The Neurobiology of Dreaming

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Chapter 48

Abstract

Dreaming is a universal human mental state characterized by hallucinatory imagery congruent with a confabulated, temporally ordered, storylike experience. As in waking consciousness, such experiences in both rapid eye movement (REM) and non-REM (NREM) sleep are associated with activation of forebrain structures by ascending arousal systems of the brainstem, hypothalamus, and basal forebrain. Differences between forebrain activation patterns in waking and REM sleep suggest bases for their phenomenological differences. In REM compared to waking, there is relatively more activation of the brain's limbic system and relatively less activity of cortical areas involved in higher-level cognition. REM sleep dreaming may activate anterior and midline portions of the brain's "default mode," a network of structures that supports self-related cognition when the brain is unoccupied by external stimuli. A variety of neurochemical systems can influence dreaming, including the neuromodulators acetylcholine, dopamine, serotonin, and norepinephrine. Dream phenomena are strikingly similar to neuropsychiatric symptom complexes such as complex hallucinosis and spontaneous confabulation as well as delirium and misidentification syndromes. A descriptive model of dream generation links sleep imaging studies with known regional specialization in waking neurocognitive functions.

COGNITIVE NEUROSCIENCE AND DREAMING

Dreaming is a universal human experience occurring during sleep in which fictive events follow one another in an organized, storylike manner and into which are woven hallucinatory, primarily visual, images that are largely congruent with an ongoing confabulated plot. Most often, this wholly imaginary experience is uncritically accepted in the same manner as are veridical waking percepts and events. The neuroscientific significance of dreams becomes apparent by considering just two of the many remarkable aspects of this universally human mental state. The first, dreaming's "single-mindedness and isolation," was eloquently described by Rechtschaffen,[1] and refers to the dreamer's absorption in the dream world and plot without awareness of an alternate reality in waking excepting rare "lucidity" (the awareness that one is dreaming). From this condition of limited insight, upon awakening, one abruptly regains sufficient insight to conceptualize alternate states of mind and decide which of these one is currently experiencing. The second is the occurrence in dreams of entirely de novo imagery, plots, personages, and even motor skills (e.g., flying), emotion (e.g., religious feelings) and memory (e.g., deja vu). Therefore, dreaming is an imprecise experiential simulacrum of waking resulting from neurobiological processes that must differ from those that generate waking consciousness. Because no published functional neuroimaging study has yet awoken subjects during dreaming to link subjectively experienced features of a dream report with immediately preceding brain activity, the wealth of information on the cognitive neuroscience of waking and the neurophysiology of sleep must be related to the less experimentally accessible dream state.

THE ASSOCIATION OF DREAMING WITH BEHAVIORAL STATE

Early speculation that rapid eye movement (REM) sleep was the exclusive physiological substrate of dreaming[2] was soon followed by awakening studies showing substantial recall of mental experiences from non-REM (NREM) sleep.[3] Nonetheless, REM reports are more frequent, longer, more bizarre, more visual, more motoric, and more emotional than are NREM reports (see review in Hobson et al.[4]). In an extensive review, Nielsen estimates an NREM mental-experience recall rate of 42.5% contrasting with 81.8% from REM and suggests that brain activation processes occurring outside polysomnographically scored REM ("covert REM") may account for NREM dreaming.[5]

Recent Electrophysiological Findings

Fast and Slow Oscillations and Dreaming

REM sleep shows much more gamma frequency (30 to 80 Hz), fast brain waves ("oscillations" or "rhythms") than does NREM sleep as measured by scalp electroencephalography (EEG),[6,7] intracranial EEG (iEEG)[8,9] and magnetoencephalography (MEG).[6] In waking, these fast oscillations are associated with attention to stimuli and other forms of active or effortful cognition.[10] During REM dreaming, fast oscillations have been hypothetically associated with cognitive and perceptual processing,[11] memory processes[12,13] and the temporal binding of dream imagery.[14]

In contrast to REM sleep, human slow-wave sleep shows very little gamma activity. It is instead associated with slower oscillations produced by recurrent interactions between the thalamus and cortex (intrinsic "corticothalamocortical" rhythms) such as sleep spindles and delta waves, and with the cortical slow (<1 Hz) oscillation that groups in time the other corticothalamocortical oscillations.[15,16] The slow oscillation consists of periods of neuronal quiescence (hyperpolarized or "down" states) that alternate with shorter periods of rapid neuronal firing (depolarized or "up" states).[17] Slow intrinsic oscillations may interfere with ongoing mental activity and lead to a lower frequency of dreams in NREM sleep.[4]

Cortical Connectivity in Sleep

Declines in phase synchrony ("coherence") of EEG rhythms between different brain regions occurring during sleep relative to waking may reflect functional

disconnections that contribute to the cognitive features of dreaming. Corsi-Cabrera and colleagues have shown that, compared to waking and NREM sleep, gamma frequency oscillations in REM sleep become desynchronized between areas near the front (anterior or frontal) and those near the back (posterior) of the brain.[6,7,18] These investigators suggest that loss of anteroposterior gamma coherence reflects a functional disconnection of perception-related posterior cortical areas from executive control by the frontal cortex that may contribute to the "hypofrontal" (resembling frontal-lobe dysfunction) features and bizarreness of REM sleep dreaming.[6,7,12,18] During REM sleep preceding dream reports, such frontoposterior gamma decoupling was accompanied by increased gamma coherence between posterior perceptual areas, possibly enhancing perceptual vividness in REM dreams.[7] Similar sleep-related declines in gamma frequency coherence between corticocortical and corticohippocampal sites have been demonstrated using iEEG.[12,13] Even EEG oscillations at frequencies slower than gamma have been shown to have lower coherence between anterior and posterior recording sites in REM versus NREM sleep[7,19] despite the fact that slower oscillations tend to be more globally synchronized in NREM versus REM sleep[20] due to the influence of intrinsic corticothalamocortical rhythms.[16]

Transcranial magnetic stimulation studies demonstrate reduced functional influence between different brain regions during REM sleep.[21,22] Transcallosal inhibition of motor-evoked potentials is greatly reduced immediately following REM awakenings compared to both NREM stage 2 awakenings and waking,[21] and transcranial magnetic stimulation of the premotor cortex during NREM sleep fails to persist or propagate to other sites as seen in waking.[22]

Dreaming and Phasic Activity in Sleep

In cats, a close temporal association exists between REM sleep rapid eye movements (REMs or REM saccades) and ascending potentials originating in the brainstem termed ponto-geniculo-occipital (PGO) waves.[4,23] In the Activation-Synthesis (AS) hypothesis of dreaming,[23] Hobson and McCarley suggest that the brainstem's activation of the forebrain in REM allows the forebrain to synthesize dream scenarios based upon currently available information. They suggest that the PGO wave, originating in the pons and arriving at primary visual occipital cortex via the dedicated visual pathway through thalamic lateral geniculate nucleus (LGN), might be interpreted by the brain as visual information thereby leading to the visual hallucinosis of dreams.

Efforts to identify human correlates of the feline PGO wave have focused on the phasic periods of REM in which clusters of REMs and other transient muscle potentials occur. Phasic REM periods are contrasted with tonic periods that are lacking in or have only isolated REMs. Conduit and colleagues[24] showed that in NREM sleep stage 2, awakenings preceded by eyelid movements (ELMs) yielded a higher frequency of visual imagery reports, and they suggested both ELMs and PGOs reflect an alerting mechanism similar to the startle response.

Early evidence of human PGO waves used scalp EEG recordings temporally locked to REMs (reviewed in Hobson et al.[4] and Pace-Schott[25]). Compelling evidence for human PGO waves has recently emerged. First, using MEG tomography, Ioannides and colleagues[26] have shown that correlated phasic activity in the pons and frontal eye fields begins before a REM saccade and intensifies with increasing temporal proximity to saccade onset, suggesting a buildup of neuronal excitability that culminates in the saccade. Because such activity is greatest in the pons, they suggest that accumulating excitability is driven by the pons with correlated frontal eye field activity representing feedback from pontine activity.[26] Second, in a patient with Parkinson's disease who was implanted with depth electrodes, Lim and colleagues[27] described phasic signals, with wave form and temporal characteristics very similar to the feline PGO, originating in the pedunculopontine nucleus (PPT)—a structure at the pons-midbrain (mesopontine) junction crucial for generating the feline PGO (reviewed in Hobson et al.[4]).

Ogawa and colleagues[28] provide event-related potential evidence that REMs generate perceptual experiences that could contribute to dream imagery. Brain potentials accompanying voluntary waking saccades were compared with those accompanying REM saccades. In waking, an EEG wave form known to reflect preparation for voluntary movement ("readiness potential") was temporally locked to saccade onset, and another wave form believed to reflect visual processing of the saccade target was time-locked to saccade offset. In contrast, during REM, the wave form time-locked to saccade offset occurred in the absence of the presaccade readiness potential, suggesting that REM saccades themselves may trigger visual experiences. Using low resolution brain electromagnetic tomography, Abe and colleagues[29] observed a pre–REM-saccade potential, temporally closer to saccade onset than waking readiness potentials, with current sources estimated to lie in anterior limbic regions (ventromedial, anterior cingulate, premotor, insular, temporopolar and parahippocampal cortices, basal forebrain, and uncus). Using MEG, Ioannides and colleagues[26] also described REM-saccade onset linked current sources estimated to lie in the amygdala and orbitofrontal and parahippocampal cortices. The latter two groups link this presaccade limbic activity to phasically enhanced emotional processing.[6,26,29]

During phasic REM (versus tonic REM) sleep, increased gamma-frequency spectral power is observed across widespread scalp derivations using EEG[6,11] and MEG[6] as well as at specific orbitofrontal sites using iEEG.[9] Gamma enhancement is accompanied by power attenuation at slower frequencies,[9,11] and it is further enhanced during a 62.5 msec time window immediately preceding an actual REM saccade.[6] Corsi-Cabrera and colleagues[6] report that gamma coherence displays two distinct topographic changes during phasic and immediately presaccade REM relative to tonic REM. First, there is further uncoupling between frontal and parietal association areas that they suggest represents further decline in frontal control of posterior cortical perceptual-binding processes that may transiently increase cognitive distortions in dream mentation. Second, there is transient enhancement of frontolateral to midline gamma coherence that they suggest reflects phasically enhanced attentional processes subserved by midline structures.

In summary, EEG and MEG studies suggest that brain activity accompanying phasic REM sleep may be related

to dream phenomena. Such phenomena include visual imagery,[24,28] enhanced cognitive activity and attention,[6,9,11] decoupling of executive control and perception,[6,7,12,18] and enhanced emotional processing.[6,26,29]

Experimental Manipulation of Sleep Stage and Dreaming

Takeuchi and colleagues used a sleep interruption technique to elevate the frequency of sleep onset REM periods (SOREMPs) in normal subjects.[30] Dreams elicited from SOREMPs were more bizarre and had different EEG correlates than NREM dreams that occurred at similar circadian phases preceded by similar sleep–wake durations.[30] For example, whereas SOREMP dreams were correlated with the amount of REM in a sleep period and with absence of alpha frequency in the EEG spectrum, NREM dreams were correlated with the presence of arousals and the persistence of alpha rhythms.[30]

There is now evidence that "covert REM" processes can enhance NREM dreaming. For example, partial REM deprivation (REMD) increases both REM pressure and the dreamlike quality of NREM dreams at sleep-onset,[31] a time when the EEG power spectrum is very similar to that during REM sleep.[32] Additionally, when Suzuki and colleagues[33] experimentally constrained sleep to 20 minute naps alternating with 40 minutes of waking across 3 days, NREM-only naps yielded more dream reports at times when, in REM-containing naps, REM duration was longest (peak at 8 AM). Therefore, increasing REM propensity by REMD or circadian manipulations can intensify NREM dreams.

NEURAL ACTIVATION ACROSS THE WAKE-NREM-REM CYCLE

Deactivation of frontal cortices is one of the first signs of human sleep observed using EEG, MEG, and functional neuroimaging (reviewed in Pace-Schott[25] and Maquet[34]). Positron emission tomography (PET) studies of NREM sleep show declines in brain activity relative to waking both globally[34] and in many specific regions of the subcortex and cortex[35,36]; findings now replicated using functional magnetic resonance imaging (fMRI).[37] Global and regional cerebral activity further declines with the deepening of NREM sleep[34,36-38] (although, on a microscopic time frame, activity in specific regions may become transiently elevated during the depolarized "up" phase of the slow oscillation[39]). Following sleep onset, EEG studies show greater slow wave spectral power in frontal versus posterior scalp-sites.[40] Synchronization of slow-wave spectral power then spreads progressively to posterior regions,[41] a trajectory also traveled by the slow (<1 Hz) oscillation.[42]

From these deactivated NREM conditions, in REM, there is then a prominent increase of neural activity in subcortical brain regions, including the pons and midbrain,[35,43] thalamus,[35,43] basal ganglia,[35] limbic subcortex including the amygdala,[43] hypothalamus, and ventral striatum.[35] Increases are also seen in limbic-related cortices anteriorly in the rostral and subcallosal anterior cingulate,[35,43] the anterior insular, more posterior (caudal) orbitofrontal and paracingulate Brodmann area (BA) 32 cortices, BA 10 in medial prefrontal cortex (mPFC),[35] as well as more caudally in the parahippocampal gyrus and temporal pole.[35] Certain visual association cortices (areas that process higher-order aspects of vision) are also active.[35,44] However, multiple neuroimaging modalities show that lateral prefrontal cortices remain deactivated after the transition from NREM to REM sleep.[35,43-45]

When REM sleep is directly compared to waking, there is relative deactivation of the lateral prefrontal cortex.[35,43,45] Maquet and colleagues[45] show that regions most consistently hypoactive in REM compared to waking include middle and inferior frontal gyri as well as inferior parietal and temporoparietal junction association cortices. However, compared to waking there is greater activation of limbic and paralimbic regions.[35,43,45-47] Nofzinger and colleagues[46,47] have termed this area the "anterior paralimbic REM activation area" (APRA) and describe it as a "bilateral confluent paramedian zone which extends from the septal area into ventral striatum, infralimbic, prelimbic, orbitofrontal and anterior cingulate cortex"[p. 192] including the hypothalamus, ventral pallidum, hippocampus, and uncus, as well as supplementary motor, pre- and subgenual anterior cingulate and insular cortices.[46]

Although lacking the temporal resolution of EEG and MEG, glucose metabolic ^{18}FDG (2-deoxy-2[^{18}F] fluorodeoxyglucose) PET studies correlating REM density with regional glucose metabolism also suggest activation of arousal, attention, and emotion networks in association with REM saccades.[48] Using fMRI, Hong and colleagues[49] have recently reported widespread blood oxygen level–dependent activity correlated with REMs that includes not only brainstem, thalamic, and limbic areas, but also primary and secondary sensory cortices and areas subserving oculomotor control and visuospatial attention. Recent oxygen use ($H_2{}^{15}O$) PET[50] and fMRI[51,51a] studies also correlate REMs with activation of structures corresponding to the feline PGO wave including the rostral brainstem,[50,51a] LGN, and occipital cortex.[50,51,51a] Phasic REM episodes arising from a tonic REM background show characteristic fMRI blood oxygen level–dependent changes in forebrain activity that include increased functional connectivity (the tendency to activate together) between the thalamus and a broad cortical-limbic-striatal network.[52] Wehrle and colleagues[52] suggest these changes represent activation, during phasic REM, of networks important to memory and emotional processing. Therefore, like EEG and MEG studies, functional neuroimaging suggests that phasic REM is associated with brain activity that might reflect intensified dream imagery, attention, and emotion.

DREAMING AND "DEFAULT MODE" NETWORKS

Regions that characteristically show deactivation in response to a wide variety of goal-directed cognitive tasks have been termed the brain's default mode.[53,54] In the absence of an exteroceptive focus, these regions are believed to carry out cognitive and emotional processes relating to self-directed concerns ("self-referential cognition").[53,54] Default network regions include a posteromedial parietal region (posterior cingulate, precuneus, and retrosplenial cortices), and a lateral-inferior-parietal/superior-temporal region, the hippocampal formation (hippocampus and

parahippocampal cortex), ventromedial prefrontal cortex (vmPFC), and dorsomedial prefrontal cortex (dmPFC).[53,54] Posterior default-network regions are linked to autobiographical memory retrieval and anterior regions with self-referential cognition.[53,55] Default network activity in the vmPFC has been associated with the integration of internal stimuli reflecting bodily sensations with external, sensory stimuli[54] as well as a feelings-based appraisal of whether or not such stimuli are self-related.[55] Activity in the dmPFC has been associated with self-referential cognitive, behavioral, and emotional imagination ("simulation") and its rehearsal,[53,54] as well as cognitive appraisal of self-related stimuli.[55] The dmPFC regions are also strongly activated by social cognition tasks such a those that engage abilities to infer others' feelings, thoughts, and intentions ("theory-of-mind").[55]

The default network contains two interacting subsystems, centered on the dmPFC and hippocampal formation respectively, activity in both of which correlates positively with a core network (vmPFC, posterior cingulate, retrosplenial and inferior parietal cortices) but negatively with each other.[53] The hippocampal formation may access personally relevant memory whereas the dmPFC may simulate future scenarios.[53] Notably, both retrospective (autobiographical) remembering and prospective simulation (imagining the future) engage much the same regions of the default network.[53]

Using fMRI, temporal synchrony of low frequency (0.01 to 0.1 Hz) spontaneous fluctuations of the blood oxygen level–dependent signal in waking reflects anatomical and functional connectivity among regions of the default network.[56] Such synchronized fluctuations persist into attentional lapses following sleep deprivation,[57] light NREM sleep[58] and even stage 2 NREM sleep,[59,59a] but not slow-wave sleep[59,59a] (although default areas may transiently activate during the "up" phase of the slow oscillation[39]). However, reactivation of default network structures during REM, as measured by PET, is only partial.[46,47] The anterior default network, vmPFC, and portions of dmPFC, as well as hippocampal and parahippocampal areas, reactivate.[35,43,44,46,47] In contrast, posterior, parietal default network areas, especially the lateral inferior parietal and posterior cingulate cortex, remain deactivated.[35,43,45]

REM sleep dreams may, therefore, reflect default network processing with disconnection between network subsystems due to a partially deactivated core. Specifically, self-referential, emotional and social cognitive simulation, subserved by anterior default-network structures (vmPFC, dmPFC), may be isolated from hippocampally-retrieved autobiographical memory due to absence of memory-access facilitation by posterior default network structures (posterior cingulate and retrosplenial cortices). With limited access to episodic, autobiographical memory, REM-sleep dreaming might simulate lifelike events[53] in a manner unconstrained by past realities.[60]

THE NEUROCHEMISTRY OF DREAMING

Three major neurochemical hypotheses explain differences between dreaming and waking consciousness. The activation-synthesis and activation-input-modulation models of Hobson and colleagues suggest that the massive increase in cholinergic (relative to noradrenergic and serotonergic) activation from the ascending reticular activating system (ARAS) during REM sleep contributes strongly to the unique nature of dream consciousness.[4,23] Solms suggests that stimulation of limbic and prefrontal reward networks by dopaminergic projections from the midbrain ventral tegmental area (VTA) generates motivational impulses that initiate dreaming.[61] Gottesmann suggests that dopaminergic stimulation of the cortex during REM, in the absence of waking's inhibitory serotonergic and noradrenergic modulation, allows emergence of psychotomimetic (psychosis-like) aspects of dream consciousness.[62]

Acetylcholine

The activation-synthesis[23] and activation-input-modulation[4] models suggest that forebrain activation in REM dreaming originates in ascending activation of the thalamus by mesopontine cholinergic nuclei. Much evidence exists for cholinergic enhancement of both REM and dreaming. Higher mesopontine-brainstem derived acetylcholine (ACh) concentrations during wake and REM sleep versus NREM sleep are seen in the thalamus, including the LGN.[63] Cholinergic stimulation potentiates REM sleep when microinjected into the animal brainstem or when systemically administered to humans.[4] Cholinesterase inhibitors can induce REM sleep with dreaming,[64] and increase nightmares[65] and hypnagogic hallucinations.[66] Transdermal nicotine[67] and its partial agonist varenicline[68] intensify dreams. Nightmares induced by beta-blockers[69] probably result from disinhibition of cholinergic-brainstem REM-generating mechanisms.[70]

Nonetheless, the most common pharmacological precipitant of waking hallucinosis is the delirium resulting from blockade of muscarinic ACh receptors.[71] Moreover, extensive cholinergic deficits may cause the visual hallucinations of Lewy body dementia.[71] The apparently paradoxical association of waking hallucinosis with hypocholinergic and REM dreaming with hypercholinergic brain conditions may arise because dreaming and waking hallucinations are differently generated. Perry and Perry[71] suggest that, in waking, ACh from the basal forebrain excites the GABAergic interneurons of the cortex thereby inhibiting cortical pyramidal neurons and improving the signal-to-noise ratio at their synapses. In contrast, during REM sleep, ACh from the mesopontine brainstem inhibits GABAergic interneurons of the thalamus thereby disinhibiting, as well as directly exciting, thalamocortical neurons (thalamic neurons that project to and excite the cortex) possibly, in part, via nicotinic receptors that are especially abundant in the thalamus.[71] Therefore, reduced ACh in waking allows intrusion of weaker inputs, whereas increased ACh in REM sleep excites the cortex in the absence of any perceptual input—two differing conditions but both conducive to hallucinosis.[71] Notably, by combining a cholinergic challenge with fMRI, Furey and colleagues[72] have shown that, in waking, ACh enhances the activity of visual association cortices (in REM sleep, possibly favoring hallucination) while at the same time reducing dorsal prefrontal cortical activity (in REM sleep, possibly diminishing logic and insight).

Dopamine

Because mean firing rates of dopaminergic cells in the substantia nigra pars compacta and VTA do not vary with behavioral state in the same manner as do the other aminergic nuclei, dopamine (DA) has received less study by sleep and dream researchers (reviewed in Hobson, Pace-Schott, and Stickgold[4] and Hobson and Pace-Schott[70]). However, a key role is assigned to DA in reward-based[61] and psychotomimetic[62] theories of dreaming. Recent findings in rodents have begun to identify roles for DA in REM sleep. For example, enhancing REM intensity by prior REMD increases c-*fos* expression in the VTA,[73] and DA concentrations in the mPFC and nucleus accumbens are greater during REM sleep than they are during NREM sleep.[74] Because transition to a burst-firing mode releases more presynaptic DA,[74] synaptic DA concentrations can vary without change in dopaminergic neurons' mean firing rate. Dahan and colleagues[75] have demonstrated just such a transition during REM sleep in DA neurons of the VTA. The REM-related increase of burst firing in the VTA may result from increased cholinergic excitation from the PPT[74] that innervates[76] and strongly excites[77] the VTA. Although L-dopa and certain other dopaminergic agents can enhance dreaming in persons with Parkinson's disease and other clinical conditions (reviewed in Solms,[61] Pagel,[69] and Hobson and Pace-Schott[70]), psychostimulants are not associated with dream enhancement, neuroleptics do not prevent dreaming, and there exist DA agonists that reduce, and antagonists that enhance, dreaming.[70] Thus DA's dream effects may be dependent on dosage, as well as receptor type and location.

Serotonin

Selective serotonin (5-HT) reuptake inhibitors and other serotonergic drugs can intensify dreaming.[78] Animal studies on serotonergic hallucinogens by Aghajanian and colleagues suggest that low or fluctuating cortical 5-HT levels may induce cortical output conducive to hallucinosis.[79] Serotonergic hallucinogens act presynaptically as partial 5-HT_{2A} (serotonin-2a) receptor agonists at glutamatergic inputs to apical dendrites of layer V cortical pyramidal neurons causing an "asynchronous" release of glutamate to follow the larger action-potential mediated ("synchronous") release.[79] This late, slow release of glutamate induces prolonged excitatory postsynaptic potentials (EPSPs) that are hypothesized to underlie the cognitive-perceptual effects of the hallucinogens.[79] 5-HT itself does not produce such prolonged EPSPs presumably due to its inhibitory effects at 5-HT_1 receptors.[79] However, under conditions of decreasing 5-HT concentration, such EPSPs do emerge, and low 5-HT concentrations may generally favor asynchronous transmitter release–evoked EPSPs.[79] The naturally occurring lowest levels of 5-HT occur during REM sleep, and fluctuations of 5-HT release occur during sleep stage transitions.[4] Thus, these conditions may promote the natural occurrence of hallucinosis during dreaming. Notably, Nofzinger's APRA[46] includes anterior limbic cortices that contain the highest cortical concentrations of the inhibitory 5-HT_{1A} receptor and 5-HT transporter.[80] Decreased cortical 5-HT during REM sleep may allow strong cholinergic activation of these areas to enhance the cognitive and emotional dream features they support.

NEUROPSYCHIATRIC SYNDROMES THAT INFORM THE STUDY OF DREAMING

Despite striking differences between dreaming and waking experience, the same brain subserves both of these states.[35] It is therefore worthwhile to examine brain alterations that shift waking consciousness toward dreaming. Table 48-1 illustrates alterations of waking cognition that may help explain certain formal characteristics of dreaming.[4] We focus here on analogies of dream plots with waking spontaneous (versus provoked) confabulation ("confabulation") and of dream hallucinations with complex visual hallucinosis ("hallucinosis").

Confabulation Shares Neural Substrate with Dreaming

Patients with confabulation recount false events, assert false beliefs, and act upon them with unshakable conviction as to their veracity.[81,82] Confabulatory beliefs and memories are usually based upon real autobiographical events including those in the remote past.[81,83] Confabulation results from lesions of the vmPFC, the orbitofrontal cortex, and their connections with the basal forebrain, amygdala, mediodorsal thalamic nucleus, and hypothalamus.[81-83] These regions broadly overlap with Nofzinger's APRA.[46]

One theory on the cognitive deficit resulting in confabulation suggests that vmPFC lesions disrupt a reality-monitoring function that preconsciously suppresses spontaneously activated memories not pertaining to present circumstances.[83] Memories of past experiences are thus perceived as related to the present.[83] An alternative theory posits temporal deficits to be a subset of a more general deficit in strategic retrieval and verification of memories.[82]

Moskovitch and colleagues[84] suggest vmPFC regions subserve an early stage in memory verification—a "feeling of rightness" (FOR)—after which further evaluation of a retrieved memory takes place in dorsolateral prefrontal cortices (dlPFC). Gilboa and colleagues[82] suggest impaired FOR resulting from lesions to the vmPFC and orbitofrontal cortex is crucial and sufficient for producing confabulation. The salience and strength of autobiographical memories cause self-related content to dominate the content of confabulations.[82,85]

Dreaming may represent a potent form of confabulation in which imaginary events are not only created and believed, but also are vividly experienced as organized, multimodal hallucinations.[25,70] For example, confabulators create plausible but false explanations for inconsistencies in their stories[81] closely resembling ad-hoc explanations for improbable dream occurrences.[86] Hirstein[81] suggests that confabulation represents an extreme example of false belief disorders such as anosognosias and misidentification syndromes. "Pathological false recognition"[81] in confabulation parallels dreamers' assigning a known identity to dream characters perceptually dissimilar to their waking counterpart,[87] a phenomenon Schwartz and Maquet[88] liken to Fregoli syndrome (see Table 48-1). In both confabulation[81] and dreaming, altered function of the vmPFC and the orbitofrontal cortex may release from normal

Table 48-1 Neuropsychiatric Syndromes Which Inform the Study of Dreaming

PHENOMENON, SYMPTOM, OR SYNDROME	WAKING SYMPTOMATOLOGY RESEMBLING DREAM FEATURE	REPRESENTATIVE SYNDROMES EXPRESSING SYMPTOMATOLOGY	BRAIN SUBSTRATES OF SYMPTOMATOLOGY	W: WAKING SYMPTOM DESCRIBED D: DREAMING PHENOMENON OR SYMPTOM DESCRIBED (REFERENCE NO.)
Complex, realistic visual hallucinations	Complex visual hallucinosis	Peduncular hallucinosis Charles Bonnet syndrome Hallucinogen intoxication	RAS/diencephalon Retino-geniculo-striate Visual association cortex Serotonergic pathways Cholinergic pathways	W: Manford and Andermann 1998 (91) W: Collerton et al. 2005 (94) D: Hobson 2001 (58a)
Narrative form with delusionality, disorientation, lost insight, & poor self-monitoring	Spontaneous confabulation Disorientation to time	Amnesia with anterior limbic pathology Traumatic brain injury Delirium	Caudomedial OPFC Subcallosal cingulate Basal forebrain Chemical homeostasis	W: Schnider 2003 (83) W: Gilboa et al. 2006 (82) D: Hobson 2001 (58a)
Recognition with episodic memory deficits	Relative preservation of recognition memory	Amnesias: Medial temporal Diencephalic	Hippocampal complex Parahippocampal cortices Diencephalic pathways	W: Brown and Aggleton 2001 (113) D: Fosse et al. 2003 (60)
Emotional alterations Intensification Blunting	Lability/reactivity, apathy/ hypoemotionality	Dorsolateral PFC lesion Psychosis Mood disorders Anxiety disorders	Caudomedial OPFC Subcallosal cingulate Amygdala Dorsolateral PFC	W: Phan et al. 2002 (107) D: Hobson et al. 2000 (4)
Visual distortions	Visual distortions: Micro/macropsia, polyopsia, achromatopsia	Visual cortex lesions	Visual association cortices Anterior occipital Inferior temporal Feature specific (V4, MT)	D, W: Schwartz and Maquet 2002 (88)
Nonvisual dreams	Visual irreminiscence	Temporo-occipital lesion	Visual association cortices	D, W: Solms 1997 (61)
Erroneous identification Visual hallucinosis Delusionality	Misidentification of person or place	Capgras delusion Fregoli syndrome, reduplicative paramnesia	Ventral temporal cortex Fusiform face area Prefrontal cortex Limbic (e.g., amygdala)	D, W: Schwartz and Maquet 2002 (88)
Reciprocal frequency of thought and hallucination	Acute hallucinosis and disorientation	Delirium Acute psychosis Epileptic ictus	Chemical homeostasis Visual association cortices RAS/diencephalon Limbic subcortex Prefrontal cortex	D: Fosse et al. 2001 (125)
Bizarreness Incongruity Discontinuity Ad-hoc explanation	Impaired working memory and attention Delusion-based logic	Dorsolateral PFC lesion Psychosis	Dorsolateral PFC PGO system Mesocortical DA system	D: Hobson et al. 2000 (4) Hobson 1977 (23)

ARAS, ascending reticular activating system; DA, dopamine system; MT, motion specific visual association area; PFC, prefrontal cortex; PGO, ponto-geniculo-occipital wave; V4, color specific visual association area.

inhibitory, reality-monitoring, and executive constraints, innate human tendencies to create explanatory stories and fill amnestic gaps in narratives. Notably, mPFC regions have been frequently associated with normal production of narrative (reviewed in Mar[89]).

However, prominent differences exist between dreaming and confabulation. Unlike confabulation, dreaming involves actual hallucinosis of pseudosensory elements and generates entirely novel scenes, characters, objects, and scenarios.[25] For example, in one study, 25% of dream characters were novel personages.[87] In another, an accurate replay of episodic memory was extremely rare in dream reports.[60] Another difference is that brain areas whose destruction leads to confabulation overlap the APRA.[35,43,46] Thus, hyperactivation of APRA areas in REM dreaming may alter their reality-monitoring functions in a similar manner as their damage in confabulatory[83] and dream–wake confusional syndromes.[61] Two observations may explain this paradox. First, abnormal activation of anterior limbic structures (e.g., by seizures) can profoundly alter consciousness.[90] Second, REM sleep's predominantly cholinergic activation, together with the absence of waking's monoaminergic modulation, may impair reality testing in the APRA.

Visual Hallucinosis in Waking and Dreaming

Anatomical regions associated with dreaming and with hallucinosis also overlap. Manford and Andermann[91] suggest hallucinations result when visual association cortices in the inferior occipital and temporal lobes that identify objects and scenes (the "ventral processing stream") are released from normal restraints under three conditions: (1) loss of exogenous visual input, (2) ARAS damage that alters serotonergic and cholinergic modulation of the cortex, or (3) abnormally excitatory input.[91] Conditions corresponding to each mechanisms may contribute to REM hallucinosis.

First, in conditions such as Charles Bonnet syndrome, waking hallucinosis results when perceptual input to the visual association cortex is lost due to lesions of the primary visual pathway.[91] In REM dreaming, there is no retinal input. Moreover, primary visual cortices are deactivated,[44] perhaps decreasing their regulatory input on downstream association cortices. Second, in peduncular hallucinosis, lesions of the rostral brainstem disrupt the amount and balance of serotonergic and cholinergic input to the forebrain.[91] Serotonergic raphe neurons fire at their naturally occurring minimum during REM sleep, whereas mesopontine cholinergic systems have reactivated to near-waking levels.[4] Therefore, altered serotonergic-cholinergic balance during REM sleep may also favor hallucinosis. Third, irritative excitation of visual association cortices (the areas active during hallucinations in Charles Bonnet syndrome[92]) can produce epileptic hallucinosis.[91] Ventral-stream visual association cortices are more active in REM than in either NREM or post-sleep–waking[35,44] and are a hypothesized source of dream imagery.[4,61] During REM, PGO waves originating in the mesopontine brainstem[4,27] excite many cortical regions[93] including visual association areas.

Collerton and colleagues[94] suggest that hallucinations result from combined sensory impairment, attentional deficit, and a relatively intact scene perception that allows poorly formed "proto-objects" to resolve into erroneous percepts. In REM-sleep dreaming, ascending activation of visual association cortices may evoke hallucinatory proto-objects that, under the attentionally unstable conditions of REM, resolve into hallucinatory percepts congruent with the ongoing dream plot. Internal consistency of dream plots may then arise because the evolving dream context itself biases resolution of ambiguous percepts into plot-congruent images or directly influences which proto-percepts are evoked or attended to. Dreams may thus evolve by a "boot-strapping" process whereby current images provide the context that, in turn, determines succeeding dream imagery.[95] In the absence of working memory capacities that provide continuity to waking experience, the evolving dream plot can be strongly influenced by immediately prior dream experiences. In a similar manner, top-down influences from limbic cortices may bias posterior association cortices toward generating, attending to, or disambiguating imagery in a manner that is congruent with ongoing dream emotion.[25]

A DESCRIPTIVE MODEL OF NEURONAL NETWORKS–GENERATING DREAM PHENOMENOLOGY

Behavioral states and cognitive capacities are physically instantiated in widely distributed networks with distinct epicenters of critical control in a pattern of "selectively distributed processing."[96] The following working model of neurobiological structures and networks subserving REM-dream phenomenology refers to brain areas as depicted in Figure 48-1.[4] These REM-active networks may also help explain NREM dreaming (see first two sections below).

Ascending Arousal System

Activation of the forebrain in REM sleep, as in waking, occurs through the ascending arousal systems of the brainstem,[16] basal forebrain,[97] and hypothalamus (areas 1 and 2 in Fig. 48-1).[98] However, unlike in waking, ascending activation in REM sleep is primarily facilitated by cholinergic systems whereas aminergic neuromodulation is attenuated (reviewed in Hobson et al.[4]) Since mesopontine PPT and laterodorsal tegmental (LDT) cholinergic neurons project to the thalamus and basal forebrain but not the cortex,[71] cortical activation in REM sleep is preceded by cholinergic activation of the diencephalon and basal forebrain. Intrinsic oscillations of NREM sleep are blocked at the thalamus by ascending activation from mesopontine cholinergic nuclei.[16] Cholinergic activation excites thalamocortical neurons and inhibits the GABAergic neurons of the thalamic reticular nucleus (that inhibit thalamocortical neurons during NREM sleep) thereby disinhibiting them.[16] As in waking, thalamocortical neurons then activate the cortex glutamatergically. In a second, more ventral ascending activation pathway, the LDT and PPT mesopontine nuclei project to basal forebrain nuclei that,[97,99] in turn, project cholinergically to regionally specific areas of the cortex[71] and produce cortical activation.[97,99] In NREM sleep, phasic increases in ARAS activity due to endogenous or exogenous stimulation or autonomic

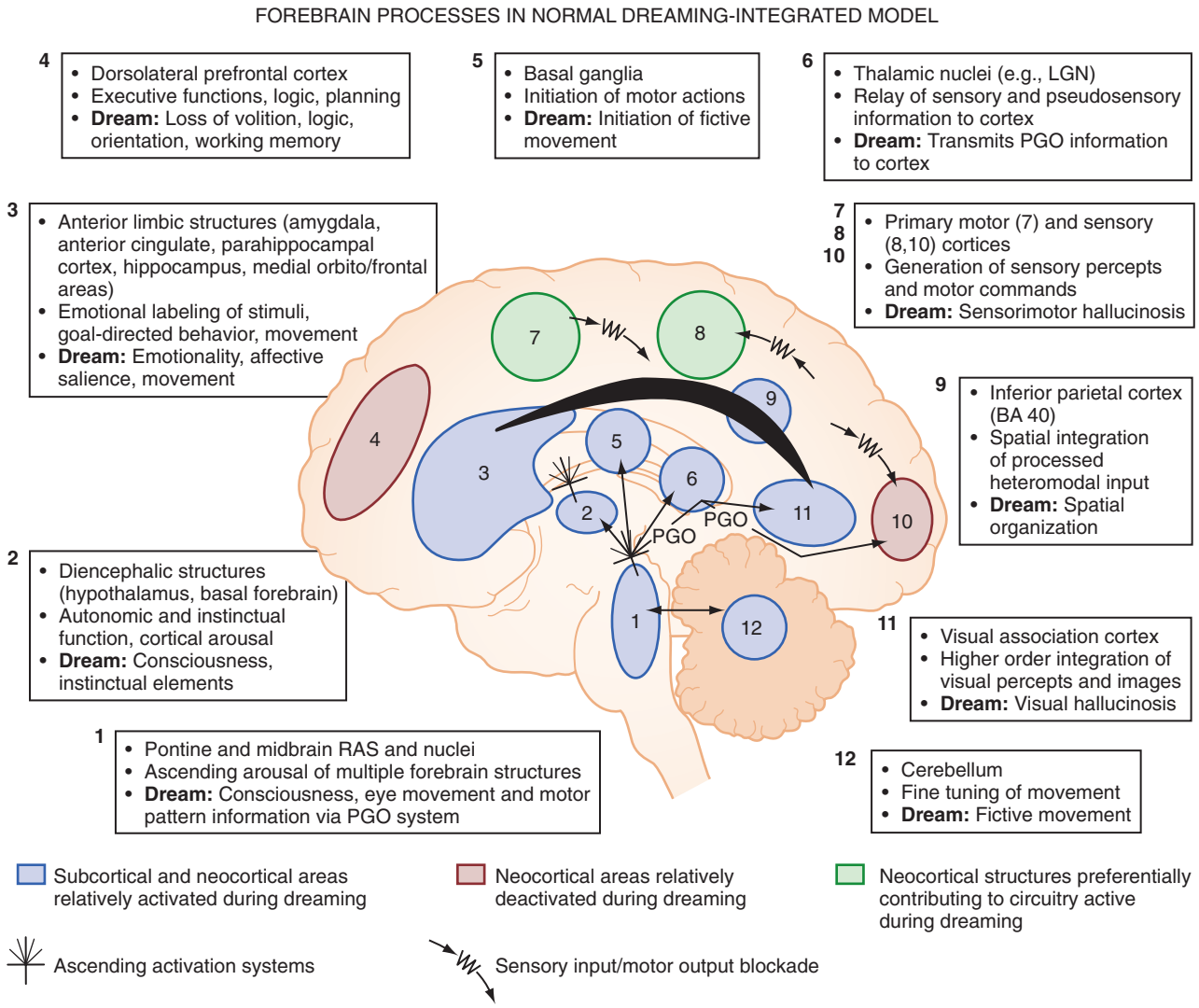

Figure 48-1 Forebrain processes in normal dreaming—an integration of neurophysiological, neuropsychological and neuroimaging data. Regions 1 and 2, ascending arousal systems; region 3, subcortical and cortical limbic and paralimbic structures; region 4, dorsolateral prefrontal executive association cortex; region 5, motor initiation and control centers; region 6, thalamocortical relay centers and thalamic subcortical circuitry; region 7, primary motor cortex; region 8, primary sensory cortex; region 9, inferior parietal lobe; region 10, primary visual cortex; region 11, visual association cortex; region 12, cerebellum. (From Hobson JA, Pace-Schott EF, Stickgold R. Dreaming and the brain: toward a cognitive neuroscience of conscious states. Behav Brain Sci 2000;23:793-842; discussion 904-1121.)

activity may transiently stimulate the same forebrain networks activated in REM sleep and waking, the subjective manifestation of which may be NREM-sleep dreaming.

Thalamocortical Relay Centers and Thalamic Subcortical Circuitry

During REM sleep, thalamocortical signaling may be interpreted as incoming sensory stimuli,[23] and may evoke local activation of stored cognitive representations (hallucinosis of known entities) or may evoke novel representations in association cortices (as in dream bizarreness) (area 6 in Fig. 48-1). The PGO wave may be only one of many pathways for ARAS activation of the cortex via thalamic or basal forebrain intermediaries during REM sleep. For example, in the rat, the pontine p-wave in REM sleep impinges directly on limbic structures such as the amygdala, hippocampus, and entorhinal cortex, as well as the visual cortex.[100] Other pathways through the thalamus might include a nonrelay sensory route through the pulvinar nucleus directly to the visual association cortex[44] or to limbic prefrontal areas via magnocellular portions of the mediodorsal nucleus. Such phasic activation of the cortex may lead to the presaccade spectral changes seen using EEG and MEG,[6,26] as well as the correlation of REM density with activity of attentional structures in PET studies.[48,49]

During NREM sleep, intrinsic thalamocortical oscillations suppress but do not completely extinguish perception and mentation.[101] NREM sleep oscillatory rhythms reflect endogenous activity of corticocortical and corticothalamocortical circuits grouped by the slow oscillation, the "up" state of which briefly returns cortical neurons to levels of high activity.[16,17,39,102] Steriade[102] has suggested that when this oscillatory pattern is impinged upon by phasic thala-

mocortical bursts, such as the isolated PGO waves in the NREM-REM transitional state, phasic elevation of regional activity may lead to vivid visual imagery. Notably, activation in NREM sleep of primary visual[38,44] and visual association[103] areas may also generate NREM-sleep imagery.

Subcortical and Cortical Limbic and Paralimbic Structures

In REM sleep, selective activation of limbic and paralimbic cortex and subcortex[35,43,44,46,47] (area 3 in Fig. 48-1) has suggested to PET researchers roles for REM sleep in the processing of emotionally influenced memories,[45,104] integration of neocortical functions with basal forebrain and hypothalamic motivational and reward mechanisms,[47] or internal information processing between visual association and limbic regions.[44] Such processes may underlie the emotionality[4,35,104] and social nature of dreaming.[25,87]

Emotion, Emotional Regulation, and Dreaming

It is often hypothesized that sleep and dreaming play an emotional regulatory role in healthy humans[105,106] that is disrupted in mood and anxiety disorders that, in turn, can alter dreaming, as in nightmares.[106] Indeed, Nofzinger's APRA includes many of the structures implicated in the experience and expression of emotion (reviewed in Phan et al.[107]). Although dreams may aid in resolution of intrapersonal conflict (e.g., see Cartwright et al.[105]), dreaming (or accompanying sleep states) may also moderate emotional extremes by universal mammalian learning processes such as habituation (decreased autonomic reactivity with repeated exposure) and extinction (learning that conditioned feared stimuli are no longer threatening), as well as by homeostatic equilibration of stress, reward, autonomic, and neuroendocrine systems.

Nielsen and Levin[106] have suggested that, in normal REM sleep, activity in limbic circuits that roughly overlap Nofzinger's APRA regulates emotion via formation of extinction memories when emotionally salient memories appear in safer contexts during dreaming. Animal[108] as well as human[109] studies link formation, retention, and expression of extinction learning to circuitry linking the amygdala, vmPFC, and hippocampus. Notably, a night's sleep promotes generalization of extinction learning.[110] Whereas such circuitry may be recruited by dlPFC-based cognitive processes in waking[111] it may function autonomously during REM sleep (see Nielsen and Levin[106]).

Reward systems are also activated, and positive and negative emotions may be modulated during REM sleep. VTA sources of mesolimbic and mesocortical dopamine are recruited by ascending cholinergic activation[77] and, like their ventral striatal and mPFC targets, lie well within the APRA.[46,47] Hypothalamic-brainstem circuits may initiate instinctively salient behavior in dreaming[112] that may, in turn, recruit additional forebrain regions to enact appetitive[61] or other adaptive behaviors.[112]

Altered Memory Processing in Dreams

A cholinergically-mediated informational barrier between cortex and hippocampus in REM sleep has been proposed to underlie the paucity of episodic memories in dreams.[60] However, despite inaccessibility of episodic memory, another aspect of declarative memory, "familiarity" or "recognition,"[113] is ubiquitous in dreams. For example, 40% of dream characters may be identified on the basis of "just knowing."[87] Schwartz and Maquet[88] suggest such phenomena result from the sleep-related disconnection of temporal lobe face recognition from prefrontal reality monitoring areas. Alternatively, frequent experiences of familiarity in the absence of accurate replay of episodic memories in dreams may reflect activity of recognition memory mechanisms in anterior perirhinal cortices (BA 35, BA 36), dissociated from hippocampally mediated recall. Indeed, double dissociations between recognition and remembering have been shown in human fMRI studies.[113] Because perirhinal areas of the anterior medial temporal lobe are proximal to the APRA,[47] altered interactions of this region with other portions of the hippocampal formation during REM sleep may produce such a dissociation.

During dreaming, frontal contributions to memory retrieval may also be altered. Ventrolateral and dlPFC regions that are deactivated in REM sleep[45] subserve cue-specification and search strategies, respectively.[84] In contrast, caudal vmPFC, which is active in REM sleep,[35,43,46,47] subserves "feeling-of-rightness"[84] and the related phenomenon "feeling of knowing"[114] for which more anterior PFC areas only later provide cognitive verification.[84] Therefore, during REM sleep, greater activation of caudo-ventromedial than anterolateral PFC regions relative to waking may favor an indiscriminate, emotional confirmation of accuracy for any item in consciousness without the benefit of strategic volitional search or critical verification. In combination, studies of self-cognition,[55] mental simulation,[53] confabulation,[82,83] and memory verification[84,114] predict that restriction of frontal activation to vmPFC would favor a self-referential, emotionally salient state prone to producing mental simulations that evoke a powerful sense of veracity and familiarity and are uncritically believed.

Social Cognition and Dreams

Medial PFC regions are recruited by both emotional and social cognition.[107,115] Theory-of-mind is a complex aspect of social cognition[115] that is preserved in dreaming despite notable degradation of reasoning about the physical world.[116,117] Brain areas most consistently activated in neuroimaging studies of theory-of-mind include mPFC (especially the paracingulate cortex, BA 32), superior temporal sulcus, and temporal poles including the amygdala.[115] REM-associated activity in these areas, especially vmPFC, has been suggested to support theory-of-mind skills in dreams and to produce the ubiquity of social interactions and highly salient interpersonal emotions in dream plots.[25,45,116]

Motor Initiation and Control Centers

Strong activation of the basal ganglia[35] (area 5 in Fig. 48-1) may mediate the ubiquitous fictive motion of dreams.[118] The basal ganglia are extensively connected not only with motor cortex, but also with mesopontine nuclei such as the PPT[119] that contain gait circuitry and other motor pattern generators as well as REM regulatory areas (reviewed in Hobson et al.[4]). Activation of brainstem vestibular nuclei

and the associated cerebellar vermis (see Braun et al.[35]) during REM sleep may additionally contribute vestibular sensations interpreted as flying or falling, as well as a sense of motor control.

Visual Association Cortex

Medial occipitotemporal cortices (area 11 in Fig. 48-1) are activated in REM sleep.[35,44] These and other visual association areas may generate the visual imagery of dreams.[4,61] As in waking, specific areas of the visual association cortex may process specific visual characteristics of dreaming. For example, the fusiform gyrus both mediates waking face recognition and is activated in REM sleep.[35,44,47] Braun and colleagues[44] suggest that REM sleep constitutes a unique cortical condition of internal information processing (between visual association and limbic cortices), functionally isolated from input (via primary visual cortex) or output (via frontal cortex) to the external world. Dream image formation may arise as ascending activation impinges on visual and multimodal association areas in occipital, temporal, and inferior parietal cortices.

Inferior Parietal Lobe

The supramarginal and angular gyri of the inferior parietal lobe (BA 39 and 40; area 9 in Fig. 48-1), especially in the right hemisphere, are essential for visuospatial awareness.[96] These areas may generate the fictive dream space necessary for the organized hallucinatory experience of dreaming.[61] Destruction of these areas is alone sufficient to produce global cessation of dreaming.[61,120] Maquet et al. have found right inferior parietal cortex to be relatively activated during REM in some[43] but not all[45] PET studies. In REM, both the above-described visual association cortex and the vmPFC are simultaneously active.[44] Therefore, in REM, self-centric reality simulation, a putative function of the vmPFC,[53] and hallucinatory imagery may arise in concert. Inferior parietal multimodal association cortices may integrate different unimodal inputs and facilitate their incorporation into the emerging plot in the virtual proscenium where the dream is experienced.

Dorsolateral Prefrontal Executive Association Cortex (Area 4 in Figure 48-1)

Lesions of the dorsolateral prefrontal cortices (area 4 in Fig. 48-1) do not cause cessation or attenuation of dreaming, which suggests that they are nonessential for the generation of dreaming.[61,120] Unlike vmPFC regions that reactivate, these dorsolateral prefrontal areas remain deactivated in REM sleep,[35,43-45] possibly explaining the prominent executive deficiencies of dream mentation that include disorientation, illogic, impaired working memory, and amnesia for dreams.[4] Additionally, because the prefrontal cortex regulates posterior sensory cortices,[121] deactivation of the dorsolateral prefrontal cortex in REM sleep[35,43,45] may promote dreaming by disconnection, release, or disinhibition of sensory association cortices (as also suggested by EEG and MEG[6,7,12,18]).

The prefrontal cortex maintains an online representation of a goal, the means to achieve it, and the ongoing context relevant to this goal in order to "bias" the functioning of networks elsewhere in the brain toward this particular outcome.[122] For example, "top-down" influence can sensitize primary and association perceptual cortices to particular stimuli while simultaneously attenuating their sensitivity to competing stimuli.[123] With diminished frontal activation during sleep, goal-directed biases in the regulation of circuits subserving working memory and attention (frontoparietal), and memory encoding and retrieval (frontotemporal) may be impaired during dreaming.[4,25] Nonetheless, top-down influence in REM sleep may bias sensitivity of sensory cortices to hallucinatory percepts related to affective and social processing subserved by the vmPFC, whereas nonemotional imagery may fail to persist in the face of weakened working memory. Additionally, diminished activity in lateral frontal cortices in REM sleep[45] may weaken the ability of frontal, top-down influence to modulate emotional responses to dream imagery as it does in waking emotion.[111] Alteration in dreaming of specific frontal-subcortical networks may underlie dream emotional salience and executive weakness. For example, the "cognitive" fronto-striatal-thalamo-cortical circuit (linking dlPFC with dorsal striatum) may be less active than "affective" (orbitofrontal-ventral caudate) and "motivational" (anterior cingulate-nucleus accumbens) circuits.[124]

CONCLUSION

ARAS, thalamocortical, and basal forebrain-cortical arousal systems activate the forebrain regions involved in dream construction in a manner that is chemically and anatomically different from waking. In REM sleep such activation may be more frequent and sustained and, perhaps, may proceed via different or more diverse pathways than in NREM sleep. Cortical circuits activated in REM dreaming are medial circuits linking visual association and paralimbic areas (central crescent in Fig. 48-1), but not the primary sensory and lateral frontal executive cortical regions that are active in waking.[44] Therefore, dreaming is both positively and negatively emotionally salient (amygdala, ventral striatum, vmPFC), often conflictual (anterior cingulate) and social (vmPFC), while also displaying profoundly deficient working memory, orientation, and logic (lateral prefrontal and parietal deactivation). Subcortical circuits involving the limbic structures, striatum, diencephalon, and the brainstem regions are selectively activated in REM sleep. They may contribute to dreaming's emotional (limbic subcortex), motoric (striatum, brainstem, cerebellum), instinctual (hypothalamus), and motivational (midbrain-ventral striatum) properties.

❖ Clinical Pearl

The physician prescribing selective serotonin reuptake inhibitors, transdermal nicotine, varenicline, beta-blockers, dopaminergic agents, or a variety of other medications[65,67-69,78] should be alert for possible dream intensification or nightmare induction. Although the percentage risks of such side effects for each particular medication are variable, patient reports are not uncommon. Other choices within the same class or a different class of medications may need to be considered if such side effects are intolerable to the patient.

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REFERENCES

1. Rechtschaffen A. The single-mindedness and isolation of dreams. Sleep 1978;1:97-109.
2. Dement W, Kleitman N. The relation of eye movements during sleep to dream activity: an objective method for the study of dreaming. J Exp Psychol 1957;53:339-346.
3. Foulkes WD. Dream reports from different stages of sleep. J Abnorm Soc Psychol 1962;65:14-25.
4. Hobson JA, Pace-Schott EF, Stickgold R. Dreaming and the brain: toward a cognitive neuroscience of conscious states. Behav Brain Sci 2000;23:793-842; discussion 904-1121.
5. Nielsen TA. A review of mentation in REM and NREM sleep: "covert" REM sleep as a possible reconciliation of two opposing models. Behav Brain Sci 2000;23:851-866; discussion 904-1121.
6. Corsi-Cabrera M, Guevara MA, del Rio-Portilla Y. Brain activity and temporal coupling related to eye movements during REM sleep: EEG and MEG results. Brain Res 2008;1235:82-91.
7. Corsi-Cabrera M, Miro E, del-Rio-Portilla Y, Perez-Garci E, et al. Rapid eye movement sleep dreaming is characterized by uncoupled EEG activity between frontal and perceptual cortical regions. Brain Cogn 2003;51:337-345.
8. Gross DW, Gotman J. Correlation of high-frequency oscillations with the sleep-wake cycle and cognitive activity in humans. Neuroscience 1999;94:1005-1018.
9. Nishida M, Uchida S, Hirai N, Miwakeichi F, et al. High frequency activities in the human orbitofrontal cortex in sleep-wake cycle. Neurosci Lett 2005;379:110-115.
10. Jensen O, Kaiser J, Lachaux JP. Human gamma-frequency oscillations associated with attention and memory. Trends Neurosci 2007;30:317-324.
11. Jouny C, Chapotot F, Merica H. EEG spectral activity during paradoxical sleep: further evidence for cognitive processing. Neuroreport 2000;11:3667-3671.
12. Cantero JL, Atienza M, Madsen JR, Stickgold R. Gamma EEG dynamics in neocortex and hippocampus during human wakefulness and sleep. Neuroimage 2004;22:1271-1280.
13. Fell J, Staedtgen M, Burr W, Kockelmann E, et al. Rhinal-hippocampal EEG coherence is reduced during human sleep. Eur J Neurosci 2003;18:1711-1716.
14. Kahn D, Pace-Schott EF, Hobson JA. Consciousness in waking and dreaming: the roles of neuronal oscillation and neuromodulation in determining similarities and differences. Neuroscience 1997;78:13-38.
15. Achermann P, Borbely AA. Low-frequency (<1 Hz) oscillations in the human sleep electroencephalogram. Neuroscience 1997;81:213-222.
16. Steriade M. Corticothalamic resonance, states of vigilance and mentation. Neuroscience 2000;101:243-276.
17. Destexhe A, Hughes SW, Rudolph M, Crunelli V. Are corticothalamic "up" states fragments of wakefulness? Trends Neurosci 2007;30:334-342.
18. Perez-Garci E, del Rio-Portilla Y, Guevara MA, Arce C, et al. Paradoxical sleep is characterized by uncoupled gamma activity between frontal and perceptual cortical regions. Sleep 2001;24:118-126.
19. Cantero JL, Atienza M, Salas RM. State-modulation of corticocortical connections underlying normal EEG alpha variants. Physiol Behav 2000;71:107-115.
20. Guevara MA, Lorenzo I, Arce C, Ramos J, et al. Inter- and intrahemispheric EEG correlation during sleep and wakefulness. Sleep 1995;18:257-265.
21. Bertini M, De Gennaro L, Ferrara M, Curcio G, et al. Reduction of transcallosal inhibition upon awakening from REM sleep in humans as assessed by transcranial magnetic stimulation. Sleep 2004;27:875-882.
22. Massimini M, Ferrarelli F, Huber R, Esser SK, et al. Breakdown of cortical effective connectivity during sleep. Science 2005;309:2228-2232.
23. Hobson JA, McCarley RW. The brain as a dream state generator: an activation-synthesis hypothesis of the dream process. Am J Psychiatry 1977;134:1335-1348.
24. Conduit R, Crewther SG, Coleman G. Spontaneous eyelid movements (ELMS) during sleep are related to dream recall on awakening. J Sleep Res 2004;13:137-144.
25. Pace-Schott EF. The frontal lobes and dreaming. In: Barrett D, McNamara P, editors. The new science of dreaming. Westport, Conn, Praeger, Greenwood Press; 2007.
26. Ioannides AA, Corsi-Cabrera M, Fenwick PB, et al. MEG tomography of human cortex and brainstem activity in waking and REM sleep saccades. Cereb Cortex 2004;14:56-72.
27. Lim AS, Lozano AM, Moro E, Hamani C, et al. Characterization of REM-sleep associated ponto-geniculo-occipital waves in the human pons. Sleep 2007;30:823-827.
28. Ogawa K, Nittono H, Hori T. Brain potentials before and after rapid eye movements: an electrophysiological approach to dreaming in REM sleep. Sleep 2005;28:1077-1082.
29. Abe T, Ogawa K, Nittono H, Hori T. Neural generators of brain potentials before rapid eye movements during human REM sleep: a study using sLORETA. Clin Neurophysiol 2008;119:2044-2053.
30. Takeuchi T, Ogilvie RD, Murphy TI, Ferrelli AV. EEG activities during elicited sleep onset REM and NREM periods reflect different mechanisms of dream generation. Electroencephalograms. Rapid eye movement. Clin Neurophysiol 2003;114:210-220.
31. Nielsen T, Stenstrom P, Takeuchi T, Saucier S, et al. Partial REM-sleep deprivation increases the dream-like quality of mentation from REM sleep and sleep onset. Sleep 2005;28:1083-1089.
32. Bodizs R, Sverteczki M, Meszaros E. Wakefulness-sleep transition: emerging electroencephalographic similarities with the rapid eye movement phase. Brain Res Bull 2008;76:85-89.
33. Suzuki H, Uchiyama M, Tagaya H, Ozaki A, et al. Dreaming during non-rapid eye movement sleep in the absence of prior rapid eye movement sleep. Sleep 2004;27:1486-1490.
34. Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. J Sleep Res 2000;9:207-231.
35. Braun AR, Balkin TJ, Wesenten NJ, Carson RE, et al. Regional cerebral blood flow throughout the sleep-wake cycle. An H2(15)O PET study. Brain 1997;120:1173-1197.
36. Dang-Vu TT, Desseilles M, Laureys S, Degueldre C, et al. Cerebral correlates of delta waves during non-REM sleep revisited. Neuroimage 2005;28:14-21.
37. Kaufmann C, Wehrle R, Wetter TC, Holsboer F, et al. Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study. Brain 2006;129:655-667.
38. Hofle N, Paus T, Reutens D, Fiset P, et al. Regional cerebral blood flow changes as a function of delta and spindle activity during slow wave sleep in humans. J Neurosci 1997;17:4800-4808.
39. Dang-Vu TT, Schabus M, Desseilles M, Albouy G, et al. Spontaneous neural activity during human slow wave sleep. Proc Natl Acad Sci USA 2008;105:15160-15165.
40. Finelli LA, Borbely AA, Achermann P. Functional topography of the human nonREM sleep electroencephalogram. Eur J Neurosci 2001;13:2282-2290.
41. De Gennaro L, Vecchio F, Ferrara M, Curcio G, et al. Changes in fronto-posterior functional coupling at sleep onset in humans. J Sleep Res 2004;13:209-217.
42. Massimini M, Huber R, Ferrarelli F, Hill S, et al. The sleep slow oscillation as a traveling wave. J Neurosci 2004;24:6862-6870.
43. Maquet P, Peters J, Aerts J, Delfiore G, et al. Functional neuroanatomy of human rapid-eye-movement sleep and dreaming. Nature 1996;383:163-166.
44. Braun AR, Balkin TJ, Wesensten NJ, Gwadry F, et al. Dissociated pattern of activity in visual cortices and their projections during human rapid eye movement sleep. Science 1998;279:91-95.
45. Maquet P, Ruby P, Maudoux A, Sterpenich V, et al. Human cognition during REM sleep and the activity profile within frontal and parietal cortices: a reappraisal of functional neuroimaging data. Prog Brain Res 2005;150:219-227.
46. Nofzinger EA, Buysse DJ, Germain A, Carter C, et al. Increased activation of anterior paralimbic and executive cortex from waking to rapid eye movement sleep in depression. Arch Gen Psychiatry 2004;61:695-702.

47. Nofzinger EA, Mintun MA, Wiseman M, Kupfer DJ, et al. Forebrain activation in REM sleep: an FDG PET study. Brain Res 1997;770:192-201.
48. Germain A, Buysse DJ, Wood A, Nofzinger E. Functional neuroanatomical correlates of eye movements during rapid eye movement sleep in depressed patients. Psychiatry Res 2004;130: 259-268.
49. Hong CC, Harris JC, Pearlson GD, Kim JS, et al. fMRI evidence for multisensory recruitment associated with rapid eye movements during sleep. Hum Brain Mapp 2009;30:1705-1722.
50. Peigneux P, Laureys S, Fuchs S, Delbeuck X, et al. Generation of rapid eye movements during paradoxical sleep in humans. Neuroimage 2001;14:701-708.
51. Wehrle R, Czisch M, Kaufmann C, Wetter TC, et al. Rapid eye movement-related brain activation in human sleep: a functional magnetic resonance imaging study. Neuroreport 2005;16:853-857.
51a. Miyauchi S, Misaki M, Kan S, Fukunaga T, et al. Human brain activity time-locked to rapid eye movements during REM sleep. Exp Brain Res 2009;192:657-667.
52. Wehrle R, Kaufmann C, Wetter TC, Holsboer F, et al. Functional microstates within human REM sleep: first evidence from fMRI of a thalamocortical network specific for phasic REM periods. Eur J Neurosci 2007;25:863-871.
53. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008;1124:1-38.
54. Gusnard DA, Raichle ME, Raichle ME. Searching for a baseline: functional imaging and the resting human brain. Nat Rev Neurosci 2001;2:685-694.
55. Northoff G, Heinzel A, de Greck M, Bermpohl F, et al. Self-referential processing in our brain—a meta-analysis of imaging studies on the self. Neuroimage 2006;31:440-457.
56. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cereb Cortex 2009;19:72-78.
57. Drummond SP, Bischoff-Grethe A, Dinges DF, Ayalon L, et al. The neural basis of the psychomotor vigilance task. Sleep 2005;28: 1059-1068.
58. Horovitz SG, Fukunaga M, De Zwart JA, Van Gelderen P, et al. Low frequency BOLD fluctuations during resting wakefulness and light sleep: a simultaneous EEG-fMRI study. Hum Brain Mapp 2008;29:671-682.
58a. Hobson JA. The dream drugstore. Cambridge, Mass: MIT Press, 2001.
59. Laufs H, Walker MC, Lund TE. "Brain activation and hypothalamic functional connectivity during human non-rapid eye movement sleep: an EEG/fMRI study"—its limitations and an alternative approach. Brain 2007;130:e75; author reply e76.
59a. Horovitz SG, Braun AR, Carr WS, Picchioni D, et al. Decoupling of the brain's default mode network during sleep. Proc Natl Acad Sci U S A 2009;106:11376-11381.
60. Fosse MJ, Fosse R, Hobson JA, Stickgold RJ. Dreaming and episodic memory: a functional dissociation? J Cogn Neurosci 2003; 15:1-9.
61. Solms M: The neuropsychology of dreams. A clinico-anatomical study. Mahwah, NJ: Lawrence Erlbaum; 1997.
62. Gottesmann C. Dreaming: Monoaminergic disinhibition hypothesis. In: Perry E, Ashton H, Young A, editors. Neurochemistry of consciousness: transmitters in mind. Amsterdam: John Benjamins Publishing; 2002. p. 123-131.
63. Kodama T, Honda Y. Acetylcholine releases of mesopontine PGO-on cells in the lateral geniculate nucleus in sleep-waking cycle and serotonergic regulation. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:1213-1227.
64. Sitaram N, Moore AM, Gillin JC. The effect of physostigmine on normal human sleep and dreaming. Arch Gen Psychiatry 1978; 35:1239-1243.
65. Kitabayashi Y, Ueda H, Tsuchida H, Yamashita T, et al. Donepezil-induced nightmares in mild cognitive impairment. Psychiatry Clin Neurosci 2006;60:123-124.
66. Yorston GA, Gray R. Hypnopompic hallucinations with donepezil. J Psychopharmacol (Oxford, England) 2000;14:303-304.
67. Page F, Coleman G, Conduit R. The effect of transdermal nicotine patches on sleep and dreams. Physiol Behav 2006;88: 425-432.
68. Lam S, Patel PN. Varenicline: a selective alpha4beta2 nicotinic acetylcholine receptor partial agonist approved for smoking cessation. Cardiol Rev 2007;15:154-161.
69. Pagel JF, Helfter P. Drug induced nightmares—an etiology based review. Hum Psychopharmacol 2003;18:59-67.
70. Hobson JA, Pace-Schott EF. Reply to Solms, Braun and Reiser. Neuropsychoanalysis 1999;1:206-224.
71. Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. Brain Cogn 1995;28:240-258.
72. Furey ML, Pietrini P, Haxby JV. Cholinergic enhancement and increased selectivity of perceptual processing during working memory. Science 2000;290:2315-2319.
73. Maloney KJ, Mainville L, Jones BE. c-Fos expression in dopaminergic and GABAergic neurons of the ventral mesencephalic tegmentum after paradoxical sleep deprivation and recovery. Eur J Neurosci 2002;15:774-778.
74. Lena I, Parrot S, Deschaux O, Moffat-Joly S, et al. Variations in extracellular levels of dopamine, noradrenaline, glutamate, and aspartate across the sleep–wake cycle in the medial prefrontal cortex and nucleus accumbens of freely moving rats. J Neurosci Res 2005;81:891-899.
75. Dahan L, Astier B, Vautrelle N, Urbain N, et al. Prominent burst firing of dopaminergic neurons in the ventral tegmental area during paradoxical sleep. Neuropsychopharmacology 2007;32:1232-1241.
76. Oakman SA, Faris PL, Cozzari C, Hartman BK. Characterization of the extent of pontomesencephalic cholinergic neurons' projections to the thalamus: comparison with projections to midbrain dopaminergic groups. Neuroscience 1999;94:529-547.
77. Kobayashi Y, Okada K. Reward prediction error computation in the pedunculopontine tegmental nucleus neurons. Ann N Y Acad Sci 2007;1104:310-323.
78. Pace-Schott EF. Serotonin and dreaming. In: Monti JM, Pandi-Perumal SR, Jacobs B, Nutt D, editors. Serotonin and sleep: molecular, functional and clinical aspects. Basel: Birkhauser-Verlag, 2008.
79. Aghajanian GK, Marek GJ. Serotonin and hallucinogens. Neuropsychopharmacology 1999;21:16S-23S.
80. Varnas K, Halldin C, Hall H. Autoradiographic distribution of serotonin transporters and receptor subtypes in human brain. Hum Brain Mapp 2004;22:246-260.
81. Hirstein W. Brain fiction, self deception and the riddle of confabulation. Cambridge, Mass: MIT Press, 2005.
82. Gilboa A, Alain C, Stuss DT, Melo B, et al. Mechanisms of spontaneous confabulations: a strategic retrieval account. Brain 2006; 129:1399-1414.
83. Schnider A. Spontaneous confabulation and the adaptation of thought to ongoing reality. Nature Rev 2003;4:662-671.
84. Moscovitch M, Winocur G. The frontal cortex and working with memory. In: Stuss DT, Knight RT, editors. Principles of frontal lobe function. New York: Oxford University Press; 2002. p. 392-407.
85. Ciaramelli E, Ghetti S. What are confabulators' memories made of? A study of subjective and objective measures of recollection in confabulation. Neuropsychologia 2007;45:1489-1500.
86. Williams J, Merritt J, Rittenhouse C, Hobson JA. Bizarreness in dreams and fantasies: implications for the activation-synthesis hypothesis. Conscious Cogn 1992;1:172-185.
87. Kahn D, Stickgold R, Pace-Schott EF, Hobson JA. Dreaming and waking consciousness: a character recognition study. J Sleep Res 2000;9:317-325.
88. Schwartz S, Maquet P. Sleep imaging and the neuro-psychological assessment of dreams. Trends Cogn Sci 2002;6:23-30.
89. Mar RA. The neuropsychology of narrative: story comprehension, story production and their interrelation. Neuropsychologia 2004; 42:1414-1434.
90. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain 1995;118:279-306.
91. Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. Brain 1998;121:1819-1840.
92. Ffytche DH, Howard RJ, Brammer MJ, David A, et al. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat Neurosci 1998;1:738-742.
93. Amzica F, Steriade M. Progressive cortical synchronization of ponto-geniculo-occipital potentials during rapid eye movement sleep. Neuroscience 1996;72:309-314.

94. Collerton D, Perry E, McKeith I. Why people see things that are not there: a novel perception and attention deficit model for recurrent complex visual hallucinations. Behav Brain Sci 2005;28:737-757; discussion 757-794.
95. Pace-Schott EF. Complex hallucinations in waking suggest mechanisms of dream construction, Commentary on: why people see things that are not there: a novel perception and attention deficit model for recurrent complex visual hallucinations by D. Collerton, E. Perry & I. McKeith. Behav Brain Sci 2005;28:771-772.
96. Mesulam M-M. Principles of behavioral and cognitive neurology, second edition. New York: Oxford University Press; 2000.
97. Sarter M, Bruno JP. Cortical cholinergic inputs mediating arousal, attentional processing and dreaming: differential afferent regulation of the basal forebrain by telencephalic and brainstem afferents. Neurosci 2000;95:933-952.
98. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature 2005;437:1257-1263.
99. Jones BE. Basic mechanisms of sleep-wake states. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine, 4th ed. Philadelphia: Saunders; 2005. p. 136-153.
100. Datta S, Siwek DF, Patterson EH, Cipolloni PB. Localization of pontine PGO wave generation sites and their anatomical projections in the rat. Synapse 1998;30:409-423.
101. Hobson JA, Pace-Schott EF. The cognitive neuroscience of sleep: neuronal systems, consciousness and learning. Nat Rev Neurosci 2002;3:679-693.
102. Steriade M. Neuronal basis of dreaming and mentation during slow wave (non-REM) sleep. Behav Brain Sci 2000;23:1009-1011.
103. Nofzinger EA, Buysse DJ, Miewald JM, Meltzer CC, et al. Human regional cerebral glucose metabolism during non-rapid eye movement sleep in relation to waking. Brain 2002;125:1105-1115.
104. Maquet P, Franck G. REM sleep and amygdala. Mol Psychiatry 1997;2:195-196.
105. Cartwright R, Luten A, Young M, Mercer P, et al. Role of REM sleep and dream affect in overnight mood regulation: a study of normal volunteers. Psychiatry Res 1998;81:1-8.
106. Nielsen T, Levin R. Nightmares: a new neurocognitive model. Sleep Med Rev 2007;11:295-310.
107. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 2002;16:331-348.
108. Quirk GJ, Mueller D. Neural mechanisms of extinction learning and retrieval. Neuropsychopharmacology 2008;33:56-72.
109. Milad MR, Wright CI, Orr SP, Pitman RK, et al. Recall of fear extinction in humans activates the ventromedial prefrontal cortex and hippocampus in concert. Biol Psychiatry 2007;62:446-454.
110. Pace-Schott EF, Milad MR, Orr SP, Rauch SL, et al. Sleep promotes generalization of extinction of conditioned fear. Sleep 2009;32:19-26.
111. Delgado MR, Nearing KI, Ledoux JE, Phelps EA. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron 2008;59:829-838.
112. Jouvet M. The paradox of sleep: the story of dreaming. Cambridge, Mass: MIT Press, 1999.
113. Brown MW, Aggleton JP. Recognition memory: what are the roles of the perirhinal cortex and hippocampus? Nat Rev Neurosci 2001;2:51-61.
114. Schnyer DM, Nicholls L, Verfaellie M. The role of VMPC in metamemorial judgments of content retrievability. J Cogn Neurosci 2005;17:832-846.
115. Amodio DM, Frith CD. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci 2006;7:268-277.
116. Kahn D, Hobson JA. Theory of mind in dreaming: awareness of feelings and thoughts of others in dreams. Dreaming 2005;15: 48-57.
117. Pace-Schott EF. Recent findings on the neurobiology of sleep and dreaming. In: Pace-Schott EF, Solms M, Blagrove M, Harnad S, editors. Sleep and dreaming: scientific advances and reconsiderations. Cambridge, Mass: Cambridge University Press; 2003.
118. Porte HS, Hobson JA. Physical motion in dreams: one measure of three theories. J Abnorm Psychol 1996;105:329-335.
119. Rye DB. Contributions of the pedunculopontine region to normal and altered REM sleep. Sleep 1997;20:757-788.
120. Doricchi F, Violani C. Dream recall in brain-damaged patients: a contribution to the neuropsychology of dreaming through a review of the literature. In: Antrobus JS, Bertini M, editors. The neuropsychology of sleep and dreaming. Hillsdale, NJ: Lawrence Erlbaum; 1992. p. 99-143.
121. Mesulam M-M. The human frontal lobes: transcending the default mode through contingent encoding. In: Stuss DT, Knight RT, editors. Principles of frontal lobe function. New York: Oxford University Press; 2002.
122. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001;24:167-202.
123. Padmala S, Pessoa L. Affective learning enhances visual detection and responses in primary visual cortex. J Neurosci 2008;28: 6202-6210.
124. Saint-Cyr JA. Frontal-striatal circuit functions: context, sequence, and consequence. J Int Neuropsychol Soc 2003;9:103-127.
125. Fosse R, Stickgold R, Hobson JA. Brain-mind states: reciprocal variation in thoughts and hallucinations. Psychol Sci 2001; 12:30-36.