are reinforced largely during sleep by self-induced, electrical slow-waves, a process referred to as "dynamic stabilization" (DS). The essence of waking brain function in the absence of volitional activity is sensory input processing, an enormous amount of which is visual. These two functions: circuit reinforcement by DS and sensory information processing come into conflict when both occur at a high level, a conflict that may have been the selective pressure for sleep's origin. As brain waves are absent at the low temperatures of deep torpor, essential circuitry of hibernating small mammals would lose its competence if the animals did not warm up periodically to temperatures allowing sleep and circuit reinforcement. Blind, cave-dwelling vertebrates require no sleep because their sensory processing does not interfere with DS. Nor does such interference arise in continuously-swimming fishes, whose need to process visual information is reduced greatly by life in visually relatively featureless, pelagic habitats, and by schooling. Dreams are believed to have their origin in DS of memory circuits. They are thought to have illusory content when the circuits are partially degraded (incompetent), with synaptic efficacies weakened through infrequent use. Partially degraded circuits arise normally in the course of synaptic efficacy decay, or pathologically through abnormal regimens of DS. Organic delirium may result from breakdown of normal regimens of DS of circuitry during sleep, leaving many circuits incompetent. Activation of incompetent circuits during wakefulness apparently produces delirium and hallucinations. Some epileptic seizures may be induced by abnormal regimens of DS of motor circuitry. Regimens of remedial DS during seizures induced by electroconvulsive therapy (ECT) apparently produce temporary remission of delirium by restoring functional or 'dedicated' synaptic efficacies in incompetent circuitry. Sparing of sensory circuitry in fatal familial insomnia seemingly owes to supernormal circuit use in the virtual absence of sleep. ECT shocks and cardioverter defibrillation may have analogous remedial influences.

Keywords: Synaptic refreshment; Sensory processing; Non-sleeping vertebrates; Deep torpor; Authentic versus illusory dreams; Delirium; Fatal familial insomnia

1. Introduction

Two major functions of the brain are the storage and maintenance of memory circuits (unless otherwise indicated, both experiential and inherited memory circuits are referred to). Experiential memories become established initially by a tailoring of circuit synaptic efficacy values for specific functions in the course of circuit use. When the functions recur sufficiently frequently, the tailored efficacy values are maintained (refreshed) by use-dependent synaptic plasticity. Many adaptive functions, however, occur only infrequently. As degradative and depletional processes are in continuous operation, synaptic efficacy values in circuits for infrequently used functions gradually would depart from their 'dedicated' values in the absence of a mechanism to refresh them over the long term. For these circuits, a self-induced brain mechanism comes into play that accomplishes long-term maintenance.

Essentially the same basic mechanism (termed "dynamic stabilization" (DS)) apparently refreshes synaptic efficacies in circuits for both frequently and infrequently occurring functions, both inherited and experiential, including inherited memories expressed only late in adult life. For frequently occurring functions, the mechanism is simply the use of the circuitry in implementation of the functions ("functional" DS). For infrequently occurring functions, the circuitry is activated repetitively during sleep by self-induced, electrical slow-waves ("non-utilitarian" DS). This latter form of reinforcement is said to be "non-utilitarian" because dedicated functions usually are not triggered (because of lesser or lower frequency inducing potentials or temporarily raised activation thresholds) [62–64].

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"Use-dependent synaptic plasticity" takes many forms, and leads, upon activation of a synapse, to a strengthening or refreshment of its efficacy for variable periods. A mild stimulus once, every few seconds, or several times per second refreshes efficacies for fractions of a second to several minutes; more frequent or intense activations do so for many minutes to hours. A sufficiently strong or frequent stimulation of synapses in some circuits may refresh efficacies for days, or even weeks ("long-term potentiation"). Refreshments lasting for weeks to months also occur; these involve the activation of genes that otherwise are unexpressed, with a resulting synthesis and incorporation of new proteins into synapses (reviewed in Ref. [62]). Some of the roles that memory maintenance mechanisms appear to play in other neural-associated phenomena are considered here. These roles relate to: the selective pressure for the evolution of sleep; the basis for the absence of a need for sleep by many ectothermic (loosely speaking, cold-blooded) vertebrates; a basic function of piscene schooling; the ability of birds to fly for days without rest; the basis for periodic arousals of small mammals from deep torpor; genesis of dreams of authentic versus illusory content; the neural substrate for organic delirium, and the mechanism of its remediation by electroconvulsive therapy (ECT); the sparing of sensory circuitry from severe pathological changes in fatal familial insomnia (FFI); the sparing of cognitive circuitry in adults with sleeping sickness; and analogies between the actions of ECT and cardioverter defibrillation.

2. The neural substrate

2.1. Reinforcement of memory circuitry during sleep

The concept that sleep benefits brain circuitry has deep roots, reaching back at least to De Manacéïne in 1899 [29], who stated with remarkable prescience that dreams "....have a direct salutary influence insofar as they serve to exercise regions of the brain which in the waking state remain unemployed." About 65 y later, Moruzzi [75] proposed that sleep facilitates recovery processes in circuitry for learned acts.

As of that time, the studies of numerous investigators have supported the paradigm that, throughout life, repetitive, self-induced activations in the brains of endothermic vertebrates (mammals and birds) reinforce memory circuits during both rapid-eye-movement (REM) and non-REM (NREM) sleep (reviewed in Ref. [64]). The origins of the repetitive activations also have received much attention, with experimental evidence implicating primarily various slow waves – irregular sharp spikes (1/50–3 Hz), spikes resulting from spindle (7–14 Hz) and delta (1–4 Hz) oscillations, theta waves (4–10 Hz), continuous synaptic bombardment from the intrinsic neocortical networks that generate the slow sleep oscillation ($\sim$ 0.3 Hz), etc. – characteristic mostly, but not exclusively, of NREM sleep (reviewed in Ref. [64]).

2.2. The major function of the awake brain

The essence of awake brain function in the absence of volitional activity is the processing of sensory input, an enormous amount of which is visual, and for which "....the brain has developed so complex and versatile a machinery.... " [133]. Numerous studies in mammals have shown that large regions of neocortex (over 50% in macaque monkeys, *Macaca fascicularis*) are devoted to visual processing [102,120]. Some of them also contain motor, auditory, and somatosensory functions, and all are interconnected by very rich subcortical networks (reviewed in Ref. [64]). Of all the afferent fibers to the CNS in man and the 'higher' apes, one-third come from the eyes [16]. Other indications of the overwhelming sensory dominance of detailed focal vision are the findings that over 2/3rd of the 5,000–7,000 vital (lethally mutable) genes of the fruit fly, *Drosophila*, are required for normal assembly of optic ganglia and compound eyes, and that about 50% of all neurons serve visual functions [117]. Also the regulatory homeobox variant *Pax-6* at the top of the cascade for eye development is a master control gene in both vertebrates and *Drosophila* [91].

2.3. The "fundamental dogma"

There is an intrinsic basis, termed the "fundamental dogma" by Rauschecker [93], for potential incompatibilities between the brain's endogenous processing of information concomitantly with its reception and processing of sensory input: learning and memory processing involve many of the same cortical regions that process sensory information and control motor output [119]. For example, neuronal activity circulating in cortical and thalamic networks is modified by activity engendered by incoming sensory information [124]. A classical example of sensory interference is blocking of the alpha rhythm (8–12 Hz) by alerting stimuli [77].

The fundamental dogma concept dates back even much earlier than the concept of sleep being of benefit to brain circuitry, having been deduced before 1796 by Erasmus Darwin [25], based on a few simple, ingenious experiments. In 1899, De Manacéïne [29] referred to it as a "law", "....the law that every reminiscence or repetition of past movement or sensation is accompanied....by changes and processes analogous to those produced during the actual accomplishment of these movements or sensations".

Considering the sometimes enormous requirement of the active wakeful brain for processing visual information, and the potential for this activity to interfere with the brain's DS of memory circuits, a strong selection against reception of superfluous visual input to central brain regions would be expected during periods of quiet wakefulness. (As employed in the following, "quiet wakefulness" [sometimes referred to as "drowsiness," "restful waking", or "rest"] of

sighted animals is characterized minimally by behavioral quiescence [that is, cessation of voluntary activity], very little altered sensory thresholds, with responsiveness to external stimuli only somewhat less than during active wakefulness, species-specific postures, vigilance and, at most, only brief and intermittent pupillary occlusion).

3. The selective pressure for sleep

As non-sleeping animals acquired increasingly complex brains, behavioral repertories, and visual competencies, together with ever enlarging memory stores, increasing amounts of DS of memory circuits would have been required during periods of quiet wakefulness. Eventually, with continued advances in brain complexity, a condition would have been attained in which greatly increased needs for DS of memory circuits conflicted significantly with the processing of sensory inputs, predominantly visual. In other words, there came to be too much overlap in the circuitry for the two functions.

The selective pressure for the evolutionary origin of primitive sleep may have been the need to ameliorate this conflict, that is, to achieve a more profound state of brain unresponsiveness to these sensory inputs during DS of circuitry than usually occurs during quiet wakefulness. If, under this selective pressure, the brain were relieved of requirements to deal extensively with environmental input (as during sleep), DS could have proceeded unimpededly. The resulting sleep typically would have been characterized by behavioral quiescence, elevated sensory thresholds, rapid arousability by moderately intense stimuli, species-specific postures, and occluded pupils.

4. Overt links between sleep and vision

Among thousands of molluscan species, sleep occurs only in those with large, image-forming eyes, and/or enlarged visual brain regions. These include octopuses, squids, cuttlefishes, and nautiluses [22,55,74,83,122]. Among other invertebrates, I know of no species with compound eyes that is known conclusively to lack behavioral sleep, nor of any species that exhibits behavioral sleep but lacks detailed focal vision.

Sleep in honey bees has been studied in detail. As judged by behavioral and physiological criteria, it greatly resembles that in many vertebrates, including decreased muscle tone, irregular changes in neck muscle tone, and twitching of the terminal segments of appendages [58,59]. Behavioral sleep also occurs in grasshoppers, wasps, flies, dragonflies, butterflies, moths, beetles, cockroaches, and scorpions. In some of them, sleep deprivation causes the accumulation of a behavioral sleep debt [19].

Evidence from cold-blooded vertebrates is of a different nature, but crucial. Sleep is unknown in any genetically blind species, including cave-dwelling fishes and salamanders [15,85,106], burrowing, worm-like hagfishes [105], and ‘primitive,’ legless amphibians, the caecilians [104]. Quiet wakefulness (without sleep), which usually is engaged in under conditions of relative safety, is known in one species of frog and three species of reptiles [19]. Negative correlations between vision and sleep in mammals and birds are even more highly suggestive. For example, to sleep, we must block patterned visual input by closing our eyelids. People who cannot keep their eyelids closed (the floppy-eyelid syndrome) must bury their faces in a pillow, or shield their eyes from visual input in some other way [18]. If eyelid closure were merely for protection of the cornea, opacity would not be required.

The most compelling negative correlation between vision and sleep is that many birds engage in NREM sleep with only one half of their brains at a time, and with the lids of only the opposite eye closed; as soon as the lids of one eye close, the opposite half of the brain falls asleep. The two actions are so closely associated that eyelid closure is regarded as the equivalent of sleep, and its most reliable behavioral indication [1,60,116].

Both right and left “unihemispheric” sleep occur in each individual. This is possible for birds because the nerves from each eye cross over (decussate) completely in the optic chiasm, making direct connections only with the opposite half of the brain [79,118]. However, secondary recrossing fibers may exist at several ‘higher’ levels of the brain, connecting the visual target regions of the two hemispheres [101].

During brief periods of REM sleep (usually lasting about 5–6 s, and not exceeding 30 s) the lids of both eyes are closed [1,6]. Even in domestic chicks, which do not sleep unihemispherically, electroencephalographic (EEG) patterns differ in the two hemispheres when visual input to one eye is blocked; the contralateral hemisphere exhibits slow wave activity while the ipsilateral one exhibits the typical pattern of arousal [81,82].

Dolphin optic nerves also decussate completely [96,125], and dolphins also engage in unihemispheric NREM sleep, in which case the open eye is said to perform a “sentinel” function. This ability allows dolphins and some other marine mammals to be active unceasingly [76,80]. The blind Indus river dolphin, inhabiting the murky, turbid Indus river, is “always on the go, day after day, year after year” [86]. Unlike birds, however, dolphins do not engage in REM sleep. They apparently do not require REM sleep, a major function of which is believed to be the non-utilitarian DS of motor circuitry [64](see, also, Section 8), because their motor circuitry undergoes virtually unremitting functional DS through continuous use.

5. Ancillary benefits of sleep

The proposed origin and primal function of sleep would not rule out the subsequent or concomitant evolution of

ancillary benefits that may have become essential in some forms. Indeed, for almost all endothermic (loosely speaking, warm-blooded) vertebrates, ancillary or secondary functions of sleep, such as bodily rest and rejuvenation, physiological restoration, regulation of hormonal secretions, and reinforcing of the immune system also appear to come into play, as well as deep-seated, circadian rhythmical changes that engage many physiological systems [32,123]. The physiological and thermoregulatory continuities between sleep and shallow and deep torpor (hibernation) in some mammals and birds indicate that energy conservation also is an ancillary benefit of sleep [10]. Carefully controlled efforts to identify sleep's basic function in mammals [95] are complicated by such ancillary benefits, and results of such studies remain ambiguous [94].

However, the ability of many fishes to swim continuously shows that bodily rest and rejuvenation, physiological restoration, energy conservation, and deep-seated, circadian rhythmical changes, at least, are not inherently indispensable. Many continuously swimming fishes would suffocate if they were to stop swimming [65].

6. Continuously-swimming fishes

Although most fishes rest or sleep, some are perpetually active, including lamnoid sharks (such as great whites, porbeagles, and makos), scombrids (such as tunas, bonitos, mackerels, and albacores), salmonids (salmon and trout) and many nocturnal, reef-dwelling fishes that school. A consideration of features common to the quite different lifestyles of these non-sleeping fishes points compellingly to a link between the generally very limited use of their vision and the absence of a need for sleep.

Four factors are believed to account for the absence of a need for rest or sleep by continuously swimming fishes: (a) their conspicuous habit of schooling, by greatly reducing needs for sensory information processing, provides the essential benefits of quiet wakefulness and sleep; (b) reduced visual input during nighttime swimming interferes minimally with non-utilitarian DS; (c) as their motor circuits are reinforced during continuous swimming, these circuits require no non-utilitarian DS; and (d) they lead a comparatively routine (including continuous predator-prey pressure), pelagic existence, with the accumulation of relatively few experiential memories, compared to fishes that rest or sleep [65].

6.1. Obtaining the essential benefits of rest and sleep by schooling

Piscene schooling is described in detail elsewhere [65]. The key consideration, pointing to a probable basic function of inactive schooling (i.e., schooling at a relatively fixed location) relates to brain activities facilitated by the lesser requirements for sensory processing. The fishes at inner positions of schools need not exercise the full range of their sensory capabilities – they have no need to 'listen' 'smell', or process complex visual information. They need only maintain awareness of their position with respect to nearest neighbors, which also can be accomplished with the lateral line system [65].

On the average, then, the amount of sensory processing carried out in the brains of inactively schooling fishes is reduced greatly compared to the amount in alert, solitary swimmers. In effect, the burden of sensory processing is shifted from individuals to the entire school collectively [43,44,65,110,127]. For these reasons, inactive schooling provides the essential benefits for schooling fishes that quiet wakefulness and sleep provide for non-schooling fishes. With the need for processing of sensory input, particularly visual, during schooling greatly reduced, conditions are favorable for the non-utilitarian DS of infrequently used memories, with minimal interference.

It will be evident that similar benefits of a reduction in needs for sensory processing that apply for inactively schooling fishes also probably apply for the members of avian flocks (perhaps even for solitary birds) on long migrations. In the conditions encountered in flight, there is little need to exclude visual input, as there is little or no detail to be seen, and almost half of the time is spent in dim light or darkness. Any employed terrestrial or celestial cues would not require detailed visual analysis. Thus, the minimal interference of sensory input with reinforcement of memories for birds flying under such conditions could account for the ability to go without rest or sleep for long periods.

7. Deep torpor

Some small mammals, for example the Arctic ground squirrel (*Spermophilus parryii*), periodically enter a state of deep torpor during winter seasons, during which body temperatures may decline to as low as −2 to 5°C and brain waves cease [24]. The adaptive value of deep torpor lies in the accompanying energy conservation, which helps to tide the animals over the winter period of nutritively poor conditions. Paradoxically, however, all mammals that engage in deep torpor, periodically – every one-to-three weeks – warm up to their 'normal' (euthermic) activity temperature range, a process that requires a great deal of energy. After sleeping for about 12–18 h at euthermic temperatures, they re-enter deep torpor.

The paradox centers around the failure to conserve even more energy by remaining in deep torpor throughout the entire winter. Its resolution is thought to lie in the circumstance that the normal restorative functions of sleep do not occur at the low brain temperatures of deep torpor, so that a 'sleep debt' accumulates. This debt has to be discharged during the sleep obtained on periodic returns to euthermic body temperatures [7,24,49].

From the perspective of the need for DS of circuitry during sleep, a more specific proposal can be made, as

follows. One-to-three weeks at −2 to 5°C is the longest period for which circuits for most memories can remain in functional states in the total absence of non-utilitarian DS. During the phase of resumption of euthermic temperatures with 12–18 h of sleep, the efficacies of synapses in these circuits are refreshed by DS. Afterwards the circuits can be sustained in functional states for another 1–3 weeks before once again requiring to be reinforced.

In a sense, the animals at the low temperatures of deep torpor approximate a 'return' to cold-bloodedness. In this condition the ancillary benefits of sleep perhaps can be dispensed with, as in many ectothermic vertebrates, but the primal function of sleep – non-utilitarian DS of memory circuitry – is indispensable. Were the animals to remain in deep torpor for longer than 1–3 weeks without refreshment of the synaptic efficacies of unused memory circuits, the circuits probably would become incompetent beyond recovery.

8. Dreaming

8.1. Dream genesis and significance

Viewed from the perspective of the paradigm of functional and non-utilitarian DS, certain implications emerge concerning the origin, content, significance, and evanescent nature of dreams [63,64]. Only those implications that are pertinent to the present treatment are dealt with here.

The view championed by Hobson and McCarley [50,52], and also espoused by Greenberg [42] and Antrobus [2,3], is that dreaming is a by-product of, and tightly linked to, the mental activities that normally occur during REM sleep.

Implications of the paradigm of DS are consonant with the above cited views, specifying the "mental activities" as being the consolidation and reinforcement of circuits encoding memories, but not restricting the activities to REM sleep. Expressed from another point of view by Llinás and Paré [69], "REM sleep can be considered as a modified attentive state in which attention is turned away from the sensory input, toward memories. " The "attention" would appear to consist of reinforcement of memory circuits, with motor circuitry being reinforced primarily during REM sleep [62–64]. The large role played by motor activity in dreams, most of which occur during REM sleep [53,87], is consistent with this proposal.

Visual memories also must be reinforced primarily during REM sleep, because dreams usually are highly visual. An association of reinforcement of motor and visual circuitry during dreaming accords with the existence of numerous visuomotor neocortical regions [102,120]. It can be suggested that, because of the abundance of visuomotor circuits, many visual memories become activated by default during DS of the closely associated motor components, even frequently used visual circuits that need no non-utilitarian DS.

Foulkes' positions as to both dream genesis and significance are similar to those expressed here and elsewhere [63,64]: dreams are formed by an arbitrary, more or less random "diffuse mnemonic activation" of recent and long-term memory circuits that accomplishes some information processing but is too ill-organized and diffuse to have semantic or communicative significance; the particular contents of dreams, in and of themselves, are unlikely to serve any adaptive function [36].

8.2. Authentic recent recall versus illusoriness or delirium

The tendency of dreams to favor current events, the "day residues" of Freud, which occur in 47%–49% of dreams [46], and of these dreams to be lengthily coordinated and more or less authentic in content, may owe to the integrative role of the hippocampus in "replaying" only relatively recent events to the neocortex [62,63]. Most of these "day residues" apparently are stored in the hippocampus with low priority, namely, the ones that are not "replayed" after the first night or two.

The illusory content or delirium of dreams doubtless traces in part to such influences as impaired binding of circuits without real world feedback, as proposed by Kahn, Pace-Shott, and Hobson [57], and altered alignments and participation of circuits during dreaming as compared to those of wakefulness, as proposed by Braun, et al. [14]. The preponderance of authentic, "ordinary and mundane" dreams [36], however, is not accounted for by such influences. Authentic dreams presumably employ the same circuit alignments and participation, and with similarly impaired circuit binding without real world feedback, as do illusory dreams. The thesis proposed here, is that the potential for dream events to be either authentic or illusory is inherent in the dream-generating mechanism, itself, that is, in the DS of memory circuits.

In this connection, very little is known of the comparative competence and priority for reinforcement of various categories of memory circuits – inherited versus experiential, recently acquired versus old – on any night when sleep begins. Presumably the vast majority are fully competent at the time of reinforcement, and merely have their competence extended for days to weeks at a time. Some experiential memories of the distant past, at least, must be in various temporary or 'permanent' states of partial efficacy decay, with their information content incomplete, garbled, or distorted.

Additionally, inasmuch as the various self-initiated brain waves that achieve non-utilitarian DS are predominantly of low frequency, and persist for long periods during every night's sleep, it is not unlikely that refreshment of synaptic efficacies occurs in small steps over lengthy periods. Such stepwise refreshment of some experiential memories of the distant past, requiring lengthy periods and having low

priority, might account for the persistence of some circuits in various states of temporary incompetence. Explicit recognition of these possible circumstances may help to account for some healthy and pathological mental phenomena (see below and Section 11).

On these assumptions, the synaptic activations of non-utilitarian DS that lead to dreams of authentic content might be those of newly consolidated circuits, and other circuits with fully refreshed (or not-yet-weakened) synaptic efficacies. The inauthentic or illusory content of some dreams may owe to playback from older, incompetent circuits, in which some efficacy values have weakened. Such circumstances are consistent with the strong tendency toward authentic dream recall of recent events, and tendencies toward illusory events in dreams of the more distant past. In this connection, 68% of adult dreams contain central features directly reminiscent of childhood experiences [54].

9. Delirium

Delirium is the most frequently occurring non-specific, acute, organic, psychiatric syndrome, for which older people are at greatest risk. Toxic metabolic disorders are the most common cause. Clouding of consciousness, fluctuating over the course of a day, is its hallmark. Onset of symptoms usually is acute and worse at night, when agitated behavior and visual hallucinations are most likely to occur. Insomnia, nightmares, intermittent night time disorientation, and anxiety appear first, gradually progressing to full-blown delirium.

Autonomic and other neurological signs accompany visual and tactile hallucinations. Associated features include purposeless movements of arms and legs and multifocal myoclonus (most often in facial and shoulder muscles) and tremor. Symptoms characteristically are global and of relatively brief duration. Delirium usually is a medical emergency. Delirious patients, particularly if under 40, are predisposed to early death, with fatality rates (7%–12%) twice those of control groups [111].

The Scottish royal physician, W. Cullen [23], was the first, in the 18th century, to remark on the similarity of dreaming to delirium. “There are in this state [dreaming] false perceptions, false associations, false judgements, and disproportionate emotions; in short all the circumstances by which I have above defined delirium. ” Today, we make an even stronger connection between the two phenomena. Thus, “....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” [51; see also 54].

Coupling this conclusion with the above analysis, it is proposed that a breakdown of normal regimens of non-utilitarian DS (i.e., any deviation from timing, magnitude, distribution, etc., of normal waveforms) of certain categories of memory circuits, leaving many with synapses in incompletely restored and/or pathologically altered states of efficacy, leads to organic delirium. (Bleuler [11] and Kelly [66] propose a different, but not incompatible, interpretation, specifically, that delusions of schizophrenics have their origin in remembered illusory dreams that masquerade as authentic experiences. However, they do not address the crucial matter of how neural circuitry evolved largely for the storage and maintenance of authentic information becomes subverted to produce cognition that includes fanciful components.)

Viewing many illusory dreams as the consequence of DS of circuits with incompletely restored or otherwise altered synaptic efficacies, it can be suggested that some other psychoses than delirium also result from a breakdown of normal regimens of DS. The proposed breakdown would leave certain categories of neural circuits in an incompetent state, with efficacies of some synapses disrupted or incompletely restored.

This incompetence, of course, would become most evident in circuits that are in frequent use, particularly cognitive and sensory circuits. Use of these incompetent circuits during wakefulness presumably gives rise to the same illusory thoughts and perceptions (hallucinations) that occur in dreams that result when similarly incompetent circuits are activated during sleep.

9.1. Delirium and the specific remedial effects of electroconvulsive therapy

ECT is of great clinical use for organic delirium; for delirium tremens, even a single use can be life saving. The key action of ECT and pharmacoconvulsive therapy is known to be the production of a generalized motor-type seizure within the brain, quite independently of whether the seizure is accompanied by motor convulsive responses [111,129,130]. Taking these considerations into account, it is proposed that the specific remedial influences of these therapies hinges upon their restoration of dedicated synaptic efficacies in incompetent circuits through remedial regimens of DS that accompany and follow the brain seizures.

Inasmuch as the regimens of DS that accompany seizures are induced by external means and may not be typical, may not target circuits in the normal manner, and are not sustained as lengthily as during sleep, it is not surprising that the seizures of ECT sometimes cause adverse side-effects, and that therapeutic effects usually are not long-lasting (without repeated treatments).

Amnesia, for example, appears to be a side-effect, consequent upon disruptions of synaptic efficacies in certain memory circuits from their dedicated values, brought about largely by the electrical shock employed to induce ECT. The prevailing view is that “....memory impairment is mainly determined by the amount of electrical current.... ” [28]. The length of time required for normal regimens of DS

of these specific 'amnesic' circuits (which were not involved in the original delirium) to achieve memory recovery during subsequent sleep probably depends on the degree to which synaptic efficacies were disrupted by the ECT shock.

This proposed mechanism of achievement of specific remedial effects of ECT – induction of remedial regimens of DS in incompetent circuitry during and following seizures – has the potential to resolve some of the classical problems of ECT. These involve "....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" [34].

The specific remedial effects of ECT previously were attributed primarily to the cerebral biochemical events that unfold in consequence of the seizure(s) [33]. From the present perspectives, for delirium, at least, the gradual post-treatment decay from therapeutically re-established synaptic efficacy values to deviant pathological values would be the consequence of a failure to achieve normal refreshment of synaptic efficacies because of the persistence of the causative abnormal regimens of DS during sleep.

This scheme of remediation also could help to account for the equal effectiveness of ECT for both severe mania and severe depression, clinically assumed to be "....opposing neurohumoral pathologic processes" (34). It also is consistent with the exertion of a specific antidelirium effect on underlying pathophysiological mechanisms in at least some conditions, including delirium tremens, typhoid catatonia, CNS syphilis, and phencyclidine psychosis (129), and the need for a period of maturation of ECT effects [33].

It was noted above that the brain waves that accomplish DS during sleep are predominantly at low frequencies (below $\sim$ 14 Hz). Thus, the nature of the remedial brain waves induced by ECT is of interest. The typical electrophysiological response in the brain after ECT is an initial, brief (0.5–1.0 s) expression of high-voltage, high-frequency electrical activity followed by extended rhythmic slow-wave activity, ending abruptly with a period of EEG silence [33]. Most of the EEG energy occurs in the delta waves at $\sim$ 3 Hz, which are suspected to be crucial to the therapeutic effect [35,114].

The increase in amplitude and building up of slow waves (both delta and theta) is of longer duration when a series of treatments are given, and tends to be non-specific to a variety of neuropathologies [130]. Usually, after 3 or 4 treatments at 2–3 day intervals, slow waves fail to disappear completely. Subsequent treatments result in the slow-wave activity becoming more widespread, of higher amplitude and lower frequency, while the alpha rhythm becomes disturbed and may disappear. At a variable period after treatments are terminated, the delta rhythm gives way to theta activity, and prolonged, synchronous alpha activity re-emerges. Finally, the EEG returns to its pre-ECT state [67].

10. Sparing of sensory circuitry in fatal familial insomnia

10.1. General considerations

FFI is an inherited, rapidly progressing, neurodegenerative, multisystem, prion disease (a subacute spongiform encephalopathy). Sleep loss associated with FFI correlates best with a consistent, severe atrophy (severe cell loss, usually well over 50%) of the anteroventral and mediodorsal thalamic nuclei and frequent atrophy of the centromedial and puvinar nuclei [73,121]. The disease has very complex, multisystem effects.

The immediate cause of death of FFI patients is uncertain but it is unlikely to be solely the insomnia. The inability of patients to recover from their malignant insomnia, and the autonomic impairments, suggest the additional involvement of progressive functional deficits in non-thalamic brain structures [88,115].

The symptomatology of FFI is of particular interest in respect to the brain's need to refresh synaptic efficacies in infrequently used memory circuitry. Recognizing the strong tendency of living systems to compensate for disease state abnormalities, one expects a number of manifestations of compensatory tendencies to appear in FFI patients. For example, with the curtailment of sleep, one anticipates a tendency to achieve some compensatory non-utilitarian DS of circuitry while awake. In normal circumstances, circuit outputs either are blocked during sleep or their activations become manifested only as inconsequential phasic events [63,64], dreams, and other sleep mentation. As these outputs usually are not blocked during wakefulness, the compensatory DS might lead to activation of the corresponding circuit functions in awake FFI patients, including motor and cognitive processes.

Moreover, during the ever shorter episodes of sleep, one expects the manifestations of non-utilitarian DS to be more intense, just as, for example, the phenomena occurring during REM sleep become more "intense" when REM sleep time is restricted [100]. One also would anticipate signs of deficits in some of the functions of circuitry normally reinforced during sleep. Lastly, there is reason to expect sensory systems to be spared, as their circuits would continue to receive functional DS. In fact, they should receive supernormal amounts of functional DS, because the further the course of the disease, with progressively less sleep and greater wakefulness, the greater the amount of use they would receive. These expectations are largely fulfilled.

10.2. Specific manifestations and proposed relationships

The commonly noted specific symptoms of FFI are as follows. There is impairment of all forms of memory, attention, vigilance, and visuomotor performance, and other losses of higher levels of cognitive function, with signs of

dementia in late stages. Dreams during actual sleep episodes are very vivid and enacted, that is, they are accompanied by complex gestures and many other fully manifested movements of the head, trunk, limbs, and fingers. These closely mimic dream content and tend to intrude spontaneously on wakefulness. Wakefulness typically is interspersed with complex hallucinations that often consist of enacted dream-like episodes [17,38,89,90].

There also are irregular muscular jerks and fine tremors of the arms, a clumsy gait – progressing to inability to stand or walk – brisk reflexes, Babinski's sign, spontaneous movements of the head, spasms in the limbs and digits, severe irregularities of heartbeat and breathing (impaired, with apnea), difficulties in speaking – progressing to unintelligibility – incontinence, increased lacrimation, salivation, and sweating, saccadic eye movements, and eventual widespread continuous muscle spasms.

Most pertinent to this analysis, the sensory systems remain unimpaired by the disease. For example, visual and somatosensory evoked potentials are normal, and geniculate nuclei, which play a large role in visual sensory processing, often are minimally affected [17,38,89,90]. This more than normal use of the senses during insomnia apparently has a protective effect on sensory systems, that is, supernormal functional DS of sensory circuitry may retard or inhibit plaque formation in neurons. A similar conclusion has been reached from studies of Alzheimer patients, from which it was concluded that an active intellect (i.e., supernormal functional DS of cognitive circuitry) appears to protect against dementia in the elderly [112].

The existence of such a protective effect of supernormal use of circuitry in FFI raises another possibility. The basis for the generally increasing vulnerability of nervous systems to plaque formation with advancing age in prion spongiform encephalopathies, such as kuru, Creutzfeldt–Jakob disease, and the Gerstmann–Sträussler–Scheinker syndrome [17,38,89], may be lesser use, that is, subnormal amounts of functional DS of some neural circuitry.

In view of the increasingly severe, widespread, multisystem, debilitating and incapacitating functional failures in FFI, in which patients lose all voluntary capabilities, and even autonomic functions ever increasingly fail, the following suggestion can be made. Those symptoms of FFI (other than the insomnia) that are not shared with other prion spongiform encephalopathies are not solely direct consequences of neurodegenerative changes; the functional failures also may trace to indirect consequences of widespread insufficiencies of DS of neural circuitry, largely non-utilitarian and resulting primarily from the inability to sleep. The death of totally sleep-derived rats [32,95] may trace to functional failures of the same origin.

10.3. Contrast with encephalitis lethargica

Having considered a greatly debilitating disease in which little or no sleep can have a strikingly protective effect on neural circuitry, a contrary situation becomes of considerable interest. This concerns another greatly debilitating disease, *encephalitis lethargica* (also known as sleeping sickness, epidemic stupor, and von Economo's disease), in which, contrariwise, it is excessive sleep that has a strikingly protective effect on neural circuitry. Both effects seemingly owe to supernormal DS, functional for FFI but non-utilitarian for *encephalitis lethargica*.

Although evidence that the major EEG effectors of non-utilitarian DS are slow waves has come from experimental studies (see, Section 2.1), this relationship also might have been deduced from symptoms and sequelae of *encephalitis lethargica*. In its commonest, hypersomnolent form, patients lapse into a catatonic stupor that may last for weeks or months (interrupted by forced arousals for eating and eliminating). The EEG is described as "diffuse, asynchronous delta and theta activity" or simply "diffuse slow-wave activity. "

Many patients recover completely, but postencephalitic parkinsonism (of long latency) is the commonest ($\sim$ 60%) sequel [13,56,103,107,128]. Except in children and adolescents, in which mental development is arrested [26], "[o]ne thing, and one alone, was (usually) spared amid the ravages of this otherwise engulfing disease: the 'higher faculties' — intelligence, imagination, judgement, and humour" [107]. These circumstances, thus, are in accord with the thesis that DS of memory circuits is effected primarily by EEG slow waves. Cognitive functions would appear to be preserved in this disease state by the supernormal non-utilitarian DS of cognitive circuitry during the lengthy periods of hypersomnia.

11. Discussion

Reasoning from the premise that some circuitry undergoing DS during sleep is partially degraded, with inauthentic stored information, leads to potentially significant conclusions. Not only could it account for the "healthy psychosis" of illusory dreaming (and hallucinations after sleep deprivation) and provide a foundation for understanding the genesis of 'healthy' delirium and some mental disorders, it could lead to an extension of knowledge of the fundamentals of synaptic efficacy refreshment.

In the latter connection, with synaptic efficacies being able to depart from their dedicated functional values (those that produce authentic memories), synapses may have set-point mechanisms that define these dedicated efficacy values, below which contained information is degraded. The set-points may either limit remedial efficacy increases to the attainment of these values or, possibly, only define minimum values. We have no information on how the efficacy enhancements by DS relate quantitatively to the type of synaptic plasticity that originally established synaptic efficacies for dedicated functions.

Assuming that the slow waves that accomplish DS act to

enhance synaptic efficacies (whether stimulatory or inhibitory), it has been suggested that elaborate controls (selectivity) would be required, lest indiscriminate DS reinforce all weak synapses, which would "negate the functional value of extinguishing incorrect, useless, or harmful responses" [94].

However, circuits in complex brains (if not all brains) typically are multifunctional, with neurons and circuits subserving more than one function. As a result, natural selection typically cannot eliminate neural circuitry for single obsolete functions, as that also would entail a concomitant loss of circuitry for many adaptive functions. Accordingly, the typical mode of elimination of maladaptive responses appears to be, not by allowing synapses in their circuits to weaken, but, rather, through the mechanisms of blocking or inhibiting specific circuit outputs, or raising activation thresholds [61].

If, as proposed, some degraded circuitry remains during active wakefulness after normal sleep, its contents must be non-intrusive or not readily accessible. Otherwise, hallucinations and faulty recall would be common among normal, active individuals. The evidence favors such a persistence of some degraded circuitry with non-intrusive, not-readily-accessible contents. Thus, hallucinations and bizarre mentation (recall from degraded circuitry) are possible during periods of quiet wakefulness (in the presence of alpha activity), and can be induced by various means in normal individuals [72].

For example, it is perhaps well known to many through self-experiences, and it has been established experimentally, that in reclining, relaxed, normal individuals, with eyes closed or in the absence of patterned visual input (a condition favorable for non-utilitarian DS), "....thought is fairly susceptible to momentary intrusions of bizarre content or hallucination....in a variety of psychophysiological conditions and without any extraordinary induction techniques" [37].

While results of regression hypnosis are not taken at face value, they also are in accord with the view that partially degraded circuits exist, at least among those containing information about the distant past. For example, when adults in a hypnotic trance are taken back in time, they may remember their first school days, including detailed images of classrooms, teachers, classmates, and even sounds and feelings. However, careful verification attempts reveal that these re-experiences can contain fantasies and inaccuracies [103,113]. (Recall Wolberg's [131] admonition, that the content of re-experiences emerging in a trance should be "....dealt with as symbolic offerings, very much like fantasies or dreams.")

From the present perspectives, the existence of this inauthentic content of re-experiences could be evidence of faithful recall, but from partially degraded circuitry. Conventionally, however, the presence of inauthentic content of re-experiences has been taken as evidence that "the psyche smoothly fills up inconvenient gaps in the mental image" [103,113].

With non-utilitarian DS being the major mechanism of consolidation and maintenance of neural circuits, as postulated, abnormalities of its operation might lie at the basis of several of the mental disorders that benefit (usually only temporarily) from ECT. Some spontaneous epileptic activity, for example, could have such a basis, with the abnormal DS of motor circuitry, itself, inducing the seizures (presumably, recurrent spontaneous seizures would not lead to progressive deterioration). Of interest in this connection, during the seizures that accompany the abnormal NREM sleep of patients with generalized epilepsies, sleep spindles, one of the putative slow-wave effectors of DS, may merge into epileptiform discharges [27].

As normal DS of circuitry during sleep is thought to be accompanied by dreams, one might expect an induction of analogous phenomena by the abnormal regimens of DS postulated to cause epileptic seizures. Indeed, temporal lobe seizures (and electrical stimulation of limbic structures of the temporal lobe) often are accompanied by illusions and hallucinations. These may consist of recall of a past event or situation – most commonly visual and auditory (a static scene or face, a voice, music), and usually more vivid and intrusive than commonplace recollections [40].

With few exceptions, such as for petit–mal seizures and delirium tremens [45,109], abnormalities in characteristics of reinforcement accompanying mental disorders, which even in extreme cases do not affect all central neural circuitry, apparently are not of such an overt nature as to result in EEGs of unique diagnostic value. Thus, "....one cannot distinguish a patient with a behavioral personality disorder, an affective disorder, or schizophrenia from a normal person....none of the EEG abnormalities is sufficiently correlated with a specific psychiatric disorder to be useful in evaluating any individual case." But when patients are compared for localized cortical differences, schizophrenics have more temporal abnormalities, and patients with affective disorders, more parieto–occipital abnormalities [68].

The thesis that a breakdown in the normal regimens of DS of circuitry during sleep is responsible for some psychoses helps to explain the previously puzzling findings that sleep deprivation of any variety (that is, any reduction in the amount of abnormal non-utilitarian DS) has mood-elevating effects in patients with affective disorders, and that significant rebound of mood depression occurs in sleep-deprived patients after they obtain recovery sleep [9,39,132]. These effects tend to support the attribution of a specific remedial influence of ECT on abnormal regimens of DS, and the attribution of various influences of abnormal regimens of DS on mood. In this connection, ECT has remedial effects even in severe depressive syndromes that are not responsive to antidepressant drug regimens [8].

The proposed remediation of abnormal regimens of DS by ECT suggests an analogy with the remediative action of cardioverter defibrillators on fibrillating hearts and tachycardia. Just as the defibrillating shock halts the fibrillations and tachycardia, followed by onset of a normal heartbeat

rhythm, the electric shock of ECT halts abnormal regimens of DS of some circuitry, followed by the onset of remedial regimens; in neither case is the remediation expected to be permanent. Whereas defibrillators act only on local circuitry, and remediation rarely is accompanied by adverse effects, some ECT-inducing potentials (depending upon electrode placement) may act on the brain globally, often also producing temporary amnesia or confusion. These analogies suggest that normal regimens of DS are intrinsic to brain regions (as also could be concluded from their spontaneous resumption in squirrels warming up from torpor), and that once abnormal regimens are halted, the normal ones resume spontaneously, only gradually to regress again under the influence of the underlying pathology. Analogies extend to remediation of cardiac arrhythmias by antiarrhythmic drugs, and to shock remediation of arrhythmias that are not responsive to pharmacological therapy [71].

The ability of neuromodulators to alter profoundly the activity of neural circuits in invertebrates supports the existence of analogies between the remedial influences of ECT and psychopharmacological agents on regimens of DS in mammals. For example, many different substances, including "classical" transmitters, biogenic amines and neuropeptides can influence the activities of anatomically fixed crustacean stomatogastric (pyloric and gastric) networks. Effects include altering of firing frequency, oscillations, phasing, duty cycle, plateau potentials, and types of responses, and exciting, inhibiting, and fusing rhythms [47]. Moreover, it also is suggestive of the basis for the general remedial influences of ECT, namely, reciprocal influences of the induced brain waves on the activities of psychoactive substances.

The less than complete compatibility of non-utilitarian DS with visual input processing during quiet wakefulness was postulated to be one of the bases for the need to exclude visual input during such inactivity, and for the origin of sleep. However, the processes are not intrinsically incompatible. This is evident from the occurrence of much synchronous, high-frequency (beta- and gamma-band) activity during sleep, including large components during dreaming [70], which is highly visual. The crucial difference is that the sensory information processing and much of the synchronous, high-frequency activity during quiet wakefulness are determined adventitiously – responsive directly to uncontrolled external events – whereas the low-frequency activity that accomplishes DS during sleep is determined endogenously.

During sleep, however, because virtually all electrical activity in the brain is initiated and controlled endogenously, its occurrence is cooperative and, accordingly, compatible. More than merely being compatible, high-frequency activity doubtless acts in concert with DS of widely distributed circuits, combining aspects of dream sequences provided by the latter, for visual and non-visual experiences, motor acts, mental activity, etc., to produce fully manifested dream events. Dreaming, then, probably reflects not only non-utilitarian DS of visual and motor circuitry, but also reinforcement of the mechanisms that combine information in different parts of the brain to form thoughts, sights, and other sensory impressions and actions. In connection with the above, manifestations of the dichotomy in processing information of exogenous, as opposed to endogenous, origin are seen in the motor cortical function of macaque monkeys [97]. To process a purely cognitive event, selected groups of distributed neurons in the motor cortex preferentially synchronize their individual spike discharges without, at the same time, changing their firing rates. However, when processing an external behaviorally relevant event (stimulus, movement), the neurons also synchronize their individual spike discharges but, at the same time, modulate their firing rates. Both actions are tightly connected to the actual occurrence of the stimulus. Also, presentation of auditory stimuli during waking not only resets 40 Hz gamma-band activity, it also increases its amplitude [84], whereas during REM sleep, 40 Hz activity is not reset by auditory activity [70].

The body of reviewed information on sleep or lack thereof in members of several vertebrate classes, considered together with physiological, ecological, and behavioral attributes, lends additional perspectives to the roles various factors play in the need for sleep and the complexity of their interactions. The treatment of non-sleeping fishes emphasized the roles played by reduced dependence on vision and the possession of relatively few experiential memories. Following that, one might have expected that, if any mammal could dispense with sleep after the needs of development and maturation of the CNS were fulfilled, blind mole rats and blind dolphins would be the most likely candidates. Yet, even totally lacking detailed focal vision, both require sleep [64,65]. Accordingly, for them, the needs of relatively large, complex brains (at the low end of the cetacean scale for the Indus river dolphin; [86]) for the refreshment of synaptic efficacies in circuits that process and store non-visual memories must play a great role.

Sharks also possess well developed, relatively large brains, with the relative development of major brain divisions paralleling those of birds and mammals [4,78]. As with blind mole rats and blind dolphins, continuously swimming sharks also have a greatly reduced dependence on visual input [41], reduced by schooling, swimming at night, etc. Yet they do not sleep. In addition to low visual input, their lack of a need for sleep also may depend on much lesser requirements for non-utilitarian DS of a relatively small number of experiential memories, as compared to the number possessed by sharks that rest and sleep.

But the brains of blind mole rats and Indus river dolphins also must have a much lesser content of experiential memories than those of sighted rodents and dolphins, yet they require sleep. The clue to the probable basis for the need for sleep in blind mole rats and blind dolphins, but not in the sharks, is suggested by findings with hibernating

ground squirrels; only at the greatly reduced metabolic rates of deep torpor are needs for reinforcement of mammalian brain circuits sufficiently reduced to allow sleep to be dispensed with lengthily. Accordingly, the basis for the lack of a need for sleep in some sharks, but a need by blind mole rats and dolphins may lie in the lower level of metabolism of shark brains.

Why, then, is sleep also absent in partially warm-blooded fishes (principally lamnoid sharks and tunas), considering that metabolic rates in their brains also are at a high level [12,48]? Several possible, non-mutually exclusive circumstances may play roles to various degrees: (a) the brains of lamnids and tunas may have need to store comparatively few experiential memories; (b) functional DS of motor and much other circuitry occurs continuously in lamnid sharks and tunas (and river dolphins), but not in blind mole rats; (c) the higher metabolic rates in lamnids and tunas generally represent only modest elevations compared to those in endotherms.

Circumstance (c) applies because the temperature elevation attained tends to be lower the warmer the water. For example, the highest temperatures in lamnoid shark muscles were less than 29°C, and that was in water at ~22°C and ~27°C. For tunas, almost without exception, muscle temperatures were elevated significantly only at water temperatures below 23°C and only exceptionally exceeded 32°C [20,21].

Taking these considerations into account, the requirement for sleep in genetically blind mammals may hinge importantly both on their possession of relatively large, complex brains and their high metabolic rates. It is primarily the function of the brain, itself, at the high temperatures of endothermy that is being taken into account in the above considerations. Factors such as energy conservation and rejuvenation of other organs than the brain would appear to belong in the category of ancillary benefits.

From the foregoing, it would appear that factors involved in the need for sleep in blind humans (beyond needs during early development of the CNS) may not be greatly different from those in blind mole rats and dolphins, including, for the blind mole rat, significant ancillary benefits (such as rest and rejuvenation, and energy conservation). In this connection, the cortical visual regions of adventitiously and congenitally blind humans remain highly active, metabolically and electrically, with highest activity in the striate and prestriate regions. Moreover, in monkeys and cats visually deprived since birth, spontaneous electrical activity in neurons of these regions is present and resembles that in non-deprived animals [98,126].

Concerning the existence of cross-modal compensatory plasticity of human cortical visual regions, suggestive evidence has been mounting. Thus, the level of activity in the primary and secondary visual cortices of adventitiously and congenitally blind subjects during auditory and tactile tasks is higher than in sighted and blindfolded controls [108], and during auditory localization tasks, the cortical 'visual' associative areas of congenitally blind subjects become activated [5].

Some have suggested that, when the level of activation of other processing-specific cortical modules of the blind is raised, heightened activity in visual regions merely reflects non-specific coactivations [98]. However, in view of other instances of cross-modal compensatory cortical plasticity in ferrets, Syrian hamsters, cats, rats [92,99], and blind mole rats [31], the known responsiveness of neurons in the visual cortices of humans and cats to auditory stimuli (40% of those in cats), and improved auditory localization by visually deprived cats [30,92,120], this position seems unwarranted.

In brief synopsis, many sharks and teleosts require no sleep because of reduced visual input and needs to process visual information, a relatively small store of experiential memories, functional DS of most inherited memories, and relatively low levels of brain metabolism, compared to endotherms. Most reptiles and amphibians require sleep because of their great dependence on vision and other senses, and because their correspondingly great needs to process ongoing sensory information during wakefulness interfere with simultaneous reinforcement of memory circuits. Blind fishes and blind amphibians require no sleep because, in the absence of vision, interference of sensory input with reinforcement of memory circuits is at a low level.

Although blind mole rats and blind dolphins dispense with almost all needs for storing and processing visual information, the combination of comparatively large, complex brains, high level of brain metabolism, and enhanced dependence on non-visual sensory systems, leads to large requirements for memory circuit reinforcement and attendant needs for sleep. The only circumstance in which terrestrial mammals achieve a state in which absence of sleep and reinforcement of memory circuits can be tolerated for long periods without ill effect, is deep torpor, with greatly lowered levels of brain metabolism. For birds, non-utilitarian DS of memories with both eyes open and without sleep apparently can occur in migrating flocks and even during solitary flight.

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