The neuropsychology of REM sleep dreaming

J Allan Hobson*,
Robert Stickgold*,
Edward F. Pace-Schott

Introduction

The field of sleep and dream research has recently been invigorated by convergent new data from two complementary neuropsychological sources (1,4). In the brain imaging and brain lesion studies to be reviewed in detail below, the evidence for a strong pontine role in human REM sleep dream generation complements the cellular and molecular level data in animal studies and reveals an unexpectedly prominent role of the limbic system in the selection and elaboration of dream plots. The emerging picture of dreaming as the synthesis of emotional and sensorimotor data generated by the distinctive mechanisms of brain activation in REM sleep will be of interest to all who share Sigmund Freud's early vision of a psychology founded on the solid base of neuroscience (5) even as it forces revision of his highly speculative dream theory (6).

The demonstration that the human brain activation pattern of REM sleep is distinctly different from that of waking has an important bearing upon our conception of how conscious states are generated by the brain. It supports the hypothesis that quite different mechanisms underlie waking and dreaming consciousness and that those differentiated mechanisms are causally determinant of the diferences in our subjective experiences of the two states. For some time, it has been the cognitive similarities between waking and dreaming that have been emphasized by dream psychologists (7-11). These similarities have been ascribed to brain activation processes that were thought to be identical in the two states and this inference of identity was supported by evidence from neurophysiology of shared electrical and ionic mechanisms for cortical EEG activation seen in both REM sleep and waking (12). Besides being unable to account for the robust differences between wake and dream consciousness (13), this inference is now clearly in need of amendment on physiological grounds.

Until now, the best available candidate mechanism for the differentiation of dreaming from waking cognition has been the drastic reduction in the release of the neuromodulators norepinephrine and serotonin which drop from their steady high leveis in waking to almost zero in the REM sleep of cats and rats (14-21). We suggest that the newly described differences in regional activation found in humans may result from the same neuromodulatory differentiation found in animal studies (reviewed in Refs 22,23) and predict that it is just a matter of time before more sophisticated imaging confirms these chemical differences in the human brain too. Indeed, a REM-related decline in CNS serotonin has recently been demonstrated in humans using depth electrodes and microdialysis (24).

Brain-mind states and the study of consciousness

One of the strongest supports for the scientifically hypothesized unity of brain and mind comes from the changes in conscious experience that we all experience when we doze off, fall deeply asleep and, later, dream. The initial loss of contact with the outside world at sleep onset with its flurry of fleeting hypnagogic images, the deeply unconscious oblivion of sleep early in the night, and the gripping hallucinoid scenarios of late night dreams all have such strong and meaningful underpinnings in brain physiology as to make all but certain the idea that our conscious experience is the brain-mind's awareness of its own physiological states (17,18). Whether or not they are accepted as firm proof of brain-mind identity, these simultaneous subjective and objective events encourage the concept of a unified system which we call the brain-mind (13). They also further encourage a detailled accounting in the separable analytic domains of neurophyslology and psychology of the events that change, or remain the same, as the brain changes state. It is within this paradigm of simultaneous conscious state and brain state change that we review and integrate data from three sources: (1) The formal and quantitative characterization of consciousness in waking, sleeping, and dreaming; (2) The cellular and molecular level brain events that have been measured in awake, NREM and REM sleeping animals; and (3) The neuropsychological analysis of the effect of brain lesions and regional blood flow changes upon the conscious states of humans.

Correspondencia: Laboratory of Neurophysiology, Department of Psychiatry, Harvard Medical School, Massachusetts Mental Health Center, 74 Fenwood Road, Boston, MA 02115, USA

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REM sleep dreaming defined

Formal features of REM sleep dreams: REM sleep dreams have several distinctive formal features which the underlying brain state must somehow determine. These include sensorimotor hallucinations, bizarre imagery, the delusional belief that one is awake, diminished self-reflective awareness, orientational instability, narrative structure, intensification of emotion, instinctual behaviors, attenuated volition, and very poor memory. Table 1 summarizes these features and documents their identification and quantification. Our discussion is based upon our psychophysiological theory of brain-mind isomorphism. We assume that any enhancement (or impairment) of any psychological function (e.g. dreaming) will be mirrored by enhancement (or impairment) of its physiological substrate's function (e.g. REM sleep). We have emphasized these formal aspects of dreaming because they are noted in all REM sleep dreams regardless of their specific narrative content. We expect that REM sleep neurobiology will be able to explain more about such features than it now can about specific dream content.

Four features of dream psychology – motor hallucinosis, emotion, bizarreness and memory deficits can now be mapped onto the physiological findings.

Dream motor hallucinosis-fictive movement: The nature of the motor hallucinations of dreams deserves special comment because it suggests that brain mechanisms subserving active motor behaviors are brought into play during REM. Thus, even office-bound intellectuals never dream of what they do every day: sitting at their desks reading, writing or analysing data (61). Instead they ski, swim, fly, or play tennis in their dreams whether or not they have recently done any of these things in their waking lives. In contrast to the deficits in memory functions discussed below, REM sleep dream consciousness routinely has *more* motor hallucinatory content than NREM consciousness and perhaps even more than most waking fantasy. In this case we must look for what has been *added* to brain function in REM. We might expect to find an enhancement of those physiological processes which subserve internal visuomotor activation. We would then predict selective activation of the visual system, the basal ganglia, the motor cortex or subcortical motor pattern generators. The neurophysiological studies and PET data from humans confirm these predictions.

Table 1. The formal features of REM sleep dreaming

Hallucinations	especially visual and motoric, but occasionally in any and all sensory modalities.[14,25-27]
Bizarreness	incongruity (imagery is strange, unusual or impossible), discontinuity (imagery and plot can change, appear or disappear rapidly), uncertainty (persons, places and events often bizarrely uncertain by waking standards).[14,19,21,25,29,33]
Delusion	We are consistently duped into believing that we are awake (unless we cultivase lucidity).[28,34,38]
Seif-reflection	Seif-reflection absent or greatiy reduced relativa to waking.[34,39,40]
Lack of orientational stability,	persons, times and places are fused, plastic, incongruous and discontinuous.[14,25,28,29,32,33,41-43]
Narrative story lines	explain and integrase all the dream elements in a confabulatory manner.[14,44-48]
Emotions increased	intensified and dominated by fear-anxiety.[49,50]
Instinctual programs	(especially fight-flight) often incorporated.[14,52]
Volitional control Memory deficits	greatly attenuated.[38,53] across dream-wake, wake-dream and dream-dream transitions.[54-60]

Dream emotion: Emotion is a subjective experience that is intensified in dreams. To account for the documented prominence of anxiety-fear, elation, and anger in dreams (49-51) we would not be surprised to find selective activation of the limbic brain and this is the prediction most strongly supported by the new neuropsychological evidence (1-3). That dream emotion is usually consistent with the dream narrative (62) and bizarre incongruities between emotion and narrative are rarer than incongruities among other dream elements (50) can be explained by viewing dream emotion as a primary shaper of plots rather than as a reaction to them (63). Thus in a classic anxiety dream, the plot may shift from feeling lost, to not having proper credentials, adequate equipment or suitable clothing, to missing a train. These plots all satisfy the driving emotion, anxiety, while being only very loosely associated with one other.

Dream cognition: The distinctively discontinuous and incongruous nature of dream cognition can be measured as a construct termed bizarreness (14,29). Bizarreness in turn reflects the hyper-associative quality of REM sleep dream consciousness. The instability of time, place and, most strikingly, person is a qualitatively unique feature of REM sleep dreams. A dream character may thus have the name of one of our friends but the wrong face, hairstyle or clothing. Other dream characters are true chimeras having some of the features of one individual and some of another. Even the sexual identity of dream characters is fluid and this ambiguity can be anatomically explicit, not just psychological.

Dream amnesia and related cognitive deficits: The loss of memory in REM sleep makes dreaming consciousness much more difficult to recall than waking consciousness. This phenomenological deficit logically implies a physiological deficit: some functional process, present and responsable for memory in waking is absent, or at least greatly diminished, in REM sleep.

In our attempt to explain dream amnesia, we look with interest at such functional deficits as the loss of noradrenergic and serotonergic modulation in REM sleep. This is because these very neuromodulators have been shown, in many human and animal studies, to be critical to learning and memory and to such memory enhancing cognitive functions as perception and attention via their direct CNS effects as well as their indirect peripheral mechanisms (64-77). This REM related aminergic demodulation is best viewed as a subtraction of

noradrenaline and serotonin from the varied neuromodulatory mixture facilitating waking cognition, a mixture which, of course, includes acetylcholine (78), which remains abundant during REM.

The loss of orientational stability (which is at the cognitive root of dream bizarreness) and the loss of self-reflective awareness (which is the basis of the delusion that we are awake in our dreams) are two related deficits which could be caused by the aminergic demodulation of the brain in REM sleep, but is there more to it than that? Could the frontal lobes be selectively inactivated during REM sleep? At least two PET studies suggest that this is so (1,2).

REM sleep neurophysiology

In 1953, Aserinsky and Kleitman (79), working in Chicago, discovered that the brain-mind, exhibited periodic self-activation during sleep. At regular 90-100 min intervals they observed the spontaneous emergence of EEG desynchronization, accompanied by clusters of rapid saccadic eye movements (or REMS) together with acute accelerations of heart and respiration rates. When subjects were awakened and asked to report their antecedent mental activity, REM sleep was associated with longer, more vivid, more motorically animated and more bizarre accounts than NREM (7,9,13,14,30,46,80-90) Thus, while some dreaming can occur in other states of sleep (82,83) (for reviews see Refs) (9,13,46,91), it is REM neurophysiology which most strongly supports dream psychology (13) For this reason, we restrict our integrative efforts to the neuropsychology of REM sleep dreaming.

The reciprocal interaction hypothesis: The discovery of the ubiquity of REM sleep in mammals provided the brain side of the brain-mind state question with an animal model (92-96). While animal studies showed that potent and widespread activation of the brain did occur in REM sleep, it soon became clear that Moruzzi and Magoun's (97) concept of a brain stem reticular activating system required extension and modification to account for the differences between the behavioral and subjective concomitants of waking and those of REM sleep (98).

A conceptual breakthrough was made possible by the discovery of the chemically specific neuromodulatory subsystems of the brain stem (100) (for reviews see Refs 22,100,101) and of their dlfferential activity in waking (noradrenergic and serotonergic systems on, cholinergic system damped) and REM sleep (noradrenergic and serotonergic systems off, cholinergic system undamped) (23,102-114).

The resulting model of reciprocal interaction (110) provided a theoretical framework for experimental interventions at the cellular and molecular level that has vindicated the notion that waking and dreaming are at opposite ends of an aminergic-cholinergic neuromodulatory continuum, with NREM sleep holding an intermediate position (Fig. l). This spectrum of brain activity across the states of wake, NREM and REM must be the neurobiological substrate of the conscious experience associated with these states. We now devote our careful attention to a review of the cellular and molecular level details, in the context of the reciprocal interaction concept, to provide a basis for our later discussion of the new human imagery data.

The reciprocal interaction hypothesis (110) provided a formal model for the aminergic-cholinergic interplay at the synaptic level and a mathematical model of the dynamics of the neurobiological control system (Fig. l). In this section we review subsequent work that has led to the alteration and elaboration (Fig. 2) of the model.

Cholinergic REM sleep generation: Although there is abundant evidence for a pontine peribrachial cholinergic mechanism of REM generation centered in the pedunculopontine (PPT) and laterodorsal tegmental (LDT) nuclei (for recent reviews see Refs 115-120), not all pontine PPT and LDT neurons are cholinergic (121-126) and cortical acetylcholine release may be as high during wakefulness as during sleep (127-129).

The original claim that the medial pontine reticular formation (mPRF) was cholinergic was clearly in error. While many of the mPRF cells are excited by acetylcholine as originally hypothesized, their own excitatory neurotransmitter now appears to be glutamate, not

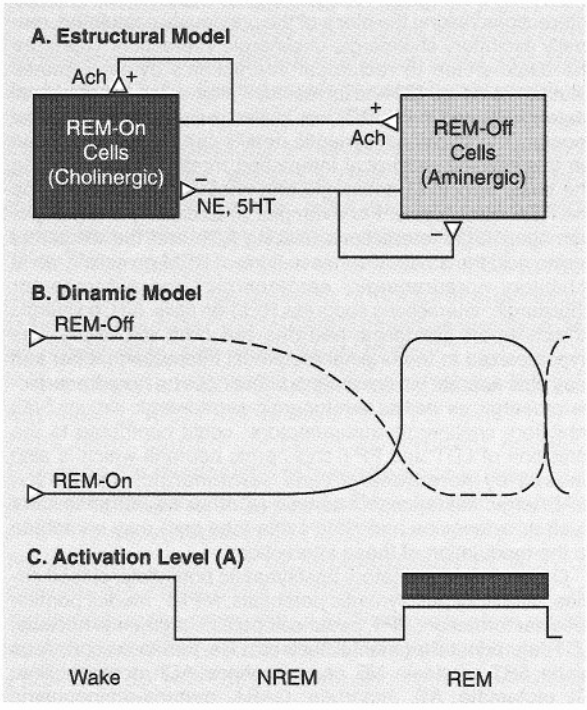

Figure 1. The original reciprocal interaction model of physiological mechanisms determining alterations in activation level. (**A**) Structural modal of reciprocal interaction: REM-on cells of the pontine reticular formation are cholinoceptively excited andior cholinergically excitatory (ACH+) at their synaptic endings. Pontine REM-off celis are noradrenergically (NE) or serotonergically (5HT) inhibitory (−) at their synapses. (**B**) Dynamic model: during waking the pontine aminergic system is tonically activated and inhibits the pontine cholinergic system. During NREM sleep aminergic inhibition gradually wanes and cholinergic excitation reciprocally waxes. At REM sleep onset aminergic inhibition is shut off and cholinergic excitation reaches its high point. (**C**) Activation level. As a consequence of the interplay of the neuronal systems shown in (A) and (B), the net activation level of the brain is at equally high levels in waking and REM sleep and at about half this peak level in NREM sleep. (Taken from Ref. 16).

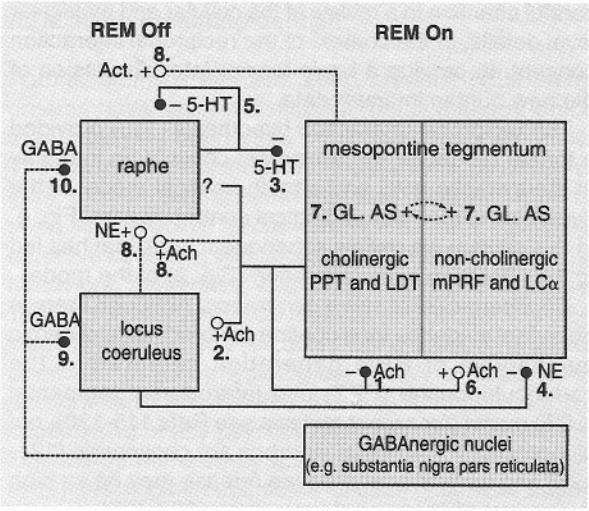

Figure 2. Synaptic modifications of the original reciprocal interaction model based upon recent findings. Reported data from animal (cat and rodent) are shown as solid lines, some of the recently proposed putative dynamic relationships are shown as dotted rines, and references are indicated by numbers (sea key below). The exponential magnification of cholinergic output predicted by the original model (sea Fig. 1) can also occur in this model with mutually excitatory cholinergic-non-cholinergic interactions[7] taking the place of the previously postulated, mutually excitatory cholinergic-cholinergic interaction. Therefore the basic shape of reciprocal interaction's dynamic model (illustrated in Fig. 1B) and its resultant alternation of behavioral state (illustrated in Fig. 1C) would also result from this revisad modas. The additional synaptic details can be superimposed on this revised reciprocal interaction modal without altering the basic effects of aminergic and cholinergic influences on the REM sleep cycle. For example: (i) Excitatory cholinergic-non-cholinergic interactions utilizing ACh and the excitatory amino acid transmitters enhance firing of REM-on cells[6-7] while inhibitory noradrenergic[4] serotonergic[3] and autoreceptor cholinergic[1] interactions suppress REM-on cells. (ii) Cholinergic effects upon aminergic neurons are both excitatory,[2] as hypothesized in the original reciprocal interaction model and may also operate via presynaptic influences on noradrenergic-serotonergic as well as serotonergic-serotonergic circuits.[8] (iii) Inhibitory cholinergic autoreceptors[1] could contribute to the inhibition of LDT and PPT cholinergic neurons which is also caused by noradrenergi[4] and serotonergic[3] inputs. (iv) GABAergic influences[9,10] as well as other neurotransmitters such as adenosine and nitric oxide (see text) may contribute to the modulation of these interactions.

Open circles, excitatory postsynaptic potentials; closed circles, inhibitory postsynaptic potentials; MPRF, medial pontine reticular formation; PPT, pedunculopontine tegmental nucleus; LDT, laterodorsal tegmental nucleus; LCa, peri-locus coeruleus alpha; 5HT, serotonin; NE, norepinephrine; ACh, acetylcholine; GL glutamate; AS, aspartate; GABA, gamma-aminobutyric acid. References: *1*: 123-125, 132, 158, 163-166; *2*: 167, 168; *3*: 124, 169-142; *4*: 125; *5*: 173; *6*: 125, 137, 140, 141, 174; *7*: 124, 125; *8*: 175; 9: 153, 176, 177; *10*: 178.

acetylcholine. For this and other reasons to be discussed below, reciprocal interaction (110) and reciprocal inhibition (130) models for control of the REM sleep cycle by brain stem cholinergic and aminergic neurons have recently been questioned (124). Specifically, the self-stimulatory role of acetylcholine on pontine PGO-bursting neurons has not been confirmed in *in vitro* slice preparations (124). For example ACh has been shown to hyperpolarize cell membranes in slice preparations of the rodent parabrachial nucleus (131), LDT (124,132), and PPT (124). Similarly, LDT and PPT neurons with burst discharge properties most like those hypothesized to occur in PGO-burst neurons (type I neurons) may not be cholinergic (123).

Much evidence remains, however, that the reciprocal interaction model accurately describes essential elements of REM sleep cycle control even though some of its detailed synaptic assumptions need correction as shown in Fig. 2. Numerous findings confirm the hypothesis that cholinergic mechanisms are essential to the generation of REM sleep and its physiological signs (for recent reviews see Refs 22, 23, 115-118, 130, 133, 134). A selection of many recent examples follows.

Experimental REM sleep induction and suppression: Microinjection of cholinergic agonist or cholinesterase inhibitors into many areas of the paramedian pontine reticular formation induces REM sleep (118,135-141). In addition to these short term REM induction sites, carbachol injection into a pontine site in the caudal peribrachial area has been shown to induce long-term (over 7 days) REM enhancement (142-144). In rats, it has been difficult to enhance REM sleep with carbachol (145), but rat strains which are genetically supersensitive to ACh show enhanced REM sleep (146). In addition to the well-known suppression of REM by muscarinic antagonists (133), the new presynaptic anticholinergic agents have also been shown to block REM (147,148).

Cholinergic neurons and REM sleep: Cholinergic (type II and III) PPT and LDT neurons have firing properties which make them well suited for the tonic maintenance of REM (123) and both PPT and LDT neurons show specifically c-Fos and Fos-like immunoreactivity (Fos-LI) following carbachol induced REM sleep (149,150), suggesting that they participate in the genesis of that state. Low amplitude electrical stimulation of the LDT enhances subsequent REM sleep (151) while electrical stimulation of the cholinergic LDT evokes excitatory post synaptic potentials in pontine reticular formation neurons and these EPSPs can be blocked by scopolamine (152). The excitatory amino acid, glutamate, when microinjected into the cholinergic PPT increases REM sleep in a dose-dependent manner (153,154).

Acetylcholine release and REM sleep: Microdialysis studies show enhanced release of endogenous acetylcholine in the medial pontine reticular formation during both natural (155) and carbachol-induced (156) REM sleep. Thalamic ACh concentration of mesopontine origin is higher in both wake and REM than in NREM, 157 and a REM-specific increase of ACh in the lateral geniculate body has been observed (158). Both muscarinic and nicotinic receptors participate in the depolarization of thalamic nuclei by the cholinergic brain stem (159).

Cholinergic mediation of PGO waves: PGO input to the LGB is cholinergic (126), and can be antidromically traced to pontine PGO-burst neurons (160). Stimulation of mesopontine neurons induces depolarization of cortically projecting thalamic neurons (159). Neurotoxic lesions of pontomesencephalic cholinergic neurons reduce the rate of PGO spiking (161) and PGO waves can be blocked by cholinergic antagonists (162).

It may not be an exaggeration to state that the evidence for cholinergic REM sleep generation is now so overwhelming and so widely accepted that this tenet of the reciprocal interaction model is an established principle.

Aminergic inhibition of the cholinergic REM generator: At the heart of the reciprocal interaction concept is the idea that cholinergic REM sleep generation can only occur when the noradrenergic and serotonergic mediators of waking release their inhibitory constraint of the cholinergic generator. The evidence for inhibitory serotonergic and noradrenergic influences on cholinergic neurons and REM sleep is now also quite strong.

Decreased serotonin release in natural REM sleep: In the cat, extracellular levels of serotonin are higher in waking than in NREM and higher in NREM than REM in the dorsal raphe (179) and the medial pontine reticular formation (180). This same state-dependent pattern is observed in the hypothalamus of the rat (181,182). Moreover, reduced extracellular serotonin concentration in REM sleep has recently been demonstrated in the human amygdala, hippocampus, orbitofrontal cortex and cingulate cortex (24). Since most of these structures show selective activation in PET images of REM sleep, it can be inferred that the human limbic system is turned on but demodulated during dreaming.

Serotonergic suppression of cholinergic systems and REM sleep: Serotonergic neurons from the dorsal raphe synapse on LDT and PPT neurons (169). Serotonin has been shown to hyperpolarize rat cholinergic LDT cells *in vitro* (124,171) and reduce the proportion of REM sleep *in vivo* (170), Serotonin counteracts the REM-like carbachol-induced atonia of hypoglossal motoneurons (183-185).

Suppression of REM by serotonin agonists: Microinjection of the serotonin agonist 8-OH-DPAT into the peribrachial region impedes REM initiation in cats (186) and systemic injection of 8-OH-DPAT into serotonin-depleted rats also suppresses REM (187). Simultaneous unit recording has shown that microinjection of 8-OH-DPAT selectively suppressed the firing of REM-on but not REM- and wake-on cells of the cholinergic LDT and PPT (172). *In vivo* microdialysis of serotonin agonists into the dorsal raphe nucleus (DRN) decreased DRN levels of serotonin (presumably via serotonin autoreceptors on DRN cells) which in turn increased the proportion of REM sleep (173). Mesopontine injection of a serotonin agonist depressed ACh release in the lateral geniculate body (158).

Suppression of REM by endogenous norepinephrine and its agonists: Locus coeruleus neurons become quiescent during REM in the monkey (188) as well as in the cat and rat (22). Electrical stimulation of the pons in the vicinity of the (noradrenergic) locus coeruleus reduced REM sleep in rats (189). The $\alpha 2$ noradrenergic agonist clonidine suppresses REM in humans (190,191) and in the cat (192), while the noradrenergic antagonist idazoxan increases REM when injected into the pontine reticular formation of cats (193). That the REM, suppressive effects of serotonin and norepinephrine are additive is indicated by the suppression of REM sleep in humans by acute dosage of antidepressant drugs which inhibit the reuptake of serotonin, norepinephrine or both (194-196).

Like cholinergic enhancement, aminergic suppression of REM sleep is now an established principle. The 5-HT_{1A} serotonin receptor may be of the greatest importance in the inhibition of cholinergic firing in the cat PPT (186) and LDT (197) while the α 1 receptor may be the most important site for adrenergic REM suppression (198).

Modification of the reciprocal interaction model. Modification of simple reciprocal inhibition or interaction models, which are constant with recent findings, have been proposed for the brain stem control of REM sleep. All such modifications retain one or both of the major tenets of the reciprocal interaction model: cholinergic facilitation and adrenergic inhibition of REM.

Leonard and Llinas (124) suggest in regard to the McCarley and Hobson (108) model that ". . . 'indirect feedback' excitation via cholinergic inhibition of an inhibitory input or cholinergic excitation of an excitatory input or some combination of the two could replace direct feedback excitation in their model." A similar mutually excitatory or mutually inhibitory interaction between REM-on cholinergic and REM-on non-cholinergic mesopontine neurons has also been proposed (125). Such a mechanism is depicted in Fig. 2.

Recent *in vitro* studies in the rat have led to the following elaboration of reciprocal interaction being proposed by Li *et al* (175). During waking, presynaptic nicotinic facilitation of excitatory locus coeruleus noradrenergic inputs to the dorsal raphe enhances serotonergic firing. During REM, when the locus coeruleus is silent, this same presynaptic nicotinic input may facilitate serotonergic self-inhibition by the raphe neurons themselves. *In vivo* microdialysis studies of GABA in the cat further suggest selective suppression of noradrenergic locus coeruleus neurons by GABAergic inhibition during REM, as proposed by Nitz and Siegel (176).

It is important to realize that many of the studies questioning reciprocal interaction (123,124,131,171) have been carried out on *in vitro* rodent models. Exploring the relationship of these findings to the *in vivo* mechanisms generating REM sleep signs in the cat is only in its early stages (115,118,125). It seems possible, for example, that the hyperpolarization by ACh of cholinergic cells cited in these studies might be explained by the presence of ACh autoreceptors which contribute to homeostatic control of cholinergic activity (123-125,158,163-166). In contrast to the hyperpolarization of some mesopontine cholinergic neurons by cholinergic agonists, *in vitro* studies have shown the majority of medial pontine reticular formation (mPRF) neurons to be depolarized by carbachol (199). This suggests that the exponential selfstimulatory activation which can be triggered by cholinergic stimulation in diverse meso- and medial pontine sites (22,23,118,133) may involve excitatory neurons which are non-cholinergic. Such cholinergic selfregulation combined with cholinergic-noncholinergic mutual excitation is shown in Fig. 2.

We conclude that the two central ideas of the model are strongly supported by subsequent research: (1) noradrenergic and serotonergic influences enhance waking and impede REM via anticholinergic mechanis-

ms; (2) cholinergic mechanisms are essential to REM sleep and come into full play only when the serotonergic and noradrenergic systems are inhibited. By restricting our discussion to cholinergic and aminergic mechanisms, we do not exclude the contributions to the modulation of behavioral state by other neuromodulatory systems such as GABAergic systems (176), nitroxergic systems (200), glutamatergic systems (201), glycinergic systems (202), histaminergic systems (203), adenosinergic systems (120) or the neuropeptides (204). Nor do we exclude the contributions of numerous non-pontine structures such as the basal forebrain (205), hypothalamus (203), amygdala (206), thalamic nuclei (207), central gray area (208) or the medulla (209). These other systems are reviewed elsewhere (13,210). Rather, whe emphasize here those aminergic and cholinergic mechanisms associated with the executive control of REM sleep in reciprocal interaction/inhibition models (23,110,130).

While the studies we have reviewed here are necessarily restricted to data obtained in subhuman models of REM sleep, an abundant psychopharmacological literature provides indirect evidence that the same mechanisms operate at the cellular and molecular level in the human brain (22,194,196,211-215). We now turn our attention to new, more direct evidence supporting the assumption of cross-species homology.

Human neuropsychology

Until recently, the experimental study of human REM sleep dreaming has been limited on the physiological side by the poor resolving power of the EEG. Even expensive and cumbersome evoked potential and computer averaging approaches have not helped to analyse and compare REM sleep physiology with that of waking in an effective way. This limitation has probably reinforced the erroneous idea that the brain activation picture of REM sleep and waking are identical or at least, very similar. Fortunately, technological advances in the field of human brain imaging have now made it possible to describe a highly selective regional activation pattern of the brain in REM sleep. At the same time, experiments of nature, in the form of strokes, have allowed the locale of brain lesions to be correlated with deficits or accentuations of dream experience in patients.[4,216] The remarkably complementary results of these two approaches are summarized in Table 2.

TABLE 2
Imaging of brain activation in REM and the effects of brain lesions on dreaming

Region	*PET studies of activation in REM*	*Lesion studies of effects on dreaming*
Pontine tegmentum	↑	–
Limbic structures	↑	↓
Striate cortex	↓	–
Extrastriate cortex	↑	↓
Parietal operculum	↑ (right)	↓
Dorsolateral prefrontal cortex	↓	–
Mediobasal frontal cortex	–	↓

Key: ↑ increase; ↓ decrease; – no change.

PET imaging studies of REM sleep dreaming: Two very recent and entirely independent PET studies confirm the importance of the pontine brain stem in the REM sleep activation of the human brain.[1-3] This is an important advance because it validates, for the first time, the experimental animal data on the critical and specific role of the pontine brain stem in REM sleep generation. At the same time these new studies also provide important new data for our understanding of dream synthesis by the forebrain. Instead of the global, regionally nonspecific picture of forebrain activation that had been suggested by EEG studies, all of these new imaging studies indicate a preferencial activation of limbic and paralimbic regions of the forebrain in REM sleep compared to waking or to NREM sleep.[1-3] One important implication of these discoveries is that dream emotion may be a primary shaper of dream plots rather than playing the secondary role in dream plot instigation that was previously hypothesized.[52]

Maquet *et al.*[2] used an $H_2{}^{15}O$ positron source to study REM sleep activation in their subjects who were subsequently awakened for the solicitation of dream reports. In addition to the pontine tegmentum, significant activation was seen in both amygdalae and the anterior cingulate cortex (Table 3). Significantly, despite the general deactivation in much of the parietal cortex, Maquet *et al.* reported activation of the right parietal operculum, a brain region thought to be important for spatial imagery construction, an important aspect of dream cognition. As Maquet emphasized,[217] those cortical areas activated in REM are rich in afferentation from the amygdala (anterior cingulate, right parietal operculum) while those areas with sparse amygdalar afferentation (prefrontal cortex, parietal cortex and precuneus) were deactivated in REM. Maquet *et al.* interpreted their data in terms of the selective processing, in REM, of emotionally influenced memories (see also Refs 1,218).

In another $H_2{}^{15}O$ PET study, Braun *et al.*[1] replicated these findings of a consistent REM-related brain stem, limbic and paralimbic activation. When REM sleep brain activity was compared with brain activity in delta NREM, with pre-sleep waking and with post-sleep waking, Braun *et al.* showed relative activation of the pons, the midbrain, the anterior hypothalamus, the hippocampus, the caudate, and the medial prefrontal, caudal orbital, anterior cingulate, parahippocampal and inferior temporal cortices in REM sleep, compared with each of the above three conditions (Table 3). Based on these observations, they offered the following five speculations which are relevant to the neurology of dreaming. (i) First, the ascending reticular activation of REM sleep may procced relatively more via a ventral cholinergic route from the brain stem through the basal forebrain rather than via the dorsal route through the thalamus which is preferred in waking. (ii) Second, the activation of the cerebellar vermis in REM sleep may reflect an input from the brain stem vestibular nuclei and thus constitute a source of neuronal activation causing fictive movement in dreams (219,220). (iii) Third, the strong REM sleep-related ac-

TABLA 3
Subcortical and cortical regional brain activation and deactivation revealed by recent PET studies comparing REM sleep with waking and with NREM sleep

	REM vs all other stages ($H_2^{15}0$)2	*REM vs waking (I8FDG)3*	*REM vs pre- (and post*-) sleep waking (H20)[1]*	*REM vs NREM 3 and 4 (H2'50)'*
Subcortical areas				
Brain stem				
Pontine tegmentum	increase		increase (R*)	increase
Midbrain			increase*	increase
Dorsal mesencephalon	increase			
Diencephalon				
Thalamus	increase L			increase
Hypothalamus		increase R lateral	increase anterior preoptic area (A-POA)	increase A-POA
Limbic sistem				
Left amygdala	increase	increase		
Right amygdala	increase			
Septal nuclei		increase		
Hippocampus			increase*	increase
Basal ganglia/striatum				
Caudate		increase, anterior,	increase*	increase
Putamen		inferior, L		increase
Ventral striatum (n. accumbens, sub. innominata)		increase		increase
Cerebellum			increase (vermis)*	increase (vermis)
Cortical areas				
Frontal				
Dorsolateral prefrontal	decrease: L-10,11,46,47; R-8,9,10,11,46		increase	decrease 46*
Opercular			decrease 45*	
Paraolfactory		increase		
Lateral orbital		increase, 11,12	decrease 11*	
Caudal orbital			increase	increase
Gyrus rectus		increase		
Parietal				
Brodman area 40 (supramarginal gyrus)	increase R anterior 40, decrease L40		decrease 40*	
Angular gyrus			decrease 39*	
Precuneus	decrease			
Temporal				
Middle		increase R		
Posterior superior				increase 22
Inferior/fusiform			increase 37,19 (post-sleep only)	increase 37,19
Occipital				
Post-rolandic sensory			increase	
Limbic-associated				
Media¡ (prelimbic) prefrontal		increase R32	increase 10	increase 10
Anterior cingulate	increase 24	increase 24	increase 32*	increase 32
Posterior cingulate	decrease 31	decrease R sm. areas	decrease*	
Infralimbic		increase 25		
Insula		increase L	decrease posterior	increase anterior 1
Parahippocampal		increase	increase 37'	increase 37
Entorhinal	increase	increase (in fusiform)		
Temporal pole				increase 38

R, right; L left; all numerals refer to Brodman's areas.

tivation of the basal ganglia suggests that these subcortical structures may play an important role in ascending thalamocortical activation. The mediating network links brainstem to the basal ganglia via the intralaminar thalamic nuclei and proceeds to the cortex via the ventral anterior and ventromedial thalamic nuclei. Because this network contains multiple regulatory back-projections to the pedunculopontine tegmentum, a possible role for the basal ganglia in the rostral transmission of PGO waves is suggested. The basal ganglia may initiate motor activity and be related to the ubiquity of hallucinated motion in dreams (14,86). (iv) Fourth, the REM-associated activation of unimodal associative visual (Brodmann areas 19 and 37) and auditory (Brodmann area 22) cortex contrasts with the maintained (NREM and REM) sleep-related deactivation of heteromodal association areas in the frontal and parietal cortices. Interestingly, the inferior temporal cortex (Brodmann areas 19 and 37) contains the fusiform gyrus, a structure known to be involved in human face

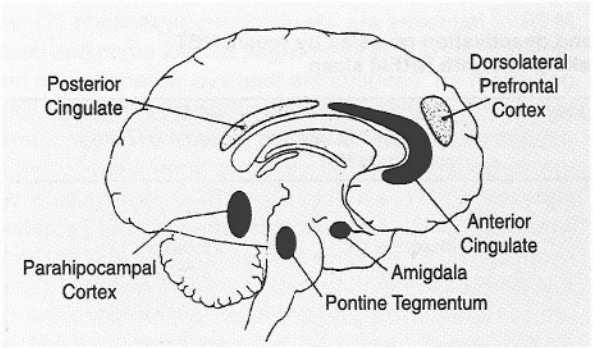

Figure 3. Convergent findings on relative regional brain activation and deactivation in REM compared with waking. Schematic sagittal view of the human brain showing those areas of relative activation and deactivation in REM sleep compared to waking and/or NREM sleep which were reported in two or more of the three PET studies published to date.[1-3] Only those areas which could be easily matched between two or more studies are schematically illustrated here and a realistic morphology of the depicted areas is not implied. Note that considerably more extensive areas of activation and deactivation are reported in the individual studies and these more detailed findings are given in Tabla 3. The depicted areas in this figure are thus most realistically viewed as representative portions of larger CNS areas subserving similar functions (e.g. limbic-related cortex, ascending activation pathways and multimodal association cortex).

recognition (221) —another common, if often bizarrely uncertain, dream feature. (v) Finally, the REM-associated increase in activation of the limbic associated medial prefrontal area contrasts with the prominent decrease in the executive portions of the frontal cortex (dorsolateral and orbital prefrontal cortices). This medial area, which has the most abundant limbic connections in the prefrontal cortex, has been associated with arousal and attention. Disruption of this area has been shown to cause confabulatory syndromes formally similar to dreaming (1). Interestingly, lesions of the anterior limbic cortex, especially the neighboring anterior cingulate, often result either in a distinctive syndrome in which dreaming increases in vivacity and reality and dreaming becomes confused with reality or such lesions result in a global cessation of dreaming (4). From these findings as well as primary visual cortex deactivation in REM, the Braun group has recently suggested that REM constitutes, in the cortex, a unique condition of internal information processing (between extrastriate and limbic cortices) functionally isolated from input (via striate cortex) or output (via frontal cortex) to the external world (245).

Confirming the widespread limbic activation of the human brain in REM, Nofzinger *et al* (3) described increased glucose utilization in the lateral hypothalamic area and the amygdaloid complex using an [^{18}F]fluorodeoxyglucose (FDG) PET technique (Table 3). Nofzinger *et al.* note that "The largest area of activation is a bilateral confluent paramedian zone which extends from the septal area into ventral striatum, infralimbic, prelimbic, orbitofrontal and anterior cingulate cortex." The authors suggest that an important function of REM sleep is the integration of neocortical function with basal forebrain hypothalamic motivational and reward mechanisms.

An equally interesting $^{15}H_2O$ PET finding, relevant to the cognitive deficits in self-reflective awareness, orientation, and memory during dreaming was significant deactivation, in REM, of a vast area of dorsolateral prefrontal cortex (1,2). Using SPECT, a similar decrease in cerebral blood flow to frontal areas during REM had earlier been noted (222). This dorsolateral prefrontal deactivation during REM, however, was not replicated by the FDG study of Nofzinger *et al.,* and this discrepancy remains to be clarified. Using the finer time resolution offered by functional MRI (fMRI) imaging (223-226), this area of research can be expected to provide more detail in the near future.

The fact that considerable portions of executive and association cortex are far less active in REM than in waking led Braun *et al* (1). to speculate that ". . . REM sleep may constitute a state of generalized brain activity with the specific exclusion of executive systems which normally participate in the highest order analysis and integration of neural information." In terms of cortical-subcortical networks, they further suggest that "... the 'limbic' loop connecting ventral striatum, anterior thalamus and paralimbic cortices, appear to be activated during REM sleep ... However the prefrontal or 'association' loop, connecting the caudate, dorsomedial thalamus and prefrontal cortices ... appears to be activated only in a partial or fragmentary way." Figure 3 integrates regional activation findings from these first three PET studies (1-3) comparing REM sleep to other states.

Loss of dreaming after cerebral lesions: An entirely complementary set of findings and conclusions has been reached following a neuropsychological survey of 332 clinical cases with cerebral lesions (4). The 112 patients who reported a global cessation of dreaming had damage either in the limbic system, the parietal convexity, or suffered disconnections of the mediobasal frontal cortex from the brain stem and diencephalic limbic regions. Solms, who was apparently unaware of the recent PET studies, cited the much earlier single subject report of a PET glucose activation of limbic and prelimbic structures in REM (227). With respect to the visual imagery aspect, a decrease in the vivacity of dreaming was reported by two patients with damage to the seat of normal vision in the medial-occipital-temporal cortex (especially areas V_3, V_{3a} and V_4 but not V_1, V_5 or V_6). Solms (4) also reports that his patients with pontine lesions continued to dream and concludes that the pons is not necessary for human dreaming. Based upon the difficulty of suppressing REM by experimental lesions of the pons in animals, we suggest an alternative explanation. It seems to us that any lesion capable of destroying the pontine REM sleep generator mechanism would have to be so extensive as to eliminate consciousness altogether.

Emotionally salient memory processing: Concerning the functional significance of the imaging results, all three of the image study authors assign REM sleep a role in the processing of emotion in memory systems (1,2,3,218). Additionally, both the Maquet and Braun groups suggest the possible origin of dream emotionality in REM-associated limbic activation and dream-associated executive deficiencies in REM-associated frontal deactivation (1,218). Additional findings support this

proposed cortico-limbic interaction. First, as shown in Table 3, the cingulate cortex has consistently shown increased activation in REM in other PET studies (228). Second, FDG PET activation of anterior medial structures, including the anterior cingulate and medial frontal cortex, was found to correlate with REM density in the REM period during which FDG uptake occurred (229). Although these authors interpret this medial activity correlation with REM density as resulting from the activity of midline attentional systems in response to cortically generated dream imagery (229), it is equally possible that activation of these structures reflects the limbic and paralimbic activity in REM suggested by other studies (1-3). Finally, a recent study of human limbic structures with depth electrodes has shown that a distinctive rhythmic delta-frequency EEG pattern occurs only during REM sleep (230).

The regional activation during REM may reflect a specific activation of subcortical, and cortical, limbic structures for the adaptive processing of emotional and motivational learning (2,3). Such processing may, in turn, account for the emotionality and psychological salience of REM sleep dreams (1,14). Some support for this comes from a PET (glucose) study showing, correlation between content-analysed dream anxiety and medial frontal activation (231).

From the neuron to the dream

Taken together, these new neuroimaging and brain lesion studies strongly suggest that the forebrain activation and synthesis processes underlying dreaming are very different from those of waking. Not only is REM sleep chemically biased but the preferential cholinergic neuromodulation and aminergic demodulation are associated with selective activation of the subcortical and cortical limbic structures (which mediate emotion) and with relative inactivation of the frontal cortex (which mediates directed thought). A unifying neurobiological hypothesis is that the regional blood flow changes are causally linked to the neuromodulatory dynamics in the following way: Those areas which are inactivated in REM are those undergoing aminergic demodulation but are uncompensated by cholinergic modulation while the activated areas are those heavily targeted by cholinergic modulatory neurons.

Whatever the link between the neuromodulatory and regional blood flow data, these findings greatly enrich and inform the integrated picture of REM sleep dreaming as emotion-driven cognition with deficient memory, orientation, volition, and analytic thinking. And now that we know that there is a close fit between the animal and human data regarding the mechanism and pattern of brain activation in REM sleep, we are in a much stronger position to strengthen the brain-based theory of dreaming first proposed 20 years ago (52). We will now attempt to integrate the newly discovered facts from the human imaging studies with the cellular and molecular level findings gleaned from the animal model in order to answer four questions: What is the origin of dreaming? Why are dreams cognitively distinctive? Why are dreams forgotten? And what is the function of dreaming?

The origin of dreaming: Dreaming is a state of consciousness arising from the activation of the brain in REM sleep. The brain activation which underlies dreaming is, like that of waking, a result of the excitation of forebrain circuits by impulses arising in the ascending activation systems of the brainstem (e.g. pontine and midbrain reticular activating systems) and basal forebrain (e.g. cholinergic nucleus basalis of Meynert). This activation process prepares the forebrain to process data with associated cognitive awareness. But REM sleep brain activation differs from that of waking in three important ways: (i) There is selective activation of occipital, parietal and limbic zones with a selective inactivation of frontal regions. (ii) The mechanism of the brainstem triggering of forebrain activation involves the spontaneous excitation of cholineric neurons in the pontomesencephalic LDT and PPT nuclei. This occurs as the inhibitory restraint upon them declines with the near total arrest of firing by noradrenergic neurons in the locus coeruleus and serotonergic neurons in the raphe nuclei. (iii) Besides the recruitment of the pontine and mesencephalic reticular formation (which mediate the tonic thalamocortical activation) the disinhibited cholinergic system appears to play a role in providing the activated forebrain with phasic activation signals, the PGO waves, that have two targets of particular relevance to dream theory: (a) the lateral geniculate body and posterolateral cerebral cortex, the presumed substrates of visual imagery in dreaming; and (b) limbic and paralimbic structures, the presumed substrates of emotion and emotionally salient dream memories.

The distinctive nature of dream cognition: The selective activation process described above may account for such distinctive cognitive features of dreaming as: (i) the intense and vivid visual hallucinosis (which is due to autoactivation of the visual brain); (ii) the intense emotions, especially anxiety, elation and anger (which are due to the autoactivation of the amygdala, and more medial limbic structures); (iii) the delusional belief that we are awake, the lack of directed thought, the loss of self-reflective awareness, and the lack of insight about illogical and impossible dream experience (which are due to the combined and possibly related effects of aminergic demodulation and the selectiva inactivation of the frontal cortices); (iv) the bizarre cognition of dreaming which is characterized by incongruities and discontinuities of dream characters, loci, and actions (due to an orientational instability caused by the chaotic nature of the pontine autoactivation process and its sporadic engagement of association cortices, the absence of frontal cortical monitoring, and the memory deficits); and (v) the emotional salience of dream imagery (which is due to the activation of the paralimbic cortices by the amygdala).

Figure 4 presents a schematic model for the generation of these cognitive dream features by combining the above findings on state-dependent regional activation with a model of the neuromodulation of conscious states (15,16,18,20).

Dream forgetting: The practically total amnesia that most humans have for their dream consciousness is probably a joint product of the aminergic demodulation and the frontal deactivation of REM sleep. Cellular and

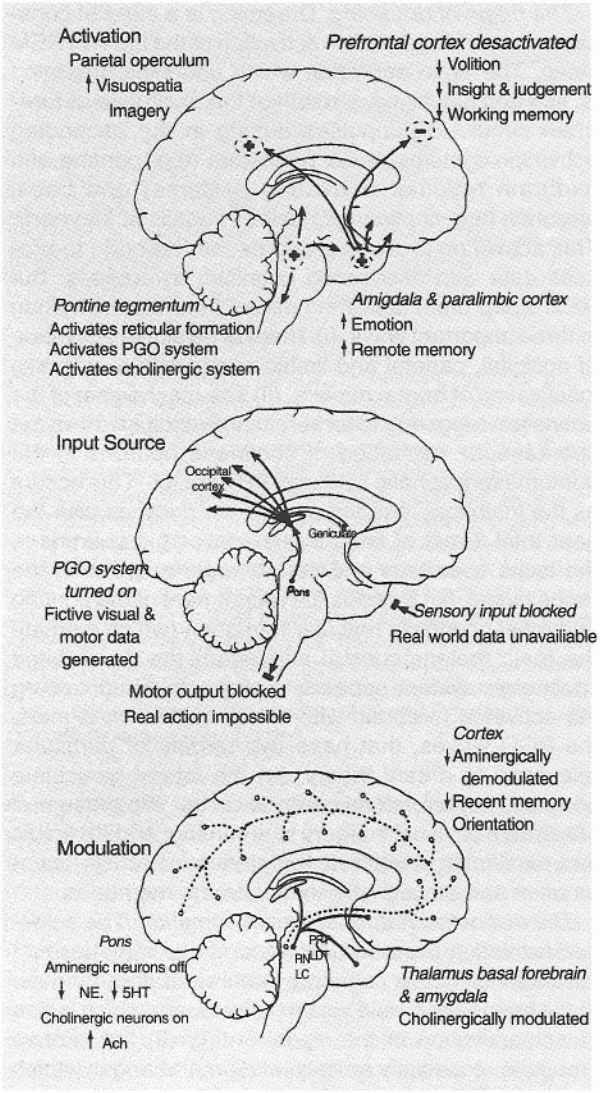

Figure 4. Physiological signs and regional brain mechanisms of REM sleep dreaming separated into the activation (A), input source (I) and modulation (M) functional components of the AIM model. Dynamic changes in A, I and M during REM sleep dreaming are noted adjacent to each figure. Note that these are highly schematized depictions which illustrate global processes and do not attempt to comprehensively detail all the brain structures and their interactions which may be involved in REM sleep dreaming (see text and Tabla 3 for additional anatomic details).

molecular level studies of learning and memory all concur in supporting a role for the aminergic neuromodulators, especially serotonin, norepinephrine and dopamine (64,65,69,70,71,73-75,232-235). Without their mediation, signals which arrive at a post-synaptic neuron may have instantaneous effects upon its membrane potential but lack the specific second messenger instruction needed by intracellular metabolic substrates to store a record of the membrane events.

At first glance, this failure to record intercellular transactions would seem to be at odds with the enhancement of learning hyphotesis advanced in the next section. But if we recall that it is consolidation, not acquisition that is hypothetically enhanced, it may be quite useful to direct the brain-mind to the exclusive task of processing information already acquired in waking and to ignore, or even discard, the information that it necessarily generates as it selfactivates in the interests of consolidation. On this view, the dream is the often meaningless, but sometimes meaningful, noise that is made when the brain enters its active, memory consolidation mode.

Of course, it is also quite possible, and even probable, that a key aspect of memory consolidation involves emotional salience. But whether this aspect is very different from that operating in the waking state, as those psychologists who regard dreaming as a privileged communication from the unconscious mind still hold, remains to be established.

The function of dreaming: If dream bizarreness indeed arises from the chaotic autoactivation process and the absence of top down control from the frontal cortex in REM sleep, the apparent nonsense of dreams is most likely just that and not the result of disguise and censorship as Freud's psychoanalytic dream theory proposed (5). At the same time, the instigation of emotionally salient memories is probably also just that. Hence dreams may be both nonsensical (i.e. bizarre) and transparently meaningful (i.e. emotionally salient) (14). They are therefore potentially clinically and personally informative if one discounts the bizarreness and attends to the undisguised emotional content. This approach, which is straightforward and requires no interpretation, may be well undertaken without mediation but it may also be facilitated by a sympathetic interlocutor.

Because dreams are so difficult to remember it seems unlikely that attention to their content could afford much in the way of high priority survival value. Indeed, it might instead be assumed that dreaming is an epiphenomenon of REM sleep whose cognitive content is so ambiguous as to invite misleading or even erroneous interpretation. From the neurobiological point of view it seems more likely that it is REM sleep itself, and not the subjective experience of dreaming, which has a functional significance for cognition that cannot easily be deduced from dream content. Among the many interesting theories that have been put forth, the restoration of cognitive capabilities such as attention and the enhancement of learning processes such as memory consolidation are of particular interest (236-244). We regard the testing of this memory consolidation hypothesis as a most promising area of ongoing research on sleep and dreaming.

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